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Translation of the article

Occult adenocarcinoma in adenomas. Possibilities of diagnostic methods

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ABSTRACT *AIM: to analyze the diagnostic value of the digital rectal examination, colonoscopy, MRI and ERUS for detecting occult adenocarcinoma in rectal adenomas.*

PATIENTS AND METHODS: the study included 100 patients with newly identified epithelial rectal neoplasms, which undergone transanal endoscopic microsurgery from December 2019 to December 2020. All the patients underwent digital rectal examination, colonoscopy, ERUS with sonoelastography, and pelvic MRI. The diagnostics value of this methods was estimated with determination of sensitivity and specificity.

RESULTS: the study included 67 (67%) females and 33 (33%) males. The mean age of the patients was 64.4 ± 10.7 years. The median distance from the tumor to the anal verge was 6.0 ± 2.9 cm. The sensitivity of the digital rectal examination in the occult malignancy verification was 0.44 (95% CI: 0.24–0.65), specificity — 0.93 (95% CI: 0.85–0.97). The sensitivity of the colonoscopy — 0.56 (95% CI: 0.34–0.75), the specificity — 0.84 (95% CI: 0.73–0.91). The sensitivity of MRI — 0.40 (95% CI: 0.21–0.61), specificity — 0.89 (95% CI: 0.80–0.95). The sensitivity of ERUS was 0.48 (95% CI: 0.27–0.68), the specificity — 0.73 (95% CI: 0.61–0.82). Pair wise comparison of diagnostic methods revealed the absence of significant differences in their diagnostic value (p > 0.05).

CONCLUSION: at least one of diagnostic methods allows to verify the presence of malignant transformation in 100% of cases. So, only combination of diagnostic methods can help to choose the optimal treatment option.

KEYWORDS: *occult malignancy, adenocarcinoma, rectal adenomas, diagnostics*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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INTRODUCTION

Transanal endomicrosurgery (TEM) is the standard option for benign tumors and early rectal cancer [3,13]. At the same time, the key point in determining the indications and the possibility of local excision is the preoperative diagnostics for identification of occult malignancy in adenomas.

Currently, the standard preoperative checkup of patients with rectal tumors is digital rectal examination, colonoscopy, endorectal ultrasound (ERUS) and magnetic resonance imaging (MRI).

Additional information about the risk of malignant transformation of the adenoma can be obtained by advanced instrumental methods: narrow-spectrum examination or chromoendoscopy with assessment of the pit and vascular pattern during endoscopic examination, and compression elastosonography during ultrasound examination [8,9,14].

Table 1. *Characteristics of clinical observation*

	***n* (%)**
N of patients	100
Age, S ± SD, years	64.4 ± 10.7
Gender, F/M	67/33
Height from the outer edge of the anal canal M (min-max), mm	6.0 ± 2.9 cm
The tumor site depending on the semicircle Anterior Posterior Lateral	 25 (25.0%) 38 (38.0%) 37 (37.0%)

Table 2. *Data of pathomorphological conclusion*

The result of pathomorphological study of removed specimens	***n* (%)**
Histological structure of the tumor, % Adenoma Adenocarcinoma	 75 (75.0%) 25 (25.0%)
Resection margin, % Intact Positive	 83 (83.0%) 17 (17.0%)

However, the use of instrumental diagnostic methods is strongly operator dependent, and the digital rectal examination is purely subjective.
In this regard, we initiated a study to analyze the diagnostic value of the digital rectal method, colonoscopy, MRI, and ERUS to detect occult malignancy in rectal adenomas.

