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CAPABILITIES OF PERFUSION COMPUTED TOMOGRAPHY IN COLORECTAL CANCER DETECTION AND DIFFERENTIAL DIAGNOSIS OF PATHOLOGICAL CONDITIONS OF THE COLON. EARLY RESULTS

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◆ The article presents the results of preoperative CT diagnostics of colorectal cancer using perfusion technique. It was found that CT perfusion can improve the diagnostics of local prevalence of colon cancer compared to standard computed tomography, as well as to differentiate colorectal cancer and inflammatory bowel disease.

◆ **Keywords:** CT perfusion; colon cancer; complications of colorectal cancer.

ВОЗМОЖНОСТИ ПЕРФУЗИОННОЙ КОМПЬЮТЕРНОЙ ТОМОГРАФИИ В ВЫЯВЛЕНИИ КОЛОРЕКТАЛЬНОГО РАКА И ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКЕ ПАТОЛОГИЧЕСКИХ СОСТОЯНИЙ ТОЛСТОЙ КИШКИ. ПЕРВЫЕ РЕЗУЛЬТАТЫ

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◆ Представлены результаты предоперационной КТ-диагностики колоректального рака с применением методики перфузии. Установлено, что перфузионная компьютерная томография позволяет улучшить диагностику местной распространенности рака ободочной кишки по сравнению со стандартной компьютерной томографией, а также помогает дифференцировать колоректальный рак и воспалительные заболевания толстой кишки.

◆ **Ключевые слова:** КТ-перфузия; рак толстой кишки; осложнения колоректального рака.

Introduction

Despite the introduction of screening programs and the equipment of clinics with state-of-the-art diagnostic tools, colorectal cancer (CRC) continues to be among the leading cancer disease in the world with high rates incidence and mortality. In 2018, the American Society of Clinical Oncology in the USA globally ranked CRC as the fourth and second in terms of

cancer incidence and mortality, respectively [1]. Moreover, according to the European Society for Medical Oncology, a similar situation is observed in most European countries [2]. However, in USA and Europe, there was a tendency toward a gradual decrease in morbidity and mortality of CRC from year 1980 to 2015 [1–3]. However, in contrast with the situation in Russia, the Russian Oncology Association, recorded an increase in the incidence of malignant neoplasms of the colon from year 2007 to 2017, with 18.3% incidence in men and 12.8% incidence in women [4]. In 2017, colon malignancies ranked fourth in terms of morbidity (6.8%), and third in terms of mortality (7.9%). The average age of patients with newly diagnosed CRC is between 66–67 years in men, and between 68 and 69 years in women. Gender difference has been observed in the rate of mortality due to CRC as the women (60–69 years) were ranked second while the men (70 years) were ranked fourth [4]. In 40% of the cases, patients seek medical attention at stages III–IV of the disease [4, 5] and, as a result of delayed diagnosis, are hospitalized in general surgical hospitals due to the emanating complications of CRC. Complicated forms of cancer is common among the elderly and senile patients, with a prevalence of 42.5%–86.2% [5]. Complications of CRC includes perifocal purulent and inflammation, tumor invasion into neighboring organs and tissues, acute intestinal obstruction, hemorrhage, tumor perforation, and the combinations thereof. A significant proportion of elderly patients with CRC complications is characterized by an unclear clinical presentation and the absence of pathognomonic symptoms, which makes diagnostics at the pre- and hospital stages difficult, resulting to aggravation of prognosis, as well as, treatment measures for the disease.

Computed tomography (CT) of the abdominal cavity using intravenous bolus contrast and the multiphase scanning technique, along with endoscopic colonoscopy and biopsy, is included in the standard mandatory examination of CRC patients [6]. CT is an effective diagnostic method that identifies the localization of the tumor in the intestine at stages T3 and T4, excludes the secondary changes in the parenchymal organs of the abdominal cavity and retroperitoneal space, and assesses the state of the regional and distant lymph nodes. Unfortunately, diagnosis of CRC at stages T1 and T2 is often a challenge, especially when the process is limited by the intestinal wall, and/or when difficulties arise in differential diagnosis of the tumor and its complications such as inflammatory bowel diseases. There are currently no reliable differential diagnostic strategy for CRC complications such as perifocal inflammation, tumor invasion of the paracolic fatty tissue, true invasion of surrounding organs, and for the determination of metastatic and reactively enlarged lymph nodes [6].

