ПЭТ/КТ в ранней и дифференциальной диагностике адренокортикального рака

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***Цель исследования** – разработка критериев ранней и дифференциальной диагностики адренокортикального рака (АКР) при проведении позитронной эмиссионной томографии, совмещенной с компьютерной томографией (ПЭТ/КТ), с ^{18}F-фтордезоксиглюкозой (^{18}F-ФДГ).*

***Материалы и методы.** Диагностические исследования выполнены на аппарате General Electric the Discovery PET/CT 610. После проведения сканирования и введения радиофармацевтического препарата (РФП) через 60–90 мин сформированы изображения ПЭТ, показывающие распределение РФП во всем теле как в физиологических, так и в патологических зонах. С помощью программного обеспечения проводилось автоматическое «слияние» снимков, полученных на ПЭТ- и КТ-сканерах. Первоначально врачом-рентгенологом выполнялся анализ структурных патологических изменений в органах с последующей оценкой уровня накопления РФП и определением КТ-денситометрии образований надпочечников. Метаболическую активность опухолей надпочечников определяли по уровню SUV (стандартизированный показатель накопления РФП).*

***Результаты.** Проведен ретроспективный анализ данных ПЭТ/КТ с ^{18}F-ФДГ у 50 пациентов с опухолевыми образованиями надпочечников. На основании изученных данных пациенты были разделены на 2 группы: 1-я группа (n = 21) с диагностированным последующем АКР, 2-я группа (n = 29) с доброкачественными новообразованиями надпочечников. Возраст пациентов составил 68 (32–76) лет и статистически не различался в обеих группах (p >0,05). При изучении параметров образования получены следующие результаты: средний размер опухоли у пациентов 1-й группы составил 4,5 ± 0,75 см, 2-й группы – 4,9 ± 1,1 см, при этом достоверной разницы между группами не выявлено (p >0,05). Диагностическая модель, полученная при построении и последующем анализе ROC-кривой уровня SUV у пациентов со злокачественными и доброкачественными новообразованиями надпочечников, показала высокое качество с чувствительностью метода 90 %, специфичностью 95 % (площадь под ROC-кривой (AUC) 0,93 при p <0,0001 (z = 27,37)) и точкой отсечения, равной 3. При изучении КТ-денситометрических показателей опухоли над-почечников у пациентов 1-й и 2-й групп получена прямая корреляционная связь данных параметров с диагностикой злокачественного поражения (Rs = 0,67; коэффициент τ Кендалла 0,64; p = 0,001). Интерпретация результатов ROC-анализа уровня плотности опухоли (КТ-плотность в единицах Хаунсфилда (HU)) у пациентов 1-й и 2-й групп показала 80 % чувствительность и 90 % специфичность (AUC 0,89; p <0,0001) с точкой отсечения, равной 10 HU.*

***Заключение.** Получение интегральной информации по уровню SUV вместе с измерением КТ-плотности опухоли при проведении ПЭТ/КТ с ^{18}F-ФДГ является одним из наиболее современных диагностических методов, позволяющих проводить дифференциальную диагностику патологического процесса в надпочечниках и наранних этапах обследования выявлять АКР. Перечисленные выше факторы в настоящее время указывают на высокую диагностическую ценность ПЭТ/КТ с ^{18}F-ФДГ и приоритетный характер выполнения данного исследования при подозрении на АКР у пациентов с новообразованиями надпочечников размером 1–5 см.*

***Ключевые слова:** адренокортикальный рак, SUV, ПЭТ/КТ, новообразование надпочечника, ^{18}F-фтордезоксиглюкоза*

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PET/CT in the early and differential diagnosis of adrenocortical cancer

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***The objective** of the study was to develop criteria for the early and differential diagnosis of adrenocortical cancer (ACC) during positron emission tomography combined with computed tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG).*