PATIENTS AND METHODS

The recruitment of patients took place from December 2019 to December 2020 in the Ryzhikh National Medical Research Center of Coloproctology. The study included patients aged over 18 years old with newly identified epithelial rectal neoplasm, selected for TEM. All the patients at the diagnostic stage underwent digital rectal examination, colonoscopy, ERUS with sonoelastography, and pelvic MRI. The patients with recurrent epithelial tumors, the patients who had previously undergone preoperative chemoradiotherapy for malignant rectal neoplasms, and with a history of rectal surgery were excluded.
Rectal digital examination was performed on the Rakhmanov bed in the position of the patient on his/her back with his/her legs apart. A proctoscopy was performed, followed by an assessment of the height of the tumor from the anal verge.
The assessment of the tumor presence, the infiltration of the intestinal wall by the tumor, and the status of the mesorectal lymph nodes was performed using ultrasound and magnetic resonance imaging of the pelvis on Hi-Vision Preirus and ProFocus devices (Hitachi, Japan) using a multi-frequency biplane sensor with a frequency of 5–10 MHz, and a Philips Achieva 1.5 T magnetic resonance tomograph (Philips, Niderlands) with a four-channel body coil, respectively. Pelvic MRI was used to assess the relationship of the tumor and the pelvic peritoneum when it was located in the upper rectum. Tumor strain was determined using compression sonoelastography.
Colonoscopy was performed using video endoscopic systems using EC 34-i10M colonoscopes (Pentax, Japan). The tumor site, tumor structure, and tumor shape were assessed in white light endoscopy with an optical magnification of 60–120 times (narrow-spectrum mode) for a detailed analysis of the surface and vascular network of the mucosa. The Kudo-Fujii and Sano Y. classifications were used to assess the nature of the pit-pattern and capillary pattern of the neoplasm [8,9].
Transanal endomicrosurgery was performed under combined spinal anesthesia with intravenous potentiation.
We used equipment for Transanal Endoscopic Operation (TEO) by Karl Storz (Germany): an operating proctoscope with a diameter of 40 mm, a length of 15 cm, and a video endoscopic TEO equipment.
The removed specimens were fixed with needles on a polystyrene plate, followed by a visual assessment of the resection margins.
A comparison of the sensitivity and specificity of diagnostic methods in the search for occult malignancy with the results of pathomorphology of the removed specimen was performed.
The resection margins and the dysplasia degree were assessed by patomorphology as well. The Kikuchi R. subclassification [11] was used to determine the depth of invasion of submucosa.
The statistical data analysis was performed using MedCalc and IBM SPSS Statistics for Windows 10. For a Gaussian distribution, continuous values were described by the standard deviation and

Table 3. *Results of diagnostic methods in dependence of results patomorphological conclusion*

	(Sensitivity (Se) (95% CI)	Specificity (Sp) (95% CI)	Diagnostic accuracy	+ Prognostic Significance (PVP) (95% CI)	– Prognostic Significance (NVP) (95% CI)	AUC (Area under the curve)	*p*
Digital examination	0.44 (0.24–0.65)	0.93 (0.85–0.97)	0.81	0.68 (0.40–0.90)	0.83 (0.77–0.87)	0.687	0.006
Endoscopy	0.56 (0.34–0.75)	0.84 (0.73–0.91)	0.77	0.53 (0.38–0.68)	0.85 (0.78–0.90)	0.7	0.002
MRI	0.40 (0.21–0.61)	0.89 (0.80–0.95)	0.77	0.55 (0.35–0.73)	0.81 (0.76–0.86)	0.647	0.03
ERUS	0.48 (0.27–0.68)	0.73 (0.61–0.82)	0.67	0.37 (0.25–0.51)	0.81 (0.73–0.86)	0.600	0.11
Strain ratio	0.64 (0.42–0.82)	0.64 (0.52–0.74)	–	0.37 (0.28–0.47)	0.84 (0.75–0.90)	0.650	0.013

the amplitude; for a non-Gaussian distribution, they were described by the median and quartiles. The statistical analysis of dichotomous quantities was performed using conjugacy tables. To assess the diagnostic value of the methods, the sensitivity, specificity, and diagnostic accuracy of medical imaging methods were calculated in a 95% coincidence interval.

To determine the prognostic significance, a ROC analysis (Receiver Operating Characteristic) was performed: a ROC curve was constructed, and the quality of the study was evaluated on the scale of the area under the curve (AUC).

The Youden index was used to determine the cut-off point of the SR. The $p < 0.05$ values were considered statistically significant.