The study aimed to ascertain the possible application of CT using the perfusion technique (PCT) in detecting CRC at early stages, assessing the local distribution of the process and its complications, as well as, in differential diagnosis of colon diseases that mimic CRC.

It is also aimed at optimizing the PCT technique for the diagnosis of changes in the colon, and to determine the most informative indicators of perfusion in differential diagnosis of the tumor and inflammatory changes in the intestine.

Materials and methods

The perfusion CT scan was performed in 15 patients. All patients with tumors were operated, and the diagnosis were verified by tissue histology. The studies were conducted with the instrumentation of a GE 64 Optima 660 computed tomograph. The protocol included native examination, CT perfusion, and scanning in the mixed and excretory phases. Post-processing treatment was conducted on the Advantage Workstation VS5 using the CT Perfusion 4D Multi-Organ software package. Perfusion indices were calculated using a standard algorithm and by the deconvolution method.

Scanning and data processing method. The studies were conducted on an empty stomach. To minimize respiratory artifacts, the patients were previously instructed to maintain a uniform mode of breathing, avoiding deep inspiration and expiration. The anterior abdominal wall was fixed with a wide elastic belt in order to restrict the respiratory excursions.

Native scanning was conducted on inspiration, from the level of the xyphoid process to the tubers of the ischium. The zone of interest was specified on the images obtained in such a manner that the pathological process was centered in the scanning frame, ensuring the maximum possible

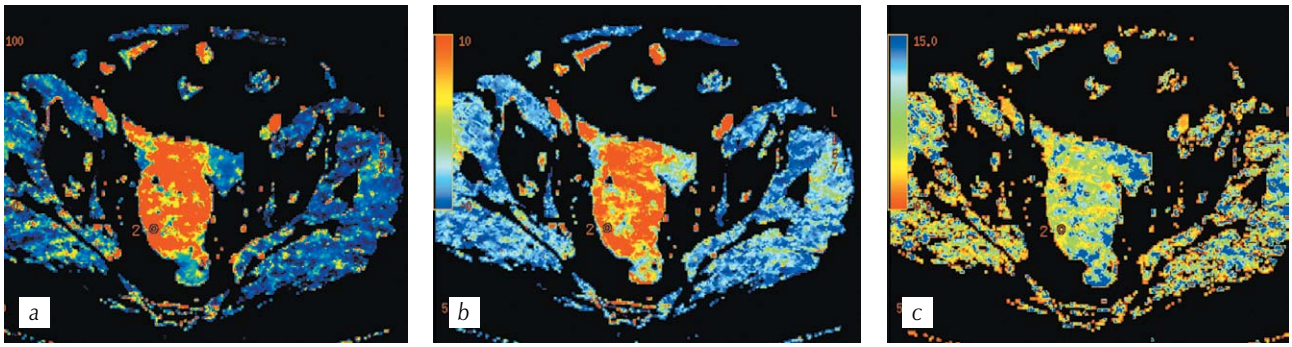


Fig. 1. CT perfusion. Parametric maps: *a* — blood volume; *b* — blood flow; *c* — mean transit time of contrast medium. Strong vascularization of the rectosigmoid junction tumor in ROI 2 area

Рис. 1. Перфузионная компьютерная томография. Цветные параметрические карты: *a* — объем кровотока; *b* — скорость кровотока; *c* — среднее время прохождения контрастного вещества. Определяется высокая васкуляризация опухоли ректосигмоидного отдела толстой кишки в метке ROI 2

coverage of the great vessels and regional lymph nodes. Further, a series of dynamic scans were performed within 60 s after a bolus injection of 50 ml of iodine-containing contrast agent, with a concentration of 350 mg/ml, at the rate of 4.5 ml/s in the selected scanning zone.

The scanning configuration is as follows: slice thickness = 5 mm, interval = 5 mm, scan type = axial-S Full, tube rotation speed = 1.0 s, tube voltage = 80 kV (220 mA), scanning zone width = 80 mm; matrix = 512 × 512, and total scan time = 60 s.

At phase 3, an additional 50 ml of contrast agent was injected, and the abdominal cavity and pelvis (if necessary) were scanned at 65–80 s andmin 5 mins from the start of scanning in order to exclude secondary damage to the abdominal organs, as well as, the retroperitoneal space, apical and other lymph nodes (in accordance with the Japanese classification of regional lymph nodes of the colon and the Japanese Society for Cancer of the Colon and Rectum, JSCCR), and also for more information about the anatomical aspects of the zone of interest, in the view of identifying concomitant pathology.

The images obtained were processed on the Advantage Workstation VS5. For parametric analysis, the CT Perfusion 4D Multi-Organ software package was used. The first images in the series did not contain a contrast agent. These images were therefore used to determine the basic level of density. A mark (ROI 1; 2–5 mm^2) was manually set on a nearby large arterial vessel (which is in most cases, depending on the process localization, an aorta or iliac artery). Afterwards, the mathematical processing of the dynamic series obtained was performed from following the appearance of the contrast agent in the tissues. Relative to the values obtained on the afferent artery and base density, the program calculated the main perfusion indicators in the zone of interest through the construction of color parametric cards (Fig. 1) and the "density–time" curve (Fig. 2).

While measuring the perfusion indices, the labels were placed on the most vascularized areas of the tumor invasive portion (with the exception

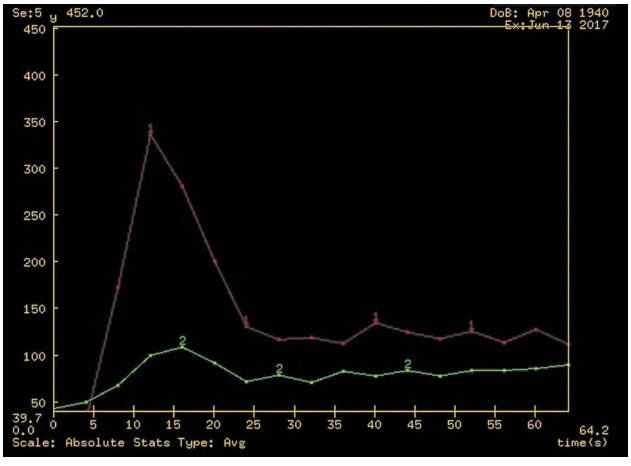


Fig. 2. The density-time graph showing the changes of contrast density in time in the area of interest (curve *2*, corresponds to ROI 2 area in Fig. 1) relative to the blood flow in the afferent vessel (curve *1*)

Рис. 2. График «плотность – время», отражающий изменение плотности контрастного вещества во времени в зоне интереса (кривая *2*, соответствует установленной метке ROI 2 на рис. 1) относительно кровотока в афферентном сосуде (кривая *1*)

of the necrosis zones and adjacent intact intestinal walls) for the epi- and mesocolic assessment of apical lymph nodes with signs of increased blood flow.

For quantitative assessment of blood flow values in each voxel, we measured numerous parameters including blood flow velocity (*BF*, ml/100 g per min); blood flow volume (*BV*, ml/100 g); mean transit time of a contrast agent (*MTT*, s); permeability surface-area product (*PS*, ml/100 g per min); mean slope of increase of density (*MSI*, HU/min); time to peak of maximum density (*TTP*, s); and maximum transit time of a contrast agent (T_{max}, time maximum, s), all of which indicate the functional state of the tissue in the zone of interest and are displayed in a table of absolute numerical values (Fig. 3).

Results

Colon tumors were analyzed in 13 patients. A tumor of the small intestine was revealed in one patient, and a paracolic abscess against colitis was found in another patient. In 9 patients, the tumor was accompanied by complications such as perifocal inflammation ($n = 4$), invasion of adjacent organs ($n = 3$), formation of fistulous passages ($n = 2$), intestinal obstruction ($n = 1$), and intestinal wall perforation with circumscribed peritonitis ($n = 1$).

Fig. 3. Summary table of perfusion parameters in ROI 2 in Fig. 1

Рис. 3. Сводная таблица числовых значений показателей перфузии в установленной точке интереса ROI 2 на рис. 1

A paracolic abscess was drained of its content. While performing the controlled CT studies during conservative therapy, there was a positive trend in the form of resolving the abscess and colitis.

The abnormal vascularization of the tumor, in contrast to the adjacent intact walls of the intestine and colitis, was determined at the stage of visual assessment of parametric cards, despite the slight thickening of the intestinal walls (Fig. 4).

Similar analysis was also conducted in the secondary altered paracolic lymph node (Fig. 5).

Perfusion CT compared with standard spiral CT enabled the visual assessment of the invasion of adjacent organs (Fig. 6).

From the result of the analysis of perfusion indices, it was revealed that the maximum changes observed were related to the *BF* index; the numerical values of which in tumors differ significantly from those in intact intestinal wall, and significantly exceeds those in the intestinal wall with colitis. Numerical values in the tumor were estimated within the range of 92 to 247 ml/100 g per min. The *BF* values in the intact intestinal wall did not exceed 16–77 ml/100 g per min, whereas, *BF* values in the intestinal wall with colitis ranged 28–67 ml/100 g per min. There was no significant correlation between the changes observed for other indicators in the sample. The *BV* values ranged 5–11 ml/100 g, *MTT* ranged 2–9 s, *PS* values ranged 3–24 ml/100 g/min, *TTP* indices ranged 15–26 s, T_{max} ranged 3–11 s, and *MSI* ranged 3–4 HU/min.

While plotting the density–time graphs for 8 patients with colon tumor, a similar trend was noted in the changes in the density–time curve, which is characterized by a slightly sloping peak that appeared within 3–8 s after the peak in the afferent vessel, and its gradual decrease within 7–11 s. However, in the patient presenting signs of colitis, the same trend was not observed.

Moderately differentiated adenocarcinoma was verified by histology of the tissue from seven of the aforementioned patients. As a result, high-grade adenocarcinoma was detected in one patient.

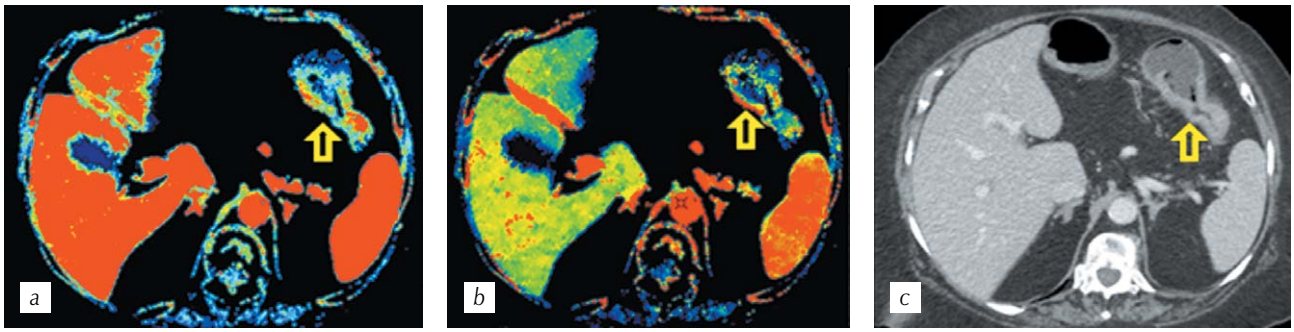


Fig. 4. CT perfusion (*a*, *b*). Parametric maps: *a* — volume and *b* — blood flow showing pathological increased blood flow in the descending colon tumor (arrows); *c* — HCT. Multiplanar reconstruction in the axial plane in the portal phase of scanning

Рис. 4. Перфузионная компьютерная томография (*a*, *b*). Цветные параметрические карты: *a* — объема и *b* — скорости кровотока, демонстрирующие патологический повышенный кровоток в стенках стенозирующей опухоли селезеночного изгиба ободочной кишки (стрелки); *c* — спиральная компьютерная томография. Мультипланарная реконструкция в аксиальной плоскости в портальную фазу сканирования

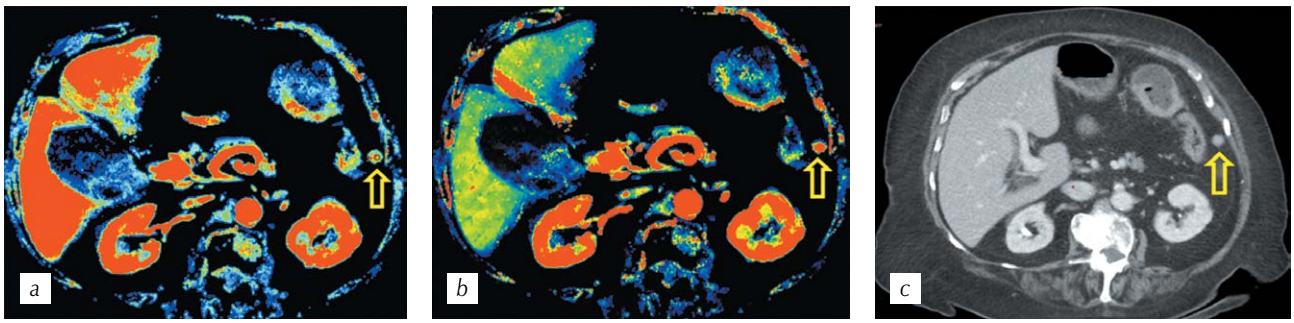


Fig. 5. CT perfusion (*a*, *b*). Parametric maps: *a* — volume and *b* — blood flow showing pathological increased blood flow in the paracolic lymph node (arrows); *c* — HCT. Multiplanar reconstruction in the axial plane in the portal phase of scanning

Рис. 5. Перфузионная компьютерная томография (*a*, *b*). Цветные параметрические карты: *a* — объема и *b* — скорости кровотока, демонстрирующие патологический повышенный кровоток в параколическом лимфатическом узле (*стрелки*); *c* — спиральная компьютерная томография. Мультипланарная реконструкция в аксиальной плоскости в портальную фазу сканирования

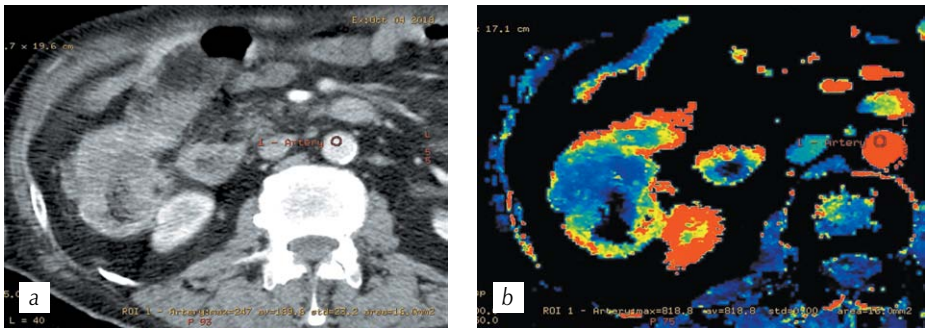


Fig. 6. CT, multiplanar reconstruction in the axial plane in the arterial phase (*a*), with a thin dividing strip of adipose tissue between ascending colon tumor and the kidney capsule; *b* — CT perfusion, parametric map of the blood volume showing the invasion of the adipose tissue and the kidney capsule by the ascending colon tumor

Рис. 6. Спиральная компьютерная томография, мультипланарная реконструкция в аксиальной плоскости в артериальную фазу сканирования (*a*), на которой между образованием восходящего отдела ободочной кишки и капсулой почки прослеживается тонкая разделительная полоска жировой клетчатки; *b* — перфузионная компьютерная томография, цветная параметрическая карта объема кровотока, демонстрирующая инвазию жировой клетчатки и капсулы почки образованием восходящего отдела ободочной кишки

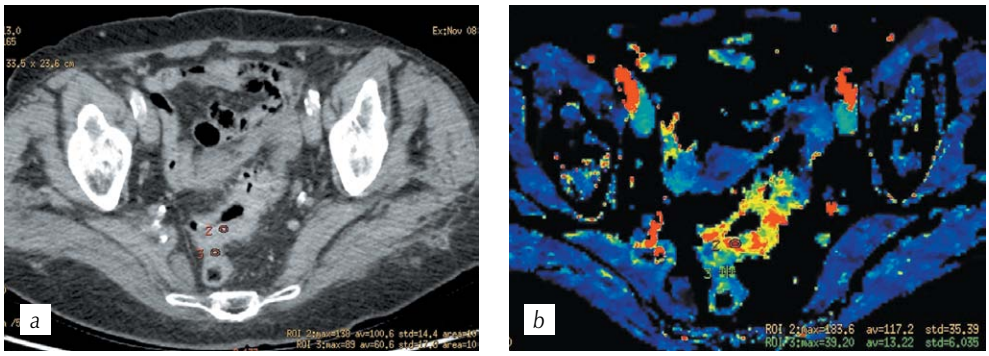
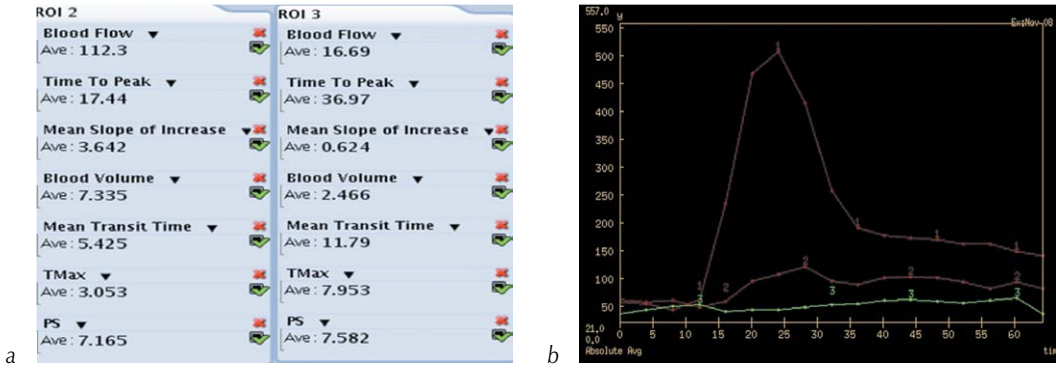


Fig. 7. HCT, multiplanar reconstruction in the axial plane in the portal phase (*a*) and CT perfusion, parametric map of the blood flow (*b*) with ROI 2 in the invasive part of the tumor and ROI 3 in the intact intestinal walls

Рис. 7. Спиральная компьютерная томография, мультипланарная реконструкция в аксиальной плоскости в портальную фазу сканирования (*a*) и перфузионная компьютерная томография, цветная параметрическая карта скорости кровотока (*b*) с метками ROI 2 в инвазивной части опухоли и ROI 3 в смежных интактных стенках кишки

It was revealed that for a moderately differentiated adenocarcinoma, the visual assessment of the parametric cards is characterized by a clear difference between the tumor vascularization and the adjacent intact intestinal walls. Further, the boundaries of infiltrative changes in the intestinal wall during PCT were wider when compared to that obtained during standard spiral CT (Fig. 7, *a, b*). Following the placement of the ROI 2 labels in the tumor, and ROI 3 labels in the wall of the intact intestine, we obtained tables of digital values that demonstrate clear differences in the blood flow velocity indicator as *BF* in the tumor wall minand intact intestine was 112 ml/100g per min and 16 ml/100 g per min, respectively (Fig. 8, *a*). The density–time plot indicates functional changes in the tumor tissue in the form of the rise in curve *2* after 15 s of scanning, with a peak at 28 s and 3 s after the appearance of a peak in the afferent vessel. The green curve indicate that changes in the intact intestinal wall had a relatively straight course without significant peaks (Fig. 8, *b*).

For a comparative assessment, the results of the examination of the patient who was admitted to the hospital with non-specific symptoms were presented. According to the ultrasound results, the mass lesion in the abdominal cavity palpable during physical examination was presumably associated with the ascending part of the colon. While performing the PCT, a paracolic abscess was detected in the right lateral canal which was associated with the lumen of the ascending colon. The walls of the intestine at the level of the mass lesion were circularly thickened (Fig. 9). On the perfusion cards, a predominantly low BF was



a *b*

Fig. 8. Summary tables of perfusion parameters (*a*), the density-time graph (*b*) for the ROI *2* area in the tumor and ROI *3* in the intact intestinal wall

Рис. 8. Сводные таблицы числовых значений (*a*), график «плотность – время» (*b*) для меток ROI 2 в опухоли и ROI 3 в интактной стенке кишки

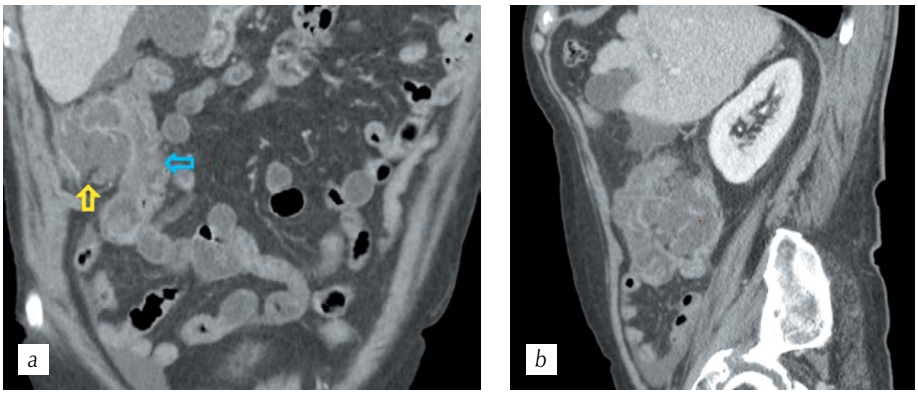


Fig. 9. HCT. Multiplanar reconstructions in: *a* — coronal and *b* — sagittal planes in the portal phase demonstrating thickened walls of the ascending colon (*blue arrow*) and paracolic abscess in the lateral canal (*yellow arrow*)

Рис. 9. Спиральная компьютерная томография. Мультипланарные реконструкции в: *a* — корональной и *b* — сагиттальной плоскостях в портальную фазу сканирования — стенки восходящего отдела ободочной кишки (*голубая стрелка*) утолщены, параколический абсцесс в латеральном канале (*желтая стрелка*)

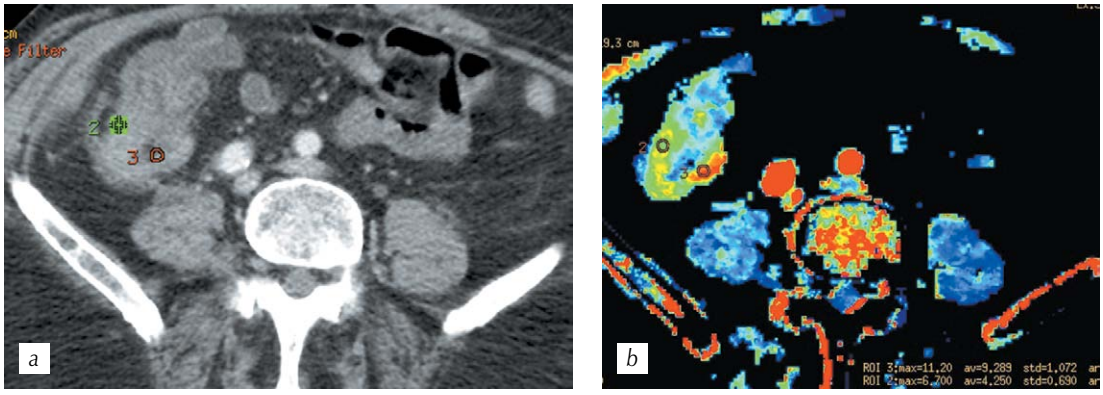
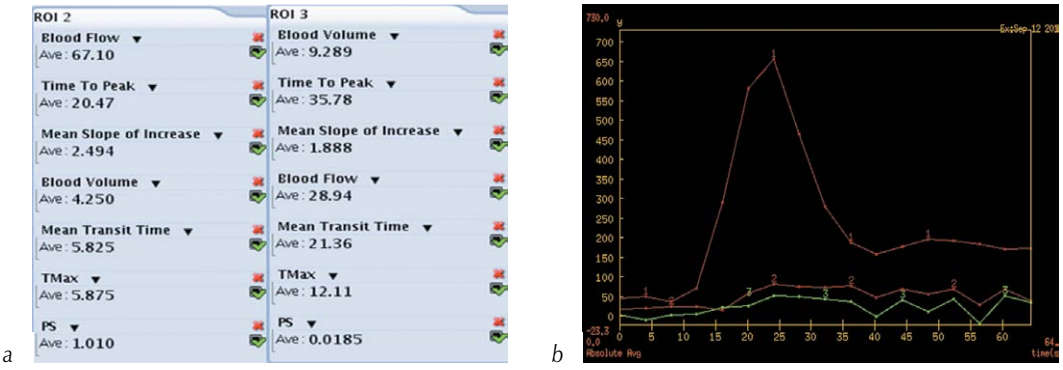


Fig. 10. HCT. Multiplanar reconstruction in the axial plane to the arterial phase (*a*) and CT perfusion, parametric map of blood volume (*b*) with ROI 2 marks in the most vascularized area and ROI 3 in the contralateral intestinal wall

Рис. 10. Спиральная компьютерная томография. Мультипланарная реконструкция в аксиальной плоскости в артериальную фазу сканирования (*a*) и перфузионная компьютерная томография, цветная параметрическая карта объема кровотока (*b*) с метками ROI 2 в наиболее васкуляризированном участке и ROI 3 в контралатеральной стенке кишки



a b

Fig. 11. Summary tables of perfusion parameters (*a*), the density-time graph (*b*) for ROI 2 and ROI 3 in thickened colon walls with signs of colitis

Рис. 11. Сводные таблицы числовых значений (*a*), график «плотность – время» (*b*) для меток ROI 2 и ROI 3 в утолщенных стенках ободочной кишки с признаками колита

detected in the thickened walls of the intestine, with an observation of single hypervascular inclusions (Fig. 10). While measuring blood flow parameters in the area of maximum perfusion (ROI 2) and the contralateral wall of the intestine (ROI 3), the range of numerical values of *BF* was 9–67 ml/100 g per min (Figure 11*a*), and the curves on the density – time plot showed similar trends in density at the points of interest, without the formation of peaks typically noted for tumors (Fig. 11, *b*). The abscess was drained, and the effects of colitis regressed following conservative therapy.

Conclusions

CT using perfusion compared to standard CT is the most optimal method for examining CRC patients, assessing the local distribution of the tumor, identifying complications, and for differential diagnostics of colon diseases. The rate of BF was the most informative indicator of perfusion in patients with moderately differentiated adenocarcinoma. Perfusion CT provides additional diagnostic information within preoperative planning, which significantly influences the reduction in the frequency of postoperative complications and mortality due to CRC.

Conflict of interests. The authors declare no conflict of interest.

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