National Medical and Surgical Center named after N. I. Pirogov



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# ACCIDENTALLY DIAGNOSED NEOPLASMS OF THE ADRENAL GLANDS. DIFFERENTIAL DIAGNOSIS AND INDICATIONS FOR SURGICAL TREATMENT

3.1.9. Surgery

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CONTENTS

# INTRODUCTION

## Relevance of the problem

Over the past four decades in surgical endocrinology, incidentally detected adrenal masses have attracted increasing attention. This interest of surgeons is primarily due to the fact that the widespread introduction into practice of modern imaging research methods (ultrasound, CT and MRI) carried out in the process of clinical examination or for various diseases not related to the pathology of the adrenal glands has led to the mass detection of such neoplasms. [Sherlock M., Scarsbrook A., Abbas A. et al., 2020; Shchetinin V. V. et al., 2002]. In 1982, the term "incidentaloma" appeared in the literature, emphasizing that the neoplasm was detected by chance (incidental - random) [Geelhoed G.W., Druy E.M., 1982]. With the improvement in the resolution of radiological methods, clinicians are faced with the hitherto unfamiliar problem of early diagnosis of asymptomatic adrenal neoplasms. Some researchers are currently writing about the "epidemic" of tumors of the adrenal glands [Maistrenko N. A. et al., 2001].

Accidentally identified formations of the adrenal glands differ in morphological structure. They can be both malignant and benign, secrete hormones and their precursors, or have no hormonal activity [Kebebew E., 2021]. In this situation, endocrinologists and surgeons are faced with the issue of rational examination and choice of management tactics for such patients (observation or surgical treatment). Meanwhile, the issue of indications for surgical treatment is still being resolved ambiguously. Operative treatment, first of all, patients with identified hormonally active neoplasms are subject. These include pheochromocytomas, aldosteromas, autonomously functioning tumors of the cortical layer that produce cortisol. Androsteromas and corticoestroms are less common. Indications for surgical treatment are easily determined in the presence of undoubted clinical and laboratory signs of a hormonally active tumor. But, unfortunately, this is not always the case. Adrenal formations that

were detected by chance, as a rule, do not have obvious clinical signs of increased hormone production [Morelli V., Palmieri S., 2019]. Targeted laboratory studies are required to confirm their hormonal activity. According to different authors, adrenal tumors with latent hormonal activity are diagnosed in 7-12% [Favia G., 2000; Vetshev P. S., 2005; Katabami T., 2005]. Meanwhile, endocrine disorders that are not diagnosed in a timely manner, caused by neoplasms of the adrenal glands, inevitably lead to irreversible changes in various organs and tissues. These include disorders of water-electrolyte and fat metabolism, serious disturbances in the activity of the cardiovascular system. Identification of the hormonal activity of a tumor is one of the direct indications for surgical treatment, regardless of its size [Kvachenyuk A. N., 2004].

Another problem is the diagnosis of malignant neoplasms of the adrenal glands before surgery. The share of adrenocortical cancer among incidentally detected adrenal tumors is 2.4-4.5% [Ioachimescu A. G., Remer E. M., Hamrahian A. H., 2015]. Various criteria have been proposed for the diagnosis of malignancy. Some authors focus on the size of the neoplasm when choosing indications for surgical intervention, and this criterion varies from 2 to 7 cm [Kameneva O. S., 2009]. A certain progress in the diagnosis of adrenocortical cancer was the improvement of radiation research methods and, above all, CT with bolus administration of a contrast agent. The study of the native density of formation, density in the arterial, venous and delayed phases improved the differential diagnosis of adrenal tumors before surgery. With the help of radiation research methods, it is possible to suggest the morphological structure of the tumor with an accuracy of 75 to 99% [McCarthy C.J., McDermott S., Blake M.A., 2016].

The technique of needle biopsy for the purpose of tumor verification before surgery has been developed in detail. However, due to insufficient information content and possible complications, it is rarely used [Aleksandrov Yu. K. et al., 2015] and only after biochemical exclusion of catecholamine-producing tumors [Bancos I., Tamhane S.,

Shah M. et al., 2016 ]. It is used, as a rule, to confirm the presence of metastases in the adrenal glands and diagnose their tuberculous lesions [Borisov A. E. et al., 2002] only if the expected result of the study is able to change the tactics of managing the patient.

Certain hopes in the differential diagnosis of benign and malignant neoplasms of the cortical layer are assigned to the study of the profile of steroids [Kerkhofs T.M. et al., 2015].

Uncertainty in the accuracy of the diagnosis has led to an increase in the number of surgical interventions. Thus, the number of adrenalectomies in the United States doubled from 1980 to 2000. A similar situation is noted in Russia, where the number of operations on the adrenal glands is growing every year. The number of unjustified interventions is also increasing everywhere [Dinnes J., Bancos I., Ferrante di Ruffano L. et al., 2016].

After removal of the adrenal neoplasm, the problem of the final diagnosis is far from always solved simply. Often there are difficulties in morphological diagnosis. Examination using light microscopy does not always allow a correct diagnosis. In such cases, it is necessary to use additional techniques, including histochemical, immunohistochemical, electron microscopic and even molecular genetic studies [Mishnev O.D., 2005].

All of the above formed the basis for this study.

**Purpose of the study**

To optimize the treatment and diagnostic tactics for incidentally detected neoplasms of the adrenal glands and to identify new diagnostic criteria that make it possible to reliably differentiate between benign and malignant tumors.

**Research objectives**

1 - To analyze the available methods for examining patients with accidentally detected neoplasms of the adrenal glands.

2 - To identify significant differences in the clinical manifestations of adrenal diseases with certain comorbidities.

3 - Determine the advantages and disadvantages of various radiation methods of research in the differential diagnosis of adrenal tumors.

4 - Determine the value of the steroid profile of urine, determined by GCMS, in comparison with other laboratory methods for the differential diagnosis of benign and malignant neoplasms of the adrenal glands.

5 - Formulate new criteria in the differential diagnosis of adrenal masses using the immunohistochemical method.

**Scientific novelty of the research**

For the first time, the clinical picture of arterial hypertension crisis in patients with somatoform dysfunction of the autonomic nervous system was compared with adrenal crisis in pheochromocytoma.

It has been shown that the phenomenon of “dark cellity” (basophilia of the cytoplasm of tumor cells) detected according to light microscopy does not occur in adrenocortical cancer.

Based on the data of modern immunohistochemical reactions Ki67, p53, p21, vimentin, AE1/AE3, melan A, beta-catenin, CyD1, CD34, inhibin according to a standardized research protocol, the malignancy potential of benign neoplasms was studied. For the first time, attention was drawn to the presence of the dot-like phenomenon in the cytoplasm of adrenocortical cancer cells during IHC studies with antibodies to B-catenin, which allows more certainty to make the correct diagnosis.

For the first time, a comprehensive assessment of the data of radiation diagnostic

methods, determination of the malignancy potential of incidentally detected formations using the determination of the steroid profile of urine using gas chromatography-mass spectrometry and the results of immunohistochemical studies in patients with incidentally detected neoplasms of the adrenal glands was carried out.

For the first time, a single-port retroperitoneoscopic adrenalectomy (patent RU 2614218 C1) has been proposed and used in the practice of the clinic to clarify the diagnosis and source of metastasis in the differential diagnosis of adrenocortical carcinoma and metastases of tumors of other organs in the adrenal gland with small neoplasms (up to 5 cm).

**Practical significance**

An algorithm for examining patients with incidentally detected adrenal neoplasms is proposed, including the use of computed tomography with intravenous administration of a contrast agent with imaging in the arterial, venous and delayed (after 10 minutes) phases and determination of the urine steroid profile using gas chromatography-mass spectrometry.

Differences in the clinical picture of arterial hypertension crisis with somatoform dysfunction of the autonomic nervous system in patients with hormonally inactive neoplasm of the adrenal gland from a crisis in hypertension and from an adrenal crisis in pheochromocytoma were revealed.

Criteria for dynamic monitoring of patients with hormonally inactive neoplasms are proposed — for patients with tumors of minus native density of small size, annual contrast-enhanced CT is not advisable during dynamic monitoring. In order to control the size of the tumor, an MRI without contrast is sufficient.