***Materials and methods.** Diagnostic tests were performed on a General Electric the Discovery PET/CT 610. PET-grams were obtained within 60–90 minutes after scanning and radiopharmaceutical injection, showing the distribution of the radiopharmaceutical throughout the body in both physiological and pathological areas. Using software, automatic «fusion» of images obtained on PET and CT scanners was* *carried out. Initially, a radiologist analyzed structural pathological changes in organs, a then assessed the level of accumulation and determination of CT densitometry of pathological adrenal formations. Subsequently, metabolic activity was determined by the level of SUV (standard uptake value).*

Results. *A retrospective analysis of ^{18}F-FDG PET/CT data was performed in 50 patients with adrenal tumors. Based on the data all patients were divided into 2 groups: group 1 (n = 21) with a subsequent ACC diagnosis, group 2 (n = 29) – with benign adrenal neoplasms. Patients' mean age was 68 (32–76) years and did not statistically differ between groups (p >0.05). After checking up tumor parameters, the following results were obtained: the average tumor size in group 1 was 4.5 ± 0.75 cm, in group 2–4.9 ± 1.1 cm, no significant difference was found (p >0.05). The diagnostic model obtained by constructing and subsequent analysis of the ROC curve of the SUV level in patients with malignant and benign adrenal neoplasms showed a high quality model with 90 % sensitivity and 95 % specificity (area under the ROC curve (AUC) 0.93 at p <0.0001 (z = 27.37)) and a cut-off point of 3. When studying tumor CT densitometric parameters in groups 1 and 2, we revealed a correlation between these parameters and the diagnosis of malignant lesions (Rs = 0.67; Kendall's τ coefficient 0.64; p = 0.001). Interpretation of the results of the ROC analysis of the tumor density level (CT density in Hounsfield units (HU)) in patients of groups 1 and 2 showed 80 % sensitivity and 90 % specificity (AUC 0.89; p <0.0001) with a cut-off point equals 10 HU.*

Conclusion. *Obtaining integral information on the SUV level together with measuring CT density during ^{18}F-FDG PET/CT is one of the most modern diagnostic methods that allow both diagnostics and differential diagnosis of ACC in the early stages of the pathological process. The above factors currently indicate the high diagnostic value of ^{18}F-FDG PET/CT and the priority nature of this study in cases of suspected ACC in patients with 1–5 cm adrenal neoplasms.*

Key words: *adrenocortical cancer, SUV, PET/CT, adrenal gland neoplasm, ^{18}F-fluorodeoxyglucose*

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Introduction

Adrenocortical cancer (ACC) is a rare malignant tumor, originating from the cortical layer of adrenal gland. It has an aggressive clinical progression and, to date, an unfavorable therapeutic prognosis. Annually, 0.5–2 cases of ACC are detected per million people, which is 0.04–0.2 % in standard oncological mortality. It is very difficult to assess epidemiological data for Russia, since ACC cases are not reported separately. Some cases of ACC can be identified as adrenal incidentaloma. ACC rarity causes objective difficulties due to the lack of prospective, randomized trials and sufficient treatment experience outside the specialized institution. The main task at the diagnostic stage is to identify ACC cases among incidetaloma or symptomatic adrenal tumors [1, 2].

Clinical guidelines of the Russian Oncology Association and Russian Association of Endocrinologists for ACC treatment recommend positron emission tomography (PET) combined with CT (PET/CT) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in cases of a small tumor size and ambiguous computed tomography (CT) data [1, 2].

A.P. Dackiw et al. as well as L. Ng et al. show, that in 80 % of patients at the time of ACC detection the tumor size is at least 10 cm, in 30–40 % of patients metastases are preoperatively detected. The probability of distant metastases in tumors of >10 cm according to postoperative observation data is >80 % [3, 4].

It should be noted, that in TNM and ENSAT (European Network for the Study of Adrenal Tumors) classifications 5 cm tumor size allows differentiating between stages I and II of adrenal cancer. A study by R. Libe in 2015 showed a significant difference in survival rates of patients with initial and advanced disease stages. The 5-year survival rate at stage I of ACC is on average 74–82 %, and at stage II – 61–64 % [5].