RESULTS

According to the inclusion criteria, 100 patients were included in the study: 67 women and 33 men. The average age of the patients was 64.4 ± 10.7 years. The average distance from the tumor to the anal verge was 6.0 ± 2.9 cm. The tumor was localized along the posterior circumference in 38%, along the lateral circumference in 37%, and along the anterior circumference in 25% (Table 1).

According to the pathomorphology of removed specimens adenoma was detected in 75 (75%) of 100 patients, adenocarcinoma — in 25 (25%) (Table 2).

We analyzed the diagnostic value of the digital rectal examination in determining occult malignancy in adenomas. According to the final pathomorphological conclusion, the incidence of false-positive (FP) results in the digital examination was 5%, and false — negative (FN) results — 14%. The sensitivity of the method was 0.44 (95% CI: 0.24–0.65), and the specificity was 0.93 (95% CI: 0.85–0.97) (Table 3).

Endoscopy showed a false positive result in 12% of cases (in 12 out of 100 patients), and a false negative result in 11% that had an invasion into the submucosa. The sensitivity was 0.56 (95% CI: 0.34–0.75), and the specificity was 0.84 (95% CI: 0.73–0.91) (Table 3).

The magnetic resonance imaging revealed the absence of tumor invasion into the intestinal wall in 67 (67.0%) out of 100 patients, while malignancy was correctly diagnosed in 10 (10.0%). A false positive result was observed in 8 (8.0%) out of 100, and a false negative result in 15% of cases. The sensitivity of MRI was 0.40 (95% CI: 0.21–0.61), specificity of 0.89 (95% CI: 0.80–0.95) (Table 3).

The sensitivity of ERUS in the diagnosis of occult malignancy was 0.48 (95% CI: 0.27–0.68), and specificity of 0.73 (95% CI: 0.61–0.82) (Table3). The ROC analysis is shown in Figure 1.

Compression sonoelastography was used to increase the sensitivity of ERUS. The threshold value of the strain ratio (SR), in which the recognition of the presence or absence of invasive growth in the adenoma will have maximum sensitivity and specificity, is considered the value obtained in the analysis of Youdene index = 0.28, and it is equal to SR = 2.88; the sensitivity and specificity was 64% ($p < 0.05$).

With the strain ratio of less than 2.88, the probability of invasive adenocarcinoma absence is 84% (95% CI: 75–90).

When comparing the diagnostic methods in pairs with each other, there were no

significant differences in their diagnostic value ($p > 0.05$).

It is important to note that when analyzing a combination of diagnostic procedures, in 100% of cases, the diagnosis was correctly made at least by one of the methods.

DISCUSSION

The need for early detection of occult rectal adenocarcinomas can be explained by the following relationship: the higher is the depth of submucosal invasion, the greater is the risk of metastatic lesion of regional lymph nodes, which reduces the possibility of local radical excision [7].

Recently, to make a correct diagnosis of a patient with a rectal neoplasm, a complex of examinations is necessary to determine the presence of the tumor and identify the presence of malignancy with a preoperative assessment of the T and N stages.

The diagnostic algorithm allows in most cases to abandon rectal resection in favor of local excision (TEM).

Digital rectal examination is a mandatory diagnostic method for the initial consultation of a coloproctologist. According to the data obtained, the sensitivity of the method was 0.44 (95% CI: 0.24–0.65), and the specificity was 0.93 (95% CI: 0.85–0.97). Despite the subjectivity of the digital study, the obtained results directly correlate with the data of the retrospective analysis of Ang C.W. et al: the incidence of false-negative results was 10% vs 14%. However, in this study, a higher sensitivity of the digital method was obtained (0.76 versus 0.44, respectively), which may be due to the nature of the sample and the inclusion of patients with more obvious deep invasion [6].