**Approbation of the dissertation**

The main stages and results of the research were presented at the 2426th meeting of the Pirogov Surgical Society (St. Petersburg, March 12, 2014), the VI International

Interdisciplinary Scientific Forum “Modern Technologies in Endocrine Surgery. Morphological diagnostics in endocrinology: clinical needs and modern reality" (St. Petersburg, May 24, 2014), international scientific and practical conference "Adrenal tumors: modern advances in diagnosis and treatment" (St. Petersburg, 6- June 7, 2014), 22 (24) Russian symposium with international participation "Endocrine Surgery 2003-2014" (St. Petersburg, September 11-13, 2014), 2439 meeting of the Pirogov Surgical Society (St. Petersburg, November 26, 2014), VIII "Nevsky Radiological Forum - 2015" (St. Petersburg, 10-12.04.2015), XXV Russian Symposium with the participation of endocrinologists "Kalinin Readings" (Samara, 1- October 3, 2015), 5th International Adrenal Cancer Symposium (University of Michigan Palmer Commons, U.S.A., Michigan, October 14-15, 2015), VII All-Russian Congress of Endocrinologists "Achievements in personalized medicine today - the result of practical healthcare tomorrow" (Moscow, March 2-5 2016), the 4th scientific and practical conference of young scientists and specialists "Translational medicine: from theory to practice" (St. St. Petersburg, April 19, 2016), V All-Russian Interregional Congress "Baltic Medical Forum" (St. Petersburg, June 14-15, 2016), All-Russian Interdisciplinary Congress "Molchanov Readings-2017" (St. Petersburg, April 14-15, 2017), All-Russian Interdisciplinary Congress "Molchanov Readings", (St. Petersburg, April 13-14, 2018), IV (XXVII) National Congress of Endocrinologists with international participation "Innovative technologies in endocrinology » ( Moscow, 22-25 September 2021), 7th ENEA VIRTUAL Workshop Cushing's Disease (Croatia, Dubrovnik, 10-11 December 2021).

**Implementation of research results**

The results of clinical studies are used in the training of students - surgeons and endocrinologists, clinical residents and senior students. The methods developed as a result of the study are used in diagnostic algorithms for the examination and treatment

of patients with neoplasms of the adrenal glands in the Department of Endocrine Surgery of the Clinic for High Medical Technologies. N.I. Pirogov St. Petersburg State University.

**Publications**

5 scientific papers have been published on the topic of the dissertation, which outline the main scientific results of the dissertation, including: in peer-reviewed scientific publications from the list approved by the Ministry of Education and Science of the Russian Federation - "3" publications; in publications indexed in scientometric databases Web of Science and Scopus - "1" publication. 1 patent for the invention has been obtained. There are 8 other publications on the topic of the dissertation.

**Author's personal contribution**

The author independently substantiated the purpose, objectives and schemes of the study, defined study groups, collected clinical material, and systematized the results obtained. The author has formed a database and performed statistical processing of the received materials. The author took part in surgical interventions, wrote scientific articles on the results of the study. The author formulated the main provisions, conclusions and recommendations.

**The scope and structure of the dissertation**

The dissertation work is presented on 199 pages of typewritten text and consists of an introduction, a literature review, a description of materials and methods, 3 chapters of research, a conclusion, conclusions, practical recommendations and a list of references. The bibliographic index contains 333 sources, of which domestic - 103, foreign - 230. The work contains 16 tables and is illustrated with 29 figures.

**Main scientific results**

1. Patients with adrenocortical cancer who do not have clinical signs of excessive

secretion of steroid hormones may have increased production of steroid precursors due to inhibition of steroidogenesis enzymes, but it is a very difficult task to identify such an increase in the content of these precursors in blood plasma. In addition, the secretion of these substances by tumors may not be constant or not pronounced. A more reliable method for determining the final and intermediate persistent products of steroid hormone metabolism is to determine their concentration in daily urine, that is, to study the steroid profile of urine [Velikanova L. I., Shafigullina Z. R., Lisitsin A. A.et al., 2016, p. 331] (personal contribution is at least 20%).

2. Determination of the steroid profile of urine as the only tool in the primary diagnosis of adrenocortical cancer has a low sensitivity compared with radiation diagnostic methods. [Shcherbakov I. E., Chernikov R. A., Rusakov V. F., Fedorov E. A. et al., 2020, p. 11] (personal contribution is at least 40%).
3. The interpretation of the steroid profile of urine is quite complex and is available only to specialists with extremely high qualifications, which makes it difficult to spread and widely apply this examination method in clinical practice. At the same time, the definition of USP in the future (after additional study) can be used as an auxiliary diagnostic method, in some cases determining therapeutic tactics in patients who have undergone adrenalectomy for ACC [Shcherbakov I. E., Chernikov R. A., Rusakov V. F., Fedorov E. A. et al., 2020, p. 11] (personal the contribution is at least 40%).
4. The clinical picture of the crisis of arterial hypertension in somatoform dysfunction of the autonomic nervous system in patients with randomly identified adrenal neoplasms differs from the sympathoadrenal crisis in pheochromocytoma and hypertensive crisis, which, however, does not exclude the need for further examination to establish a final diagnosis. [Sablin I. V., Krasnov L. M., Fedorov

E. A., Rusakov V. F., 2018, p. 52] (personal contribution is at least 80%).

5. The presence of predominant fat in the formation of the adrenal gland is pathognomonic for myelolipoma. This feature is a characteristic feature of myelolipoma, which distinguishes it from adrenocortical adenoma, therefore, MRI of the abdominal cavity, compared with ultrasound, is more effective in the differential diagnosis of these neoplasms. Due to the difference in the intensity of T1 and T2 signals, MRI demonstrates a myelolipoma-specific picture of a fatty tumor [Fedorov E. A., Sablin I. V., 2014, p. 82] (personal contribution is at least 80%).

6. A patent was obtained for the invention "method of performing posterior retroperitoneal adrenalectomy" [Fedotov Yu. N., Krasnov L. M., Fedorov E. A., Sablin I. V., Malyugov Yu. N. et al., 2017] (personal contribution is at least 20%).

**Basic provisions for defense**

1. The use of computed tomography with intravenous administration of a contrast agent with imaging in the arterial, venous and delayed (after 10 minutes) phases in conjunction with the determination of the steroid profile of urine using gas chromatography-mass spectrometry can be used as a highly informative method of differential diagnosis of benign and malignant hormonally inactive neoplasms of the adrenal glands.

2. According to computed tomography with intravenous contrast, according to the characteristic topographic location of the tumor (near the kidney vessels) and densitometric characteristics in different phases of the study, it is possible to suggest pheochromocytoma. Accidentally detected pheochromocytomas that do not have hormonal activity do not differ from functionally active ones in their densitometric characteristics.

3. The clinical picture of arterial hypertension crisis with somatoform dysfunction of the autonomic nervous system in patients with hormonally inactive neoplasm of the adrenal gland differs significantly from the adrenal crisis with pheochromocytoma.

4. Immunohistochemical study in the differential diagnosis of adrenocortical cancer and adenoma of the adrenal cortex is a mandatory addition to the traditional method of light microscopy.

# Chapter 1

## Incidentally detected neoplasms of the adrenal glands and methods for their differential diagnosis (literature review)

Over the past four decades, the interest of surgeons and endocrinologists in the problem of adrenal neoplasms has been gradually growing. According to many modern authors [Sherlock M., Scarsbrook A., Abbas A. et al., 2020; Park G. E., Cho Y. Y., Hong Y. S. et al. 2015; Papierska L. et al. 2013; Soldatova T.V., 2011; Yakhin M.M., 2003; Shchetinin V.V., Kolpinsky G.I., Zotov E.A., 2003; Makino S., Oda S., Saka T. et al. 2001; Montero F., Terrolo M., Arnaldi G. et al., 2000] this is due to both the prevalence of these diseases and the variety of clinical symptoms and syndromes that they manifest. Recently, more and more works have begun to appear in the literature on endocrinology and surgery that reveal this problem. Due to the prevalence of ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT) and other radiation diagnostic methods, there has been a sharp increase in the detection of so-called "incidental" (from the English "incidental" - random) of various organs. The term "adrenal incidentaloma" is collective, and includes a group of tumors, diverse in morphological features, accidentally detected using radiation methods of research, carried out for diseases of other organs or systems, or during preventive examinations [Kim J., Bae K.H., Choi Y.K. et al., 2013]. These formations can be both hormonally inactive and synthesize various hormones, their precursors and metabolites, can be malignant and benign, have a clear belonging to any area of the adrenal gland, or have no specific organ affiliation [Fassnacht M., Arlt W. , Bancos I. et al., 2016]. Adenoma, adrenocortical cancer, hemangioma, hematoma, hyperplasia, cyst, lymphoma, lymphangioma, metastasis, myelolipoma, neuroblastoma, pheochromocytoma, schwannoma - these are the various variants of most adrenal neoplasms that are most often encountered in clinical practice.

With an increase in the age of the examined patients, the frequency of detection of SVON increases [Dinnes J., Bancos I., Ferrante di Ruffano L. et al., 2016]. According to the presented results of various studies, adrenal incidentalomas occur in less than 1% of patients younger than 30 years old, but in patients over the age of 70 years, the frequency of detection of this pathology reaches 7% [Young W.F., 2007; Mansmann G. et al., 2004; Kloos R.T. et al., 1995].