Thus, early ACC diagnosis is a priority task to improve the treatment results. One of the most advanced diagnostic options in detecting and staging adrenal cortical cancer is PET/CT.

Today PET is an actively developing diagnostic and research method of nuclear medicine. PET/CT (or double photon emission tomography) is a radionuclide tomographic method to study internal organs, a combination of 2 methods: radioactive indication and CT. PET/CT with glucose analogue ^{18}F-FDG, which is a combination of functional and structural imaging methods, is based on detecting increased glucose metabolism in malignant tumors.

PET scanning using ^{18}F-FDG is widely used in clinical oncology. This tracer is the glucose analogue that is absorbed by cells, using glucose, and phosphorylated by hexokinase (the concentration of the mitochondrial form of hexokinase significantly increases with rapidly growing malignant tumors). Since for the next step of glucose metabolism all cells need an oxygen atom, which is replaced by ^{18}F to synthesize FDG, there are no further reactions with ^{18}F-FDG. In addition, most tissues (except liver and kidneys) cannot remove the phosphate, added by hexokinase. This means that ^{18}F-FDG is retained in any cell that absorbs it until cytolysis, since phosphorylated sugars cannot leave the cell due to ionic charge. This process leads to intense radioactive «tagging» of tissues with high glucose uptake, such as brain, liver and most types of malignant neoplasms and metastases. As a result, ^{18}F-FDG PET/CT is used to diagnose and control malignant tumors of various locations.

There are limited data on the role of ^{18}F-FDG PET/CT for ACC diagnosis. As a rule, malignant neoplasms of the adrenal glands accumulate ^{18}F-FDG well. The method allows identifying the primary tumor, local relapse and distant metastases. According to S. Leboulleux et al., tumor metabolic activity correlates with ^{18}F-FDG uptake. The degree of ^{18}F-FDG uptake (standardized uptake value of the drug (SUV) > 10, which represents the tumor load), is associated with the disease prognosis [6]. C. Ansquer et al. showed that ^{18}F-FDG PET/CT was negative in 31 (97 %) of 32 "nonsurgical" adrenal glands and positive in 35 (73 %) of 49 potentially "surgical" adrenal tumors, including 24 (89 %) of 27 malignant lesions and 12 (55 %) of 22 benign, secreting lesions [7].

It should be noted, that all previous studies of ^{18}F-FDG PET/CT use in ACC were characterized by heterogeneity of the patient sample relative to neoplasm size, which determined patients» distribution at various stages of the pathological process during ACC verification. In addition, foreign studies have not yet determined the parameters obtained with ^{18}F-FDG PET/CT in patients with adrenal neoplasms of <5 cm, though they can be extremely important in early ACC diagnosis.

Materials and methods

A retrospective analysis of ^{18}F-FDG PET/CT data was performed in 50 patients with adrenal tumors. Based on the data all patients were divided into 2 groups. Group 1 included 21 patients (13 men and 8 women) with a subsequently diagnosed

ACC, group 2–29 patients (16 men and 13 women) with benign adrenal neoplasms. The mean patients' age was 68 (32–76) years and did not statistically differ between groups (p >0.05).

Diagnostic tests were performed using General Electric the Discovery PET/CT 610 apparatus. Research boundaries: from the orbitomeatal line to the upper third of the femoral diaphysis, using the Whole Body protocol. PET images were obtained 60–90 min after scanning and radiopharmaceutical (RPC) injection, RPC was distributed in the body in both physiological and pathological zones. Using a software, we "fused" obtained PET/CT images. Initially, a radiologist analyzed structural pathological changes in organs and subsequently assessed the level of RPC accumulation and CT densitometry in pathological adrenal glands. Metabolic activity of adrenal tumors was determined based on the SUV level.

The obtained results were analyzed using Statistica 10.0. Categorical variables SUV and tumor CT density were used. To determine the differences significance and analyze their conjunction, we used Pearson's chi-squared test, Mantel–Hanzel test and Kendall's τ coefficient. For quantitative values, theirs means and standard errors of the mean are presented. Nonparametric Mann–Whitney test was used to analyze the significance of differences of quantitative factors» means. A statistical relationship between the parameters was considered significant at p ≤0.05.