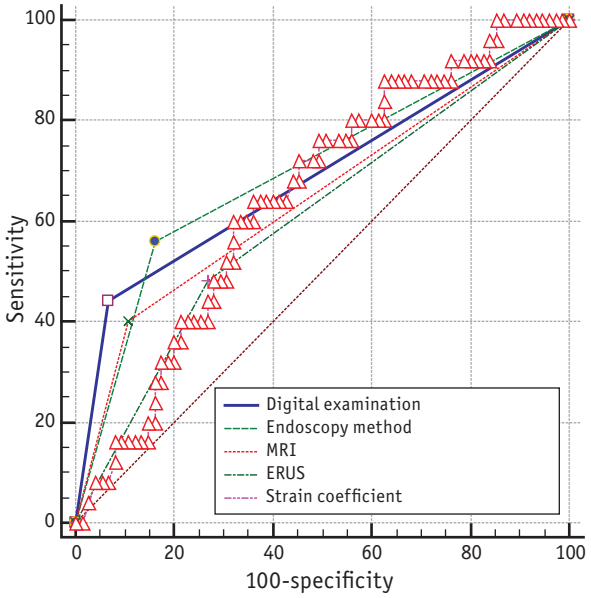

Figure 1. *ROC-curves of diagnostic methods by sensitivity and specificity in verification of hidden malignancy*

The ERUS allows to assess in detail the intestinal wall structure and analyze the lesion depth within the mucosal and submucosal layers.

The accuracy of the method can be improved by performing compression sonoelastography. According to the presented analysis, the strain ratio of the tumor to unaffected tissues exceeding 2.88 indicates a high risk of malignant transformation and the presence of occult malignancy. Prospective study by Bogdanova E.M. et al. [5] showed the highest sensitivity and specificity (0.73 and 0.68, respectively) of the strain ratio (SR) in the detection of rectal cancer at the cut-off point level of 5.71. The higher coefficient can be explained by the inclusion in the study by Bogdanova E.M. of the patients with T_2 and T_3 cancer with a deliberately higher SR.

It is important to note that the diagnostic capability of ERUS is highly dependent on the operator, and the measurement of the SR is not a standardized manipulation [21].

The magnetic resonance imaging (MRI) is highly informative in the diagnosis of malignancies that grow deep into the muscular layer of the intestinal wall or extend beyond it, or to determine indications for the need for neoadjuvant treatment. However, in cases of early cancer, it is very difficult to differentiate changes in the submucosal layer, which can cause hypo-/hyperdiagnostics of the superficial tumor invasion [15,17,18].

So, according to the study by Waage J.E. et al, the MRI specificity in the diagnosis of early cancer is only 0.07 (95%CI: 0.00–0.31): MRI correctly identified only one of the 14 adenomas.

However, it is important to note that in the course of this study, only 2 patients were selected for local excision, which may explain the difference in the diagnostic accuracy of the method [4].

Colonoscopy with examination in a narrow light spectrum often allows to suspect its malignant nature by the appearance of the formation.

The most significant endoscopic signs of malignancy with invasion deeper than 1,000 microns into the submucosal layer are: tumor density, uneven bumpy surface with retraction, convergence of folds, structureless vascular and pit pattern, as well as the contact vulnerability of the neoplasm and the absence of its deformation during insufflation.

Nevertheless, both according to our data and the results of Saito, Y.'s study, the accuracy of the endoscopic diagnosis in the verification of occult malignancy is only 74.7% and 77%, respectively [23].

Thus, it can be stated that only a combination of diagnostic methods and staging in the verification of occult malignancy at the preoperative period can improve their diagnostic accuracy. The results of the population-based study by Detering R. et al., who combined the data of 7,382 patients with early rectal cancer, showed that the combination of ERUS and pelvic MRI can reduce the percentage of hyper-diagnosis of tumors from 54.7% only when performing MRI to 31.0% in determining indications for local excision [22]. It is important to emphasize once again that in the study, in all the cases of malignant transformation, the diagnosis was correctly made at least by one of the tests. This circumstance confirms the need for the interpretation of the study results by the attending physician in conjunction with the available clinical picture and the data of the digital rectal examination.

CONCLUSION

Diagnosis of occult malignancy in rectal adenomas is a key point of selecting patients for local excision. When using a combination of diagnostic methods, at least one of them in 100% of cases allows to correctly verify the presence of a malignant transformation of the tumor and choose the optimal treatment option.

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