The probability that an incidentaloma will be a hormonally inactive adenoma is about 80% [Park G. E., Cho Y. Y., Hong Y. S. et al., 2015; Oh J. Y., 2013]. Functionally active benign tumors of the adrenal glands (adenomas and pheochromocytomas) occur in no more than 10% [Zeiger M.A., Siegelman S.S., Hamrahian A.H., 2011]. The simultaneous appearance of a functionally active adenoma and pheochromocytoma in the same adrenal gland is quite rare [Cho Y. Y, Suh S., Joung J. Y. et al., 2013; Michalopoulos N., Pazaitou-Panayiotou K., Boudina M., 2013]. In the structure of incidentally discovered tumors, adrenocortical cancer and metastatic lesions account for 2-3%. The remaining 6-7% of the total number of adrenal incidentalomas are occupied by ganglioneuromas, myelolipomas, benign cysts, lipomas, fibromas, neurofibromas and others [Oh J. Y., 2013; Zeiger M.A., Siegelman S.S., Hamrahian A.H., 2011].

In patients with known malignant neoplasms of other organs during CT, the frequency of detection of adrenal incidentalomas increases to 9-13%, and the number of metastases is 26-36% of their number [Korivi B.R., Elsayes K.M., 2013; Sahdev A. et al., 2010; Bovio S. et al., 2006; Oliver T. W. et al., 1984]. According to other data, in patients with a history of cancer, incidentaloma turns out to be a malignant tumor in about 30%, and even (according to separate reports) in 50%, while in patients without cancer, incidentaloma is rarely malignant [Sundin A ., 2012].

One of the most important tasks of modern diagnostic studies is the timely identification of incidentaloma, which implies the differential diagnosis of hormonally

active and inactive tumors, benign neoplasms, adrenocortical cancer and metastases, as well as neoplasms from neighboring organs and tissues [Nieman L.K., 2010]. Therefore, all tumors without exception should be assessed both biochemically and radiographically [Panchani R., Goyal A., Varma T. et al., 2012].

The hormonal activity of randomly detected neoplasms can be manifested by hypersecretion of cortisol, aldosterone, androgens, adrenaline, norepinephrine, their precursors and metabolites. In all patients with identified incidentaloma of the adrenal gland, an assessment of hormonal activity should be carried out in order to diagnose Itsenko-Cushing's syndrome, hyperaldosteronism, pheochromocytoma and androsteroma [Aron D., Terzolo M., Cawood T.J., 2012]. In this case, as a rule, we are talking about subclinical hypercortisolism, clinically indistinctly manifested primary hyperaldosteronism, non-functioning pheochromocytoma. Less often, androsteromas are detected without any obvious signs of hyperandrogenism.

Approximately 5–20% of all identified incidentals have an autonomous, independent of the production of adrenocorticotropic hormone (ACTH) by the pituitary gland, cortisol-producing adrenocortical tumor [Beltsevich D. G., Kuznetsov N. S., Soldatova T. V. et al., 2009]. Among accidentally detected neoplasms of the cortical layer, the proportion of incidentalomas with autonomous production of cortisol can reach 25% [Krasnov L. M., 2005]. Such autonomous production of cortisol is observed without any classical clinical symptoms of endogenous hypercortisolism (Itsenko-Cushing's syndrome [Cushing H., 1912, 1932]). This condition is referred to in the literature as subclinical Cushing's syndrome or pre-Cushing's syndrome [Tauchmanova L., Rossi R., Biondi B. et al., 2002]. At the time of accidental detection of a tumor, some patients may have obesity, high blood pressure, diabetes mellitus, which do not suggest developing Itsenko-Cushing's syndrome [Erbil Y., Ademoglu E., Ozbey N. et al., 2006]. At the same time, a detailed picture of endogenous hypercortisolism in 1.5% of cases develops within a year, and in 25% of patients within 5 years [Barzon L., Fallo F.,

Sonino N. et al., 2002; Liebe R. Dall'Asta C., Barbetta L. et al., 2002].

In its diagnosis, the determination of the content of ACTH and cortisol in the blood plasma, the excretion of cortisol with daily urine are used. Low ACTH levels, elevated plasma cortisol levels, and 24-hour urine cortisol excretion of more than 100 mcg/day confirm the diagnosis. However, these indicators in subclinical Cushing's syndrome may be normal. Particular attention is drawn to the study of the daily rhythm of ACTH and cortisol secretion. Violation of the rhythm of secretion of these hormones testifies in favor of developing endogenous hypercortisolism. In healthy people, their content in blood plasma is highest in the morning (at 6–8 o'clock), in the evening (at 21–22 o'clock) secretion is significantly reduced [Zverev Ya.F., Bryukhanov V.M., 2006]. The method for determining the content of saliva cortisol turned out to be the most sensitive [Fleseriu M., 2020; Belaya Zh.E., Ilyin A.V., Melnichenko G.A. et al., 2011]. Nighttime salivary cortisol >100 ng/dl is a sign of illness. A 1 mg dexamethasone test is also used to confirm the diagnosis. Dexamethasone is a synthetic glucocorticoid that inhibits the production of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). Taking 1 mg of dexamethasone in the evening in healthy people leads to a pronounced decrease in cortisol production in the morning. Patients with an autonomously functioning adrenal tumor are characterized by a decrease in serum cortisol levels >5.0 μg/dL (100-140 nmol/L) (or, according to other authors proposing more stringent criteria, >1.8 μg/dL (50 nmol/L /l) after a suppressive test with 1 mg of dexamethasone [Fleseriu M., 2020; Aron D., Terzolo M., Cawood T.J., 2012].

With a developed clinical picture of hypercortisolemia, an autonomously functioning benign or malignant tumor of the cortical layer accounts for about 18% of all causes of Itsenko-Cushing's syndrome. In the literature, this condition is called Itsenko-Cushing's syndrome of adrenal genesis [Maistrenko N.A., 2010; Dedov I.I.,

Kuznetsov N.S., Melnichenko G.A., 2011].

The most common cause of endogenous hypercortisolism (60-70%) is ACTH-producing pituitary adenoma [Soyustova E.L., Povarova O.Yu., Kazantseva E.E., 2012; Maystrenko N. A., 2010]. This condition is called Itsenko-Cushing's disease. It is characterized by increased production of ACTH and cortisol [Litvitsky P.F., 2011]. Morphological changes in the adrenal glands are characterized by bilateral diffuse hyperplasia of the cortical layer followed by the development of secondary adenomas. In such rare cases, endogenous hypercortisolism may present with a mild form of the disease, and an incidental adrenal adenoma is the first finding requiring further investigation.

The third cause of hypercrortisolemia is an ectopic ACTH syndrome caused by neuroendocrine tumors that produce ACTH [Isidori A.M., Lenzi A., 2007; Baylin S.B., Mendelsohn G., 1980], less often CRH. A causal relationship between the presence of such a tumor and Itsenko-Cushing's syndrome was first established in 1927 in a patient with small cell lung carcinoma [Brown W. H., 1928]. Ectopic hypersecretion of ACTH is present in 12-17% of cases of Cushing's syndrome [Rodrigues P., Castedo J.L., Damasceno M. et al., 2012]. This is a rather rare disease, occurring in about 1 case per million people per year [Tsvetkova E.V. et al., 2013]. The most common sources of ectopic ACTH-dependent syndrome are small cell lung cancer (27%), bronchial carcinoid (21%), pancreatic tumors (16%) and thymus carcinoid (10%) [Beuschlein F., Hammer G.D., 2002]. Other tumors of ectopic ACTH production can also be sources: for example, pheochromocytoma (about 5% of cases), appendix [Kuznetsov N.S., Marova E.I., Remizov O.V. et al., 2014]. Based on the peculiarities of origin in the process of embryogenesis, the localization of neuroendocrine tumors is very variable. As a result, difficulties arise in their diagnosis and classification. According to studies, as a rule, 2/3 of the tumors encountered are localized in the chest, neck, adrenal glands,

and only 1/3 of them are localized in the abdominal organs [Ilias I., Torpy D.J., Pacak N. et al., 2005]. Morphological changes in the adrenal glands develop very quickly, but they are extremely rarely the first, accidental finding. Hypercorticism in ACTH-ectopic syndrome develops against the background of very high production of ACTH and cortisol and manifests most often brightly and quickly, leading to metabolic changes such as hypokalemia and metabolic alkalosis, which, in turn, also contribute to the clinical picture of the disease [Tsvetkova E.V. et al., 2013]. According to some authors [Isidori A.M., Lenzi A., 2007], the duration of the period from the moment of manifestation of hypercortisolism to the detection of tumor localization depends on the type of neoplasm. So, for patients with small-cell carcinoma of the bronchi and a tumor of the insular part of the pancreas, this period of time is from 3 to 8 months, while in the case of a patient with bronchial carcinoid, diagnosis can take years [Kuznetsov N. S., Marova E. And ., Latkina N. V. et al., 2014].