Sensitivity, specificity, prognostic significance, as well as optimal threshold levels of parameters were analyzed using a decision matrix, formulas and ROC-curves.

Results

When analyzing PET/CT images the following data were obtained. Fig. 1 demonstrates PET image with RPC hyperfixation in the projection of the right adrenal gland, SUV equals 4. In the projection of the left adrenal gland no RPC hyperfixation was noted. CT determines bilateral adrenal tumors. The tumor»s density and size in the right adrenal gland are 20 Hounsfield units (HU) and 4.7 cm, in the left adrenal gland – 5 HU and 2.0 cm, respectively. When "fusing" the images, we see a typical picture of the malignant lesion of the right adrenal gland.

PET image (Fig. 2) shows RPC hyperfixation (indicated by the arrow), SUV equals 6. According to CT, there is a tumor of left adrenal gland (indicated by the arrow) with 20 HU density and 3.5 cm size. When "fusing" the images, we see a typical picture of malignant adrenal lesions.

PET image (Fig. 3) shows RPC hyperfixation (indicated by arrows) in the projection of both adrenal glands. SUV equals 5 for both sides. CT determines bilateral adrenal formations (indicated by arrows) with the density of >20 HU on both sides and size of 4.9 cm and 3.9 cm on the right and on the left, respectively. When "fusing" the images, we see a typical picture of the malignant adrenal lesions.

Among ACC patients, 8 were diagnosed hormone-producing tumors. Studying their parameters, the following results were obtained: the average tumor size in group 1 was 4.5 ± 0.75 cm, in group 2–4.9 ± 1.1 cm, and it did not statistically differ between groups (p >0.05).

In order to improve ACC diagnosis, distinguish benign from malignant lesions, the semi-quantitative SUV indicators, as well as the CT density of neoplasms were retrospectively analyzed. We found a significant difference in SUV level between groups 1 and 2 (p = 0.001): SUV ≥3 was determined in 20 (95 %) patients of group 1, and only in 4 (13.8 %) patients of group 2. SUV <3 was determined in 1 (5.0 %) and 25 (86.2 %) patients of groups 1 and 2, respectively. In addition, a strong correlation between SUV and malignant tumors diagnosis was found (Rs = 0.71; Kendall's τ coefficient = 0.68). The diagnostic model obtained by constructing and subsequent analysis of the ROC curve of the SUV level in patients with malignant and benign adrenal neoplasms showed a high level of sensitivity (90 %) and specificity (95 %) of the method (area under the ROC curve (AUC) is 0.93 at p <0.0001 (z = 27.37)) with cut-off point equaled 3 (Fig. 4).

CT densitometric parameters of the tumor in groups 1 and 2 also correlated with malignant lesions diagnosis (Rs = 0.67; Kendall's τ coefficient 0.64; p = 0.001): density >10 HU was determined in 18 (85.7 %) and 6 (20.7 %)

patients of groups 1 and 2, <10 HU – in 3 (14.3 %) and 23 (79.3 %) of patients, respectively. Interpreting ROC analysis results by the level of neoplasm density (CT density in HU) in patients of groups 1 and 2 showed 80 % sensitivity and 90 % specificity (AUC 0.89; p <0.0001) with a cut-off point equaled 10 (Fig. 5).

Thus, integral estimation of SUV of ≥3 with a tumor CT density of > 10 HU, measured using ^{18}F-FDG PET/CT, is a highly sensitive and specific method for differential diagnosis of 1–5 cm benign and malignant adrenal lesions.

Discussion

A large number of studies have shown that ^{18}F-FDG PET/CT allows differentiating benign and malignant adrenal tumors. According to M. Blake et al. [8], ^{18}F-FDG PET/CT is highly sensitive and specific to diagnose adrenal tumors.

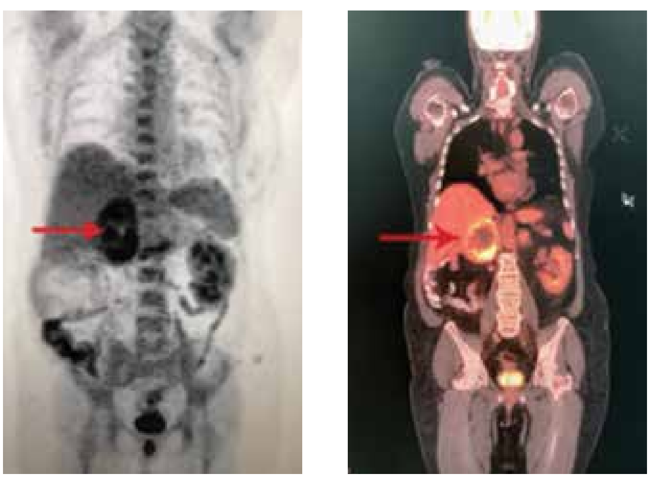

Fig. 1. *Positron-emission tomography: right adrenal metastatic tumor (indicated by an arrow)*

When diagnosing adrenal tumors using ^{18}F-FDG PET/CT, a semi-quantitative parameter such as a standard uptake value (SUV) of radiopharmaceutical capture is determined. The parameter is the measured RPC activity during its accumulation in tissues, normalized by body weight/surface area and administered drug dose. As a reference standard, in the case a dose is uniformly distributed in the body, the parameter everywhere is 1.0. Thus, SUV is a relative criterion for RPC capture by tissues. To calculate this parameter during PET/CT, the following formula is used: SUV = (RPC activity in the region of interest × body weight (g))/administered dose (mCi).

It should be noted, that for adrenal tumors the maximum SUV, divided by the maximum SUV of the 8 segment of the liver, is defined as the relative SUV. According to various authors, this parameter has 90.9 % sensitivity and 75.6 % specificity to differentiate between benign and malignant neoplasms [5, 9].

M.L. Nunes et al., based on the analysis of 23 clinical cases, showed that SUV of 1.6 has the greatest sensitivity and specificity in ACC diagnosis [10]. In an earlier study by L. Groussin et al., conducted in 77 patients, SUV parameter, which distinguishes benign and malignant adrenal lesions, was 1.45 [11]. Recent multicenter study of 73 cases of adrenal neoplasms, conducted by N.C. Paladino et al. in 2018, showed that SUV> 2.7 correlated with the presence of malignant neoplasms [12]. Thus, despite a large number of studies, today there is no universal SUV parameter to distinguish benign and malignant adrenal lesions.

It should also be noted that in all the studies, the patients were unranked with respect to neoplasms size, while at present most of detected adrenal incidentalomas are small. According to the literature, there is also a pronounced imbalance between the frequency of randomly detected tumors (incidentalomas) and advanced (locally-spread and metastatic) ACC cases. This is due to the fact

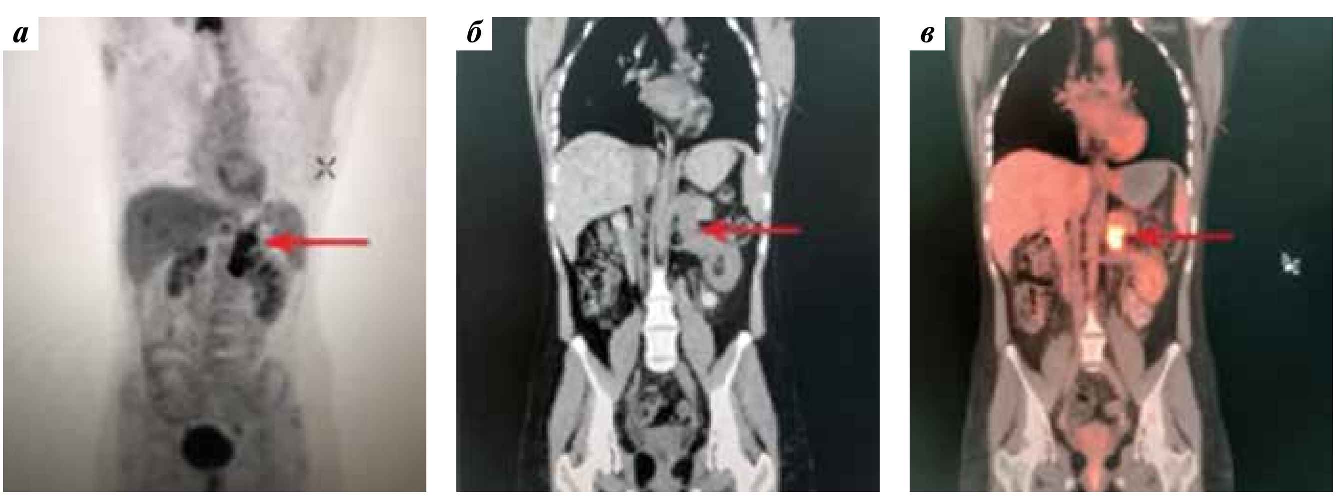

Fig. 2. *Left adrenal cancer, indicated by an arrow on positron emission tomography (а), computed tomography (б) and when both are "fused" (в)*

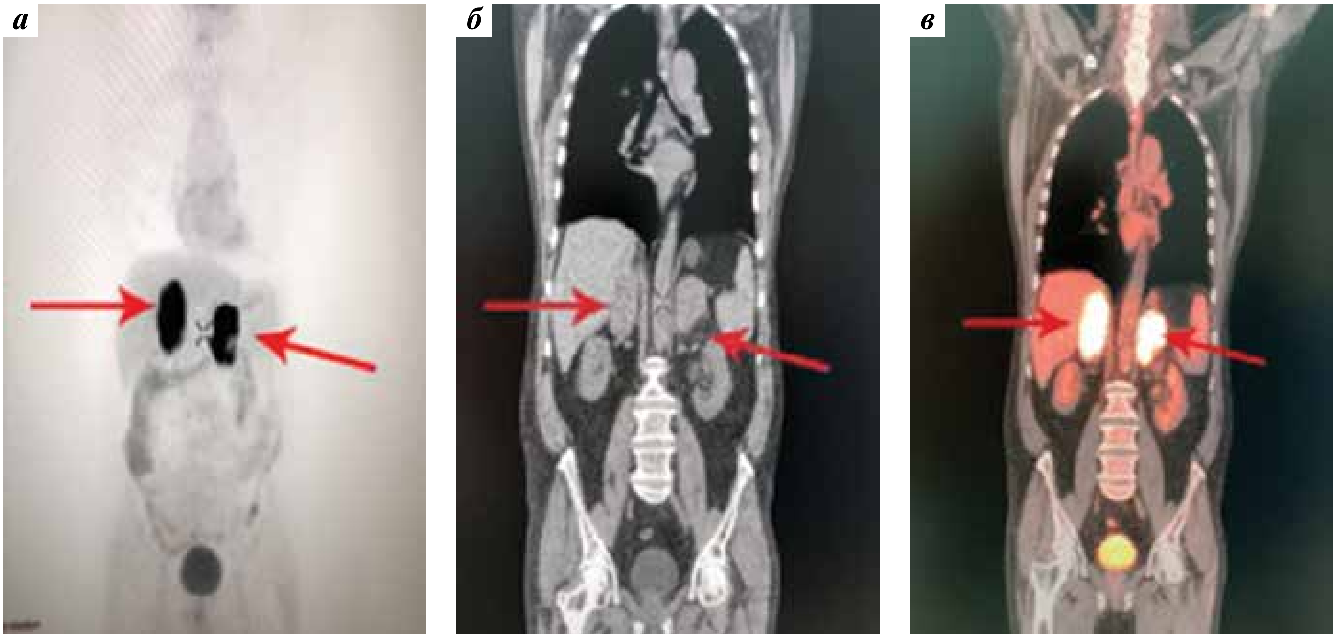

Fig. 3. *Bilateral adrenal cancer, indicated by an arrows on positron emission tomography (а), computed tomography (б) and when both are "fused" (в)*

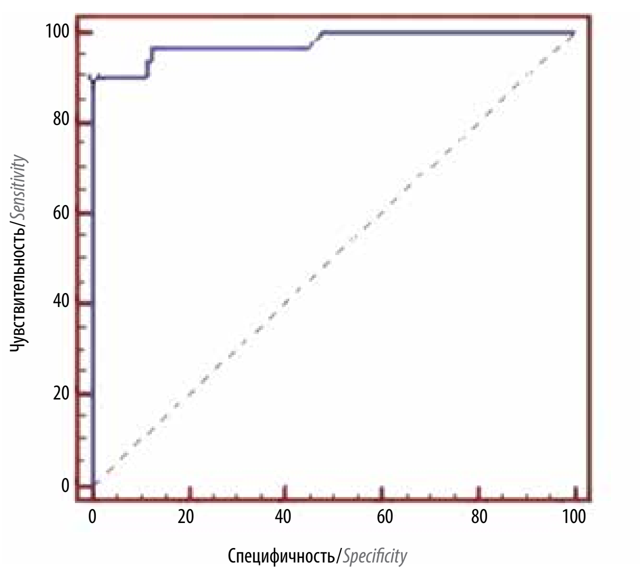

Fig. 4. *ROC curve of the standardized uptake value (SUV) in patients with malignant and benign adrenal neoplasms*

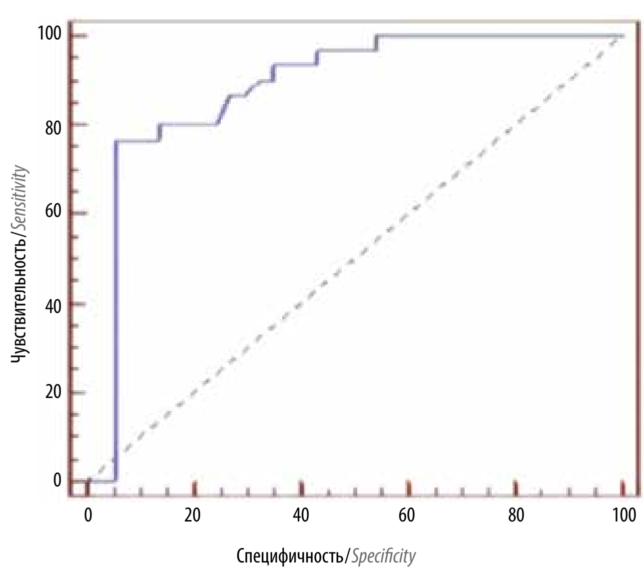

Fig. 5. *ROC curve of tumor density (in Hounsfield units (HU)) in patients with malignant and benign adrenal neoplasms*

that using CT it is not always possible to diagnose malignant adrenal tumors in the early stages.

In our study we analyzed the use of ^{18}F-FDG PET/CT combined with invesigating SUV and CT density of 1–5 cm adrenal incidentalomas. The aim of the work was to revise the reference values of these indicators for early diagnosis and to distinguish between malignant and benign adrenal lesions.

The data obtained indicate 90 % sensitivity and 95 % specificity of the ^{18}F-FDG PET/CT combined with measuring tumor CT density, in ACC differential diagnosis by SUV level of ≥3, and CT density of ≥10 HU.

Conclusion

^{18}F-FDG PET/CT is highly accurate in the differential diagnosis of benign and malignant adrenal tumors, evaluating the metabolic rate together with tumor anatomical characteristics and location based on non-contrast CT data.

Obtaining integral information on SUV level along with measuring CT density during ^{18}F-FDG PET/CT is one of the most modern diagnostic methods that allows a differential diagnosis of the pathological process in the adrenal glands and ACC detection in the early stages of the examination.

The above factors indicate a high diagnostic value and priority in using the method in cases of suspected ACC in patients with accidently revealed adrenal neoplasms (sized 1–5 cm) and ambiguous data from imaging studies.

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