A very important task in case of an accidentally detected neoplasm of the adrenal gland is the exclusion of a chromaffin tumor (pheochromocytoma). Pheochromocytoma (syn. adrenal paraganglioma, PHC / PG) is a neuroendocrine tumor of the adrenal medulla, consisting of chromaffin cells, producing catecholamines (adrenaline, norepinephrine and dopamine), is a special case of sympathetic paraganglioma (PG). PG is a tumor consisting of extra-adrenal chromaffin tissue of the sympathetic paravertebral ganglia of the chest, abdomen, and pelvis. PGs from the parasympathetic ganglia of the base of the skull and neck, which develop along the glossopharyngeal and vagus nerves, are hormonally inactive in the vast majority of cases [Rebrova D.V., Vorokhobina N.V., Imyanitov E.N. et al., 2022]. In addition to the secretion of catecholamines, in connection with the neuroendocrine origin of the tumor, extremely rare cases of ectopic hypersecretion by pheochromocytomas and other peptide hormones, such as adrenocorticotropic hormone, somatostatin, neuropeptide Y, metenkephalin, as well as vasoactive interstitial peptide, calcitonin, have also been

described [Rebrova D. V., Rusakov V. F., Fedorov E. A. et al., 2021].

According to different authors, pheochromocytoma is detected in more than 4% of all incidentalomas [Park G. E., Cho Y. Y., Hong Y. S. et al., 2015; Yukina M. Yu., Troshina E. A., 2014; Berruti A., Baudin E., Gelderblom H. et al., 2012; Beltsevich D. G., Kuznetsov N. S., Soldatova T. V. et al., 2009]. With the development of modern diagnostic methods, the frequency of detection of pheochromocytomas that do not have functional activity increases every year. Currently, it is believed that clinically silent pheochromocytoma occurs in 80% of all detected chromaffin tumors.

The population frequency of the disease has long been considered low. Although the literature drew attention to the fact that in 30-70% of cases the diagnosis of pheochromocytoma is established posthumously [Farrugia F.A., Charalampopoulos A., 2019; Sutton M.G., Sheps S.G., Lie J.T., 1981], these results of pathologist studies did not resonate with clinicians. According to some data, the detection rate was 1 case per 200 thousand of the population [Kushakovsky M.S., 1983], according to other data, the incidence ranged from 1 [Kalinin A.P., Kazantseva I.A., Polyakova G.A., 1998 ] up to 2-8 people per million population per year [Pacak K., Eisenhofer G., Ahlman H. et al., 2007]. However, these figures are now questionable. Modern research has confirmed that the prevalence of pheochromocytoma is much higher than previously reported. Firstly, it was found that among patients with arterial hypertension (AH) in 0.5-1% of cases, the cause of high blood pressure (BP) is neoplasms emanating from the chromaffin tissue [Eisenhofer G., Goldstein D.S., Walther M.M. et al., 2003; Dedov I.I., Beltsevich D.G., Kuznetsov N.S., Melnichenko G.A., 2005; Farrugia F.A., Charalampopoulos A., 2019]. Given that hypertension is detected in approximately 25% of the population, then pheochromocytoma should occur much more often than previously indicated. Secondly, targeted multicenter pathoanatomical studies have shown that pheochromocytomas were detected in 20-150 cases (average 50) per 100

thousand autopsies [Platts J.K., Drew P.J., Harvey J.N., 1995; McNeil A.R., Blok B.H., Koelmeyer T.D. et al., 2000]. The data obtained have changed the idea of the rare occurrence of these neoplasms.

Pheochromocytomas in 10% of cases can give distant metastases [Jandou I., Moataz A., Dakir M. et al., 2021].

Pheochromocytoma can be both sporadic and can be detected as part of various hereditary syndromes [Beltsevich D.G., Troshina E.A., Yukina M.Yu., 2010]. According to some authors, it is associated with various hereditary diseases in 10% of cases, according to others - in more than 30% of cases [Itani M, Mhlanga J., 2019; Amar L., Servais A., Gimenez-Roqueplo A. P. et al., 2005]. These diseases include the syndrome of multiple endocrine neoplasia type 2 (MEN 2A and MEN 2B), von Hippel-Lindau disease (VHL), type 1 neurofibromatosis, and hereditary syndromes characterized by the occurrence of paragangliomas, for example, Carney's triad [Kazubskaya T. P., Duditskaya T.K., Trofimov E.I. et al., 1996; Rebrova D.V., Vorokhobina N.V., Imyanitov E.N. et al., 2022]. With hereditary forms, bilateral tumors are detected in more than 70% of patients [Kuznetsov N.S., Beltsevich D.G., Lysenko M.A., 2002].

Multiple endocrine neoplasia type 2A (MEN-2A, Sipple's syndrome) is a familial syndrome inherited in an autosomal dominant manner, including medullary thyroid cancer, pheochromocytoma, and hyperplasia or adenoma of the parathyroid glands [Beloshitsky M.E., Polyakova G.A., 2011]. Pheochromocytoma occurs in 50-70% of MEN-2A, and is usually bilateral (in 50-80%) and multifocal; develops, as a rule, at the age of 20-40 years and, unlike sporadic pheochromocytoma, it is never extra-adrenal and malignant [Carney J.A., 2005; Rodriguez J.M., Balsalobre M., Ponce J.L., 2008]. With this hereditary syndrome, pheochromocytoma may not manifest itself clinically for a long time and be detected as an accidental finding. Their initial diagnosis

on the basis of characteristic symptoms is noted only in 10-15% of patients [Pinsky S.B., Beloborodov V.A., 1999]. The first step in the treatment of MEN-2A is the removal of the pheochromocytoma, and the second step is surgery for medullary thyroid cancer.

Multiple endocrine neoplasia type 2B is characterized by a combination of medullary thyroid cancer, pheochromocytoma, multiple mucosal neuromatosis, "marfanoid" body structure, and impaired bowel function. The parathyroid glands are rarely affected [Pinsky S.B., Beloborodov V.A., 1999]. Pheochromocytoma in this hereditary syndrome is characterized by bilateral lesions and clinically manifested hormonal activity [Lisnyansky I. E., Garkavtseva R. F., Zaletaev D. V., Kuzminov A. M., 1987].

Asymptomatic pheochromocytomas are most common in von Hippel–Lindau disease (VHL syndrome). The disease is characterized by an autosomal dominant type of inheritance and the development of various tumors and cysts in the central nervous system and other internal organs. The incidence of the disease is 1:36,000 newborns [Shadrichev F.E., Rakhmanov V.V., Shklyarov E.B., Grigorieva N.N., 2008]. Along with pheochromocytoma (up to 26%), this syndrome reveals CNS hemangioblastomas (44-72%), retinal angiomas (45-60%) and clear cell kidney cancer (40-70%) [Walther M.M., Reiter R., Keiser H.R. et al., 1999]. Cysts and neuroendocrine tumors of the pancreas, polycystic kidney disease, tumors of the inner ear, and others are also found. Such a variety of pathologies is explained by various variants of mutations on the short arm of the 3rd chromosome (3p25–26). There are different groups of combinations of tumors in VHL syndrome, while in some cases pheochromocytoma may be its only manifestation [Neumann H. P., Wiestler O. D., 1991; Brauch H., Kishida T., Glavac D. et al., 1995; Hoffman M. A., Ohh M., Yang H. et al., 2001].

VHL-associated pheochromocytomas have an exclusively norepinephrine phenotype, in most cases with adrenal localization they are bilateral (synchronous or metachronous) [Walther M.M., Reiter R., Keiser H.R. et al., 1999; Eisenhofer G., Walther M.M., Huynh T.T. et al., 2001]. Extraadrenal pheochromocytomas occur in approximately 30% of cases [Yukina M.Yu., Tyulpakov A.N., Troshina E.A., Beltsevich D.G., 2012; Neumann H.P., Berger D.P., Sigmund G. et al., 1993].

In 80% of cases BP in patients is normal and there are no clinical manifestations of this neoplasm [Gardner D., Shobek D., 2011; Neumann H.P.H., Bausch B., McWhinney S.R. et al., 2002; Brauch H., Hoeppner W., Jahnig H. et al., 1997; Van der Harst E., de Krijger R.R., Dinjens W.N. et al., 1998]. This is due to the rapid metabolism of norepinephrine in the tumor. Normetanephrine, a hormonally inactive metabolite of norepinephrine, enters the bloodstream. In other patients, blood pressure is constantly elevated. The crisis course of AH is not typical. This is due to the constant release of noradrenaline into the bloodstream, while in MEN 2 syndrome, episodic secretion of catecholamines is noted. MEN 2-associated pheochromocytomas contain higher concentrations of catecholamines due to more pronounced expression of tyrosine hydroxylase, therefore, the absence of clinical manifestations of neoplasms is much less common [Huynh T.T., Pacak K., Brouwers F.M. et al., 2005]. This also determines the differences in the clinical manifestations of the two syndromes. For example, patients with MEN 2 often complain of crisis rises in blood pressure [Ito Y., Fujimoto Y., Obara T., 1992]. It should also be noted that CNS hemangioblastomas associated with von Hippel-Lindau disease produce large amounts of erythropoietin [Vogel T.W., Brouwers F.M., Lubensky I.A. et al., 2005], which, in turn, stimulates erythropoiesis. Polycythemia or erythrocytosis can be detected by laboratory tests.

Pheochromocytomas with metastases in the lungs, liver, bones, lymph nodes are rare in VHL syndrome [Neumann H.P., Berger D.P., Sigmund G. et al., 1993; Koch

C.A., Vortmeyer A.O., Diallo R. et al., 2002]. Metastases are detected in less than 7% of cases [Walther M.M., Reiter R., Keiser H.R. et al., 1999].

The detection of pheochromocytoma in patients with VHL syndrome is especially important, given the high likelihood of surgical interventions for other tumors (CNS hemangioblastomas, etc.). An undetected clinically silent pheochromocytoma may manifest itself for the first time during surgery, and lead to life-threatening hemodynamic disturbances. The treatment of pheochromocytoma is surgical, but at the same time, there are data in the literature that six-month therapy with tyrosine kinase inhibitors leads to a decrease in the tumor by about 20% and a decrease in the level of normetanephrins and chromogranin A in plasma [Jimenez C., Cabanillas M.E., Santarpia L., Jonasch E., Kyle K.L. et al., 2009].

Pheochromocytoma in patients with neurofibromatosis type 1 can be determined in 0.1-5.7% of cases [Gardner D., Shobek D., 2011]. Neurofibromatosis type 1 (Recklinghausen's disease) is a hereditary autosomal dominant human disease caused by a mutation of the neurofibromin protein gene, which is a tumor growth suppressor, on chromosome 17q11.2. Neurofibromatosis occurs in a population with a frequency of 1:2000 to 1:4000 of the population [Schneider N.A., Gorelov A.I., 2007] and was first described by the German physician Friedrich Daniel von Recklinghausen in 1882. Depending on the prevalence and localization of neoplasms, the disease is divided into a peripheral form - neurofibromatosis type 1 (NF1), which is characterized by the presence of such additional clinical manifestations as pheochromocytoma, cognitive impairment of varying degrees, skeletal changes, etc. [De Bella K., Szudek J., Friedman J.M., 2000], and the central form - neurofibromatosis type 2 (NF2) [Ferner R.E., Hughes R.A., Hall S.M. et al., 2004].

Small groups of chromaffin cells can be located in the abdominal and chest cavities, head and neck. In 90% of cases, pheochromocytomas occur in the adrenal

medulla, in 8% - in the para-aortic lumbar paraganglia. Much less often, tumors are localized outside the retroperitoneal space: in less than 2% of cases - in the abdominal and chest cavity and in less than 0.1% of cases - in the neck. One of the most common extra-adrenal localizations of chromaffin (50-80%) is a neoplasm of the Zuckerkandl organ. It is an accumulation of chromaffin tissue located on both sides of the aorta in the area of origin of the inferior mesenteric artery [Dedov I.I., Beltsevich D.G., Kuznetsov N.S., Melnichenko G.A., 2005].

In adult patients, in approximately 90% of cases, pheochromocytoma manifests itself as a unilateral solitary tumor, in 10% as bilateral neoplasms of the adrenal glands [Anagnostis P., Karagiannis A., Tziomalos K. et al., 2009].

Pheochromocytoma can occur at any age, but is most common between 20 and 40 years of age. The incidence of pheochromocytoma in adult men and women is the same, while among sick children 60% are boys [Platts J.K., Drew P.J., Harvey J.N., 1995].

Tumors can reach large sizes (more than 3 kg), most of them have a mass of less than 100 g, and a diameter of less than 10 cm [Kuznetsov N.S., Beltsevich D.G., Lysenko M.A., 2002].

In 10-17% of pheochromocytomas are malignant, and as a rule, they are localized outside the adrenal glands. [Berruti A., Baudin E., Gelderblom H. et al., 2012]. Although the likelihood of malignancy varies among different genetic backgrounds, it is less than 10% for most sporadic pheochromocytomas, except in patients who have mutations in the succinate dehydrogenase B (SDHB) gene and/or tumor development occurs outside the adrenal gland. In this case, more than 30-50% may develop a malignant tumor [Berruti A., Baudin E., Gelderblom H. et al., 2012].

Conducting laboratory studies aimed at diagnosing pheochromocytoma is mandatory when incidentaloma is detected, due to the severity of the disease, high

mortality and unpredictable course that can characterize pheochromocytoma [Anagnostis P., Karagiannis A., Tziomalos K. et al., 2009]. Therefore, in patients with incidentally detected adrenal masses, fractionated metanephrine and normetanephrine should be determined in plasma or daily urine [Zeiger M.A., Thompson G.B., Duh Q.Y. et al., 2009]. With a threefold increase in the content of normetanephrine in the urine and (or) a twofold increase in metanephrine, the specificity reaches 98%. An increase in the "gray zone" is more often due to normetanephrine of neurogenic origin. In all doubtful cases, repeat studies are required. If a chromaffin tumor is still suspected, whole body scintigraphy with MIBG-$^{123}$I or whole body PET/CT scan with 68Ga-DOTA-TATE or 68Ga-DOTA-NOC can be used.

Scintigraphy can produce planar 2D images of the whole body and then perform specialized single photon emission computed tomography (SPECT) which can be combined or merged with CT images (SPECT/CT) of a specific region to improve visualization of a tumor that may be obscured by normal background activity, such as in the liver, bowel or kidneys. SPECT/CT provides direct, simultaneous correlation of functional and anatomical images. Whole body scintigraphy has the advantage of demonstrating additional areas of radiopharmaceutical uptake, which is particularly useful in some syndromes including pheochromocytomas and paragangliomas, and can be used for screening followed by specialized anatomical imaging. Functional imaging studies are performed using metaiodobenzylguanidine I-131 and I-123 (MIBG), pentetreotide In-111 (Octreoscan, Covidien), and several PET ligands including fluorodopamine F-18, 18F-dihydroxyphenylalanine (DOPA), fluoro-2-deoxy-D-glucose (FDG), and Ga-68 octreotate [DOTA-0-Tyr-3] (DOTATATE). Ga-68 DOTATATE is a PET radiopharmaceutical linked to a peptide that binds to somatostatin receptors [Itani M, Mhlanga J., 2019]. The sensitivity of I-123 MIBG has been reported to range from 77 to 95% with a specificity of 95–100% [Derlin T., Busch J.D., Wisotzki C. et al., 2013, Carrasquillo J.A., Chen C.C., Jha A. et al., 2021].

Before the patient undergoes radiation or invasive imaging methods, it is possible to analyze the content of chromogranin A and erythropoietin in the blood serum [Algeciras-Schimnich A., Preissner C.M., Young W.F. Jr. et al., 2008]. Determination of chromogranin A is currently often used to diagnose pheochromocytoma, although its content in blood plasma can be elevated in other endocrine tumors. The normal content in blood plasma is <100 ng/ml. Exceeding this value is usually associated with the presence of a tumor. Analysis of chromogranin A content in blood plasma shows high sensitivity and specificity in the absence of renal failure in the patient. The specificity of this method when combined with the analysis of fractionated metanephrines is about 97%, sensitivity - 98.4% [Mansmann G., Lau J., Balk E. et al., 2004; Karagiannis A., Mikhailidis D.P., Athyros V.G., Harsoulis F., 2007; D'Herbomez M., Forzy G., Bauters C., et al., 2007].

Primary hyperaldosteronism (PHA) is an uncommon pathology in patients with incidentally detected adrenal tumors. According to various authors, hypersecretion of aldosterone is observed in 1.6 - 3.8% of all incidentalomas [Aron D., Terzolo M., Cawood T.J., 2012; Beltsevich D.G., Kuznetsov N.S., Soldatova T.V. et al., 2009]. In this case, no clinical symptoms characteristic of hyperaldosteronism are determined, except for arterial hypertension. According to international recommendations for the diagnosis and treatment of PHA, the detection of an adrenal incidentaloma in a patient with high blood pressure is an indication for studies aimed at excluding this pathology [Beltsevich D.G., 2008]. The difficulties in diagnosis lie in the fact that PHA is a disease of heterogeneous causes. One of the causes is an autonomously functioning aldosterone-producing adenoma (APA) of the zona glomerulosa of the adrenal cortex (aldosteroma). It occurs in approximately 1% of all adrenal neoplasms [Cho Y. Y, Suh S., Joung J. Y. et al., 2013; Michalopoulos N., Pazaitou-Panayiotou K., Boudina M., 2013]. This disease was first described by the American pathologist Jerome Conn in 1955 [Conn J.W., 1955]. This form of hyperaldosteronism is named after him - Conn

syndrome. APA can also be one of the components of MEN-1 syndrome (Wermer syndrome) [Melnichenko G.A., Platonova N.M., Beltsevich D.G. et al., 2017]. The second cause is hyperplasia of the zona glomerulosa of both adrenal glands or the so-called idiopathic primary hyperaldosteronism (IPHA). Other forms: primary unilateral adrenal hyperplasia, familial hyperaldosteronism of type I (glucocorticoid-suppressed hyperaldosteronism), type II (glucocorticoid-unsuppressed hyperaldosteronism) and type III, aldosterone-producing carcinoma are rare. The first two dominant forms of the disease are of the most important clinical significance, as they occur most often (up to 95%). The frequency of APA, according to various data, ranges from 40 to 80%, IPGA - from 20 to 60% [Galakhova R.K., Velikanova L.I., Vorokhobina N.V. et al., 2010]. In rare cases, aldosteronoma can be located in the thyroid gland, ovaries and intestines - aldosteronectopic syndrome.

Currently, according to the majority of researchers, PHA is detected in a significant proportion of patients with elevated blood pressure even in the absence of any changes in the adrenal glands according to CT and MRI data. However, previously, the prevalence of PHA in patients with essential hypertension was estimated by most experts to be less than 1% of cases [Andersen G.S., Toftdahl D.B., Lund J.O. et al., 1988; Berglund G., Andersson O., Wilhelmsen L., 1976; Fishman L.M., Kuchel O., Liddle G.W. et al., 1968; Kaplan N.M., 1967; Strecten D.H., Tomycz N., Anderson G.H., 1979; Tucker R.M., Labarthe D.R., 1977; Sinclair A.M., Isles C.G., Brown I. et al., 1987]. The accumulated data led to a revision of the indicators: prospective studies demonstrated a frequency of PHA of 5-10% among patients with hypertension [William Ya., Ladygina D.O., Balutina O.V., Beltsevich D.G., 2020; Melnichenko G.A., Platonova N.M., Beltsevich D.G. et al., 2017; Rossi G.P., Bernini G., Caliumi C. et al., 2006; Schwartz G.L., Turner S.T., 2005; Lim P.O., Mosso L., Carvajal C., Gonzalez A. et al., 2003; Fardella C.E., Mosso L., Gomez-Sanchez C. et al., 2000; Dow E., Brennan G. et al., 2000; Loh K.S., Koay E.S., Khaw M.C. et al., 2000; Gordon R.D., Stowasser

M., Tunny T.J. et al., 1994; ; Hamlet S.M., Tunny T.J., Woodland E. et al., 1985; Grim C.E., Weinberger M.H., Higgins J.T. et al., 1977]. It is believed that there is a need to examine patients for the presence of PHA in all cases of arterial hypertension of stages 1 and 2 according to the classification of the Joint National Commission (stage 1 - BP> 160–179/100–109 mm Hg, 2nd > 180/110 mm Hg). This also includes patients with arterial hypertension resistant to drug therapy, as well as with elevated blood pressure and arbitrary (or diuretic-induced) hypokalemia. Such examination is mandatory in patients with hypertension who have a burdened family history of early development of arterial hypertension or acute cerebrovascular disorders before the age of 40, as well as first-degree relatives of patients with PHA who have hypertension [Beltsevich D.G., 2008].

Increased production of aldosterone leads to increased sodium reabsorption and stimulates potassium excretion in the urine. The hormone molecule easily penetrates the cell membrane and binds to the transport protein. Such an aldosterone-receptor complex diffuses into the nucleus, where it can, under the influence of further changes, activate one or more DNA fragments, leading to the formation of one or more types of mRNA. The latter diffuse into the cytoplasm, where proteins related to the processes of sodium or potassium transport are synthesized on ribosomes. First of all, the content of the enzyme sodium-potassium adenosine triphosphatase (Na+/K+-ATPase or Na+/K+-pump), which is the main part of the pump for the ion exchange of potassium and sodium on the basolateral membranes of tubular cells of the kidney, increases. The synthesized additional proteins are inserted into the laminal membrane of the same tubular cells, which allows sodium to quickly diffuse from the lumen of the tubule into the cell. Then sodium is pumped by the Na+/K+ pump localized in the basolateral membrane of the cell and returns to the bloodstream. With each sodium molecule, 2-3 water molecules are retained. The volume of circulating fluid increases, blood pressure rises. At the same time, with the increase in the activity of the Na+/K+ pumps,

potassium is transported in the opposite direction (into the lumen of the tubules). Hypokalemia gradually develops. Previously, hypokalemia was considered to be an indispensable criterion of PHA [Andersen G.S., Toftdahl D.B., Lund J.O. et al., 1988; Berglund G., Andersson O., Wilhelmsen L., 1976; Fishman L.M., Kuchel O., Liddle G.W. et al., 1968; Kaplan N.M., 1967; Strecten D.H., Tomycz N., Anderson G.H., 1979; Tucker R.M., Labarthe D.R., 1977; Sinclair A.M., Isles C.G., Brown I. et al.,1987]. Subsequently, it turned out that this sign has low sensitivity and specificity, the value of this symptom in relation to the prognosis of the disease is also not high. It is detected in the most severe observations and occurs in approximately 9-37% of patients with PHA [Mulatero P., Stowasser M., Loh K.S. et al., 2004]. Serum potassium concentration less than 3.5 mmol / l is detected in half of patients with APA and in 17% of patients with idiopathic hyperaldosteronism [Rossi G.P., Bernini G., Caliumi C. et al., 2006; Rossi G.P., Bernini G., Desideri G. et al., 2006]. Such a low incidence of hypokalemia in PHA is explained by the fact that the Na+/K+ pump based on ATPase is not the only regulator of sodium and potassium balance. Even after complete blockade of Na+, K+-ATPase, approximately half of the filtered sodium is reabsorbed in the kidneys. Experiments with various inhibitors have shown that, although 80% of the energy for proximal sodium reabsorption is contained in the form of ATP, only half of the sodium transport depends on Na+, K+-ATPase [Vander A., 2000; Gracheva V.V., 2012].

A significant increase in serum creatinine concentration has been described in patients with PHA; however, this does not lead to an increase in urinary protein excretion. It is assumed that the increase in microalbuminuria is associated with aldosterone-dependent mechanisms [Rebrova D. V., Rusakov V. F., Krasnov L. M. et al., 2016].

For a long time, it was believed that determination of potassium, aldosterone, and renin in blood plasma was sufficient for diagnosing PHA. Subsequently, a large number of clinical observations showed that aldosterone and potassium levels have low sensitivity, and the renin indicator has low specificity [Hiramatsu K., Yamada T., Yukimura Y. et al., 1981; McKenna T. J., Scqueira S. J., Heffernan A. et al., 1991; Stowasser M., Gordon R. D., Gunasekera T. G. et al., 2003]. For the primary detection of PHA, a more reliable and accessible method is the determination of the aldosterone-renin ratio (ARR). In addition, the determination of this ratio is a reliable and accessible method for screening PHA [Atkins D., Best D., Briss P.A. et al., 2004]. The ARR value in a healthy person fluctuates strictly within certain limits, since aldosterone secretion is normally controlled by the juxtaglomerular apparatus. In a simplified form, such a regulation scheme can be presented as follows. Juxtaglomerular cells secrete renin, which in turn catalyzes the formation of angiotensin 1. Under the influence of angiotensin-converting enzyme, angiotensin 1 is transformed into the most powerful hypertensive substance - angiotensin 2, which stimulates the synthesis of aldosterone. Aldosterone increases the reabsorption of sodium and water in the distal convoluted tubules and collecting ducts (as well as in the colon and salivary and sweat glands) and stimulates the excretion of potassium and hydrogen ions. Angiotensin 2, together with the extracellular level of potassium ions, are the most significant regulators of aldosterone synthesis. The listed processes lead to the suppression of renin production due to the activation of the following mechanisms. First, inhibition of renin production occurs upon excitation of baroreceptors, which are located in the afferent arteriole and respond to an increase in renal perfusion pressure. Second, renin synthesis decreases due to the direct action of angiotensin 2 on juxtaglomerular cells. The third factor is an increase in the NaCl level in the distal nephron. The concentration of chloride ions is controlled by the cells of the macula densa of the distal convoluted tubule of the nephron in the area adjacent to the renal corpuscle.

Thus, the main links of the renin-angiotensin-aldosterone system in a healthy person are in constant equilibrium. In the presence of autonomously functioning APA or hyperplasia of the glomerular zone, independent (completely or partially) of the regulatory influence of angiotensin 2, the aldosterone-renin ratio will change. The production of aldosterone will increase, and renin will decrease.

There are significant differences in the assessment of aldosterone and renin levels, which depend on the research method and units of measurement. Due to the lack of a unified approach in diagnostic protocols and methods, there is variability in determining the significant value of ARR in relation to PHA. The overwhelming majority of research groups use the ARR value within 20-40 when measuring the aldosterone level in ng / dL, and renin activity in ng / ml / h. Research conditions and factors affecting the ARS results are currently being supplemented and clarified by specialists in different countries. This concerns, first of all, the effect of various drugs (antihypertensive agents, oral contraceptives), blood sampling conditions on the study results. According to most authors, blood sampling can be performed on an outpatient basis in the morning after the patient has been in an upright position for about 2 hours and after being in a sitting position for 5-15 minutes [Gordon R.D., Stowasser M., Tunny T.J. et al., 1994; , Young W.F. Jr., 1997; Lim P.O., Dow E., Brennan G. et al., 2000; Loh K.C., Koay E.S., Khaw M.C. et al., 2000; Gallay B.J., Ahmad S., Xu L. et al., 2001; Mulatero P., Stowasser M., Loh K.C. et al., 2004; Tiu S.C., Choi C.H., Shek C.C. et al., 2005].

However, recently, the determination of the aldosterone-renin ratio has faded into the background, since its value depends to a greater extent on the activity of plasma renin [William Ya., Ladygina D.O., Balutina O.V., Beltsevich D.G., 2020].

If the ARS data prove or suspect the presence of PHA in a patient with an incidentally detected adrenal mass, the next recommended diagnostic step is to perform

one of the 4 confirmatory PHA tests. These tests are the oral sodium load test, the saline test, the fludrocortisone test, and the captopril test. Unfortunately, according to numerous studies, none of them can be proposed as preferable, which is due to the safety issues of load tests in hypertension, the difficulty of performing the fludrocortisone test, and the low specificity of the captopril test. Nevertheless, performing a test that verifies the presence of PHA is mandatory, since the method reduces the number of false-positive PHA diagnoses with a high degree of reliability, and therefore eliminates the need for further complex, expensive diagnostic procedures [Rogal E. Yu., 2012; Melnichenko G. A., Platonova N. M., Beltsevich D. G. et al., 2017].

Difficulties in diagnostics when detecting an incidentaloma also lie in the fact that an incidentally detected adrenal formation may in fact be hormonally inactive, but it exists in a patient with idiopathic primary hyperaldosteronism (IPHA). Against the background of bilateral adrenal hyperplasia, there may be an adenoma of the cortex that does not require surgical intervention and is not related to the underlying disease. Unilateral hormonally inactive adrenal macroadenomas are quite typical for elderly patients over 40 years old and are indistinguishable from APA on CT [Kloos R.T., Gross M.D., Francis I.R. et al., 1995]. Correct diagnostics, on the one hand, reduce the risk of “missed” undiagnosed observations of PHA, and on the other hand, makes it possible to timely and effectively remove a hormonally active tumor or optimize blood pressure control during specific treatment in patients with IPHA. Currently, it is considered proven that patients with PHA have a higher incidence of cardiovascular complications and mortality compared to patients randomized by age and gender with a similar degree of increased blood pressure in essential hypertension. The duration of hypertension is also of great importance for the prognosis. According to a number of researchers, the longer the hypertension exists, the worse the results of adrenalectomy for APA. However, according to the latest data, most patients (90%) experience either

long-term improvement or complete elimination of hypertension after unilateral adrenalectomy for APA [Aronova A., Gordon B.L., Finnerty B.M. et al., 2014; Wachtel H., Cerullo I., Bartlett E.K. et al., 2014]. The possibility of improving the quality of life with adequate treatment increases the importance of timely diagnosis [Milliez P., Girerd X., Plouin P.F. et al., 2005; Stowasser M., Sharman J., Leano R. et al., 2005; Celen O., O'Brien M.J., Melby J.C. et al., 1996].

The next step in diagnosing PGA is to establish the fact of unilateral or bilateral adrenal damage. According to various authors, unilateral adrenalectomy in APA or unilateral hyperplasia leads to normalization of potassium levels and improvement of the course of hypertension in all patients and to complete cure of hypertension in 30–60% of patients [Meyer A., Brabant G., Behrend M., 2005; Sawka A.M., Young W.F., Thompson G.B. et al., 2001]. In IPHA of bilateral hyperplasia in patients with glucocorticoid-dependent hyperaldosteronism, even total adrenalectomy practically does not improve the course of hypertension [Weinberger M.H., Grim C.E., Hollifield J.W. et al., 1979; Funder J.W., Carey R.M., Fardella C. et al., 2008]. In such patients, drug therapy is carried out [Young W.F. Jr., Klee G.G., 1988]. For the purpose of differential diagnosis of unilateral or bilateral adrenal damage, comparative selective blood sampling from the adrenal veins (CSBSAV) is performed.

The informative value of additional determination of the level of corticosterone, 11-deoxycorticosterone, 18-hydroxycorticosterone, 11-dehydrocorticosterone in the blood in CSBSAV for the purpose of differential diagnosis of APA and IPHA with borderline values of the lateralization coefficient (2.0±0.3) was established [Rebrova D. V., Vorokhobina N. V., Velikanova L. I. et al., 2016].

Determination of the level of 11-deoxycorticosterone, an aldosterone precursor with high affinity for mineralocorticoid receptors, in the blood is an informative additional criterion for the diagnosis of PHA, and also improves the accuracy of

differential diagnosis of the main forms of PHA [Rebrova D. V., Vorokhobina N. V., Sleptsov I. V. et al., 2016].

The detection rate of adrenocortical carcinomas (ACC) in patients with adrenal incidentaloma is up to 2%, and the proportion of adrenocarcinomas among incidentally discovered adrenal tumors continues to increase [Berruti A., Baudin E., Gelderblom H. et al., 2012]. The pathogenesis of ACC is still poorly understood, especially at the molecular level, since the rarity of the disease makes a comprehensive study difficult to perform [Lebastchi A.H., Kunstman J.W., Carling T., 2012]. The incidence of ACC, according to experts, is 0.5 - 2 new cases per million people per year [Melnichenko G. A., Stilidi I. S., Gobunova V. A., 2014; Gogoi G., Baruah M.P., Borah P. et al., 2012; Berruti A., Tiberio G.A.M., Sigala S., 2021]. This disease has a bimodal age distribution, with peaks in childhood up to 5 years and in the fourth to fifth decades of life. Adrenocortical cancer is more common in women than in men (ratio 1:5). Most ACCs are sporadic, but sometimes these malignancies are part of hereditary syndromes such as Li-Fraumeni syndrome, Beckwith-Wiedeman syndrome, multiple endocrine neoplasia type 1 (MEN 1), congenital adrenal hyperplasia, and familial adenomatous polyposis (FAP) [Fassnacht M., Libй R., Kroiss M. et al., 2011].

Adrenocortical cancer does not always have hormonal activity. In approximately 50% of these tumors, functional activity occurs and they synthesize hormones or their metabolites, which is clinically manifested by the corresponding syndromes [Panchani R., Goyal A., Varma T. et al., 2012]. Most hormonally active carcinomas have a mixed type of secretion. The remaining 50% are not functional and can be detected either accidentally during radiological examination, or when they or their metastases reach large sizes and begin to manifest localized symptoms [Schteingart D.E., Doherty G.M., Gauger P.G. et al., 2005].

Adrenocortical carcinomas are usually very aggressive, with a poor prognosis, which is expressed by a 5-year survival rate in the range of 16-38% [Lafemina J., Brennan M.F., 2012; Davenport C., Liew A., Doherty B. et al., 2011; Tissier F., 2010; Young W.F. Jr., 2007]. Thus, for obvious reasons, the accuracy of differential diagnosis of adrenal cortex tumors is becoming increasingly important.

Currently, many imaging methods are available for the evaluation of adrenal neoplasms, such as ultrasound, MRI, CT, and other less common methods - scintigraphy with meta-iodobenzylguanidine (MIBG) and positron emission tomography (PET) using various radiopharmaceuticals [Low G., Dhliwayo H., Lomas D.J., 2012].

Due to its availability, absence of radiation exposure and cost-effectiveness, ultrasound is a screening method in the topical diagnosis of incidentally detected adrenal neoplasms. Despite the fact that it is not always possible to visualize normal adrenal glands in obese patients (especially on the left side) [Gьnther R.W., Kelbel C., Lenner V., 1984; Dietrich C.F., Wehrmann T., Hoffmann C. et al., 1997], since their physiological thickness does not exceed 12 mm, the sensitivity of this method for tumors larger than 2 cm is more than 90% [Trojan J., Schwarz W., Sarrazin C., et al., 2002; Hsu-Chong Y., 1980]. In addition to determining the size of the neoplasm, ultrasound allows you to assess the presence of calcifications, foci of necrosis or cysts. However, this method does not provide an accurate answer to the question of whether the tumor is malignant or benign [Papierska L., Cichocki A., Sankowski A.J., Cwikła J.B., 2013]. Despite the fact that ultrasound examination has low sensitivity for detecting small neoplasms and is not always able to reliably characterize visualized tumors, this method plays an important role in the follow-up of hormonally inactive adrenal lesions [Podgyrska J., Cieszanowski A., Bednarczuk T., 2012].

CT and MRI are highly effective methods for diagnosing all types of incidentalomas - their sensitivity is 100% [Foti G., Faccioli N., Mantovani W. et al., 2012]. Using lipid-sensitive imaging methods - CT without intravenous contrast and MRI, it is possible to differentiate malignant neoplasms from benign ones, since benign tumors usually have a high lipid content [Arnaldi G., Boscaro M., 2012] - approximately 70% of adenomas contain a large amount of intracellular lipids, consisting of cholesterol, fatty acids and neutral fat [Blake M.A. et al., 2010]. Modern researchers [Song J.H., 2008; Sangwaiya M.J. et al., 2010; Jain S.M., 2013; Thampi A., Shah E., Elshimy G., Correa R., 2020] believe that neoplasms with a density of 10 Hounsfield units (HU) or less on unenhanced CT [Blake M.A. et al., 2006] or demonstrating stability in size for 6 months or longer are adenomas [Fassnacht M., Arlt W., Bancos I. et al., 2016]. An analysis of published research results showed that a threshold of 10 HU on unenhanced CT has a sensitivity of 70-90% and a specificity of about 100% [Korivi B.R., Elsayes K.M., 2013; Sahdev A. et al., 2010; Peca C.S. et al., 2000; Boland G.W. et al., 1998]. In cases where there is doubt about the interpretation of the results, contrast-enhanced CT can be used to differentiate lipid-rich and lipid-poor adenomas from other adrenal neoplasms by calculating the absolute and relative washout percentages.

Performing CT with intravenous contrast and determining the densitometric density of the formation in the delayed phase of the study after 15 minutes has a higher diagnostic accuracy than other imaging diagnostic methods. ACC is usually a large tumor with high native density (more than 10 HU), intramural necrosis and irregular shape and edges. From 2 to 10% of cases, adrenal involvement is bilateral. Metastases can be found in the liver, lungs, lymph nodes, renal vein and inferior vena cava. From 9 to 19% of tumors have invasion of the inferior vena cava at the time of their detection [Thampi A., Shah E., Elshimy G., Correa R., 2020].

MRI is also used for differential diagnostics of malignant and benign neoplasms of the adrenal glands. The sensitivity and specificity of this method are quite high and amount to 98-100% [Dovganyuk V.S., 2005; Soldatova T.V., 2011].

On MRI, ACCs are characterized by a hyperintense signal on T1- and T2-weighted images, the presence of areas of hemorrhage within the tumor, and central necrosis [Gross M.D. et al., 2010]. Adenomas appear as lipid-rich formations, which is often used to differentiate adenomas from adrenal metastases [Dunnick N.R., Korobkin M., 2002]. On MR tomograms, a characteristic feature of paragangliomas and pheochromocytomas is a high signal intensity from the tumor tissue on T2-weighted images, however, about 30% are hypointense [Blake M.A., Kalra M.K., Maher M.M. et al., 2004]. The tumor does not reduce intensity in images with signal suppression from fat [Gilyazutdinov I.A., Khasanov R.Sh., Kuryanov D.P., 2007].

Despite the high sensitivity of CT and MRI, the anatomical approach to topical diagnostics is non-specific. In some cases, when examining incidentally detected adrenal neoplasms, it is extremely important to identify the chromaffin nature of the tumor. Currently, the highest specificity of functional topical diagnostics is achieved by using scintigraphy with metaiodobenzylguanidine labeled with the isotope $I^{123}$ (MIBG-$^{123}$I). However, scintigraphy with MIBG-$^{123}$I can be avoided in the case of adrenal tumors less than 5 cm in diameter, in which a significant increase in the level of metanephrine in the plasma or urine is observed. This is explained by the fact that small tumors rarely metastasize, and tumors with predominant secretion of adrenaline are in most cases located in the adrenal gland. The fact that metaiodobenzylguanidine (MIBG-$^{123}$I) scintigraphy frequently fails to detect VHL-associated adrenal pheochromocytomas [Taieb D., Sebag F., Hubbard J.G. et al., 2004] may be explained by a relative lack of storage granules or reduced expression of membrane norepinephrine or vesicular monoamine transporters [Eisenhofer G., 2001]. PET with 6-18F-fluorodopamine is a

more sensitive method for diagnosing these neoplasms [Bryant J., Farmer J., Kessler L.J. et al., 2003]. Thus, despite the advantages of MIBG-$^{123}$I scintigraphy, its sensitivity leaves much to be desired, especially in the diagnosis of metastatic lesions [Beltsevich D.G., Troshina E.A., Yukina M.Yu., 2010]. In this regard, other methods of functional imaging are used. When performing positron emission tomography (PET) for the diagnosis of pheochromocytoma, new promising specific radionuclides are used: 6-^18F-fluorodopamine, ^18F-dihydroxyphenylalanine (DOPA), $^{11}$C-hydroxyephedrine, or $^{11}$C-adrenaline. Recent studies have demonstrated the superiority of these methods compared to MIBG-$^{123}$I and MIBG-$^{131}$I scintigraphy. Such methods of cumulative diagnostics as octreoscan and PET with ^18F-fluorodeoxyglucose are not recommended as the first stage of topical diagnostics. These examination options can be used in patients with a negative result of scintigraphy with MIBG-$^{123}$I, in rapidly growing tumors with high metabolic activity or in formations with somatostatin receptors [Furuta N. et al., 1999; Ilias I. et al., 2002].

PET with 18F-2-fluoro-2-deoxy-D-glucose (18FDG-PET) is able to differentiate benign from malignant adrenal tumors, demonstrating high uptake of the substance in the latter. This is due to the fact that most malignant tumors show increased glucose utilization associated with high metabolic activity [Low G., Dhliwayo H., Lomas D.J., 2012].

Unfortunately, none of the listed methods of radiation diagnostics have 100% sensitivity and specificity in relation to differential diagnostics of benign and malignant neoplasms of the adrenal glands. In this regard, great hopes are placed on the study of the steroid profile of blood and urine. The advantage of studying the steroid profile of urine is the ability to study the metabolites of those substances that quickly disappear from the blood.

Determination of the urinary steroid profile (USP), i.e. quantitative determination of the totality of steroid concentrations and ratios, using gas chromatography-mass spectrometry (GC-MS) has been proposed as a method for diagnosing adrenal cortex tumors [Shackleton C.H., Marcos J., 2011]. This method, which differs from the usual biochemical analysis for studying the synthesis of hormones by the adrenal glands, is another promising technique for differentiating incidentalomas [Lebastchi A.H., Kunstman J.W., Carling T., 2012], since it allows determining most steroids at a level of 10 ng/ml [Orlov E.N., 2000]. However, given its low sensitivity as a method for primary diagnosis of ACC, associated with the complexity of interpretation of the technique, the dissemination and wide application of this examination method in clinical practice is currently very difficult. At the same time, the determination of USP in the future (after additional study) can be used as an auxiliary diagnostic method in combination with imaging research methods, as well as a method determining treatment tactics in patients who have undergone adrenalectomy for ACR [Shcherbakov I. E., Chernikov R. A., Rusakov V. F. et al., 2020; Shcherbakov I. E., Rusakov V. F., Krasnov L. M. et al., 2021].

For many decades, fine-needle biopsy has been proposed as the most effective method for determining the structure of a tumor and determining the degree of its malignancy. However, its performance in cases of incidentally detected adrenal tumors for the purpose of establishing a diagnosis is currently abandoned for a number of reasons. Thus, if pheochromocytoma is suspected, biopsy is contraindicated [Berruti A., Baudin E., Gelderblom H. et al., 2012], because percutaneous biopsy can cause hypertensive crisis of adrenal genesis [Bancos I., Tamhane S., Shah M. et al., 2016; Korivi B.R., Elsayes K.M., 2013]. If ACC is suspected, biopsy is not justified due to the possibility of local metastasis by insemination [Berruti A., Baudin E., Gelderblom H. et al., 2012]. Other complications, such as pneumothorax and infection, occur in approximately 3% of cases and require treatment [Mody M.K., Kazerooni E.A.,

Korobkin M., 1995]. Only for the diagnosis of adrenal tuberculosis the main method is biopsy, since CT imaging does not allow to distinguish isolated adrenal tuberculosis from other benign and malignant neoplasms [Almahrezi A., Balkhair A., Al-Yaarubi S. et al., 2008]. But isolated adrenal tuberculosis is extremely rare and is accompanied by acute or chronic adrenal insufficiency.

The study of tissue taken by fine-needle, and in many cases by core-needle, biopsy presents great difficulties due to the small amount of material obtained. In light microscopy, immunohistochemical analysis of incidentally detected tumors has shown its value in their differential diagnosis. Thus, Kouyama R. et al. (2011) indicated that unorganized production of steroidogenic enzymes such as 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase and DHEA sulfotransferase and excessive expression of insulin-like growth factor (IGF-II) in the tumor are distinctive features of ACC, which can be used as biochemical and molecular markers for the diagnosis of adrenal cancer [Kouyama R., Hiraishi K., Sugiyama T. et al., 2011].

However, the use of immunohistochemical molecular markers in the diagnosis of adrenocortical carcinomas remains controversial at present. In a study by Pereira S.S. et al. [Pereira S.S., Morais T., Costa M.M. et al., 2013] using quantitative determination of markers StAR, IGF2, IGF1R, p53, MDM2, p21, p27, cyclin D1, Ki-67, β-catenin, E-cadherin using a morphometric computer program, it was found that the content of markers IGF2, p27, cyclin D1, and Ki-67 was significantly higher in carcinoma samples than in adenoma samples. Ki-67 and p27 are the markers that are most important for differential diagnostics between carcinoma and all types of adenomas, while IGF2 and StAR make sense to detect only for differentiation of carcinoma from functionally inactive adenoma and carcinoma from adenoma accompanied by Cushing's syndrome. It is known that the use of Ki-67 in differential diagnostics of malignant tumors has been recognized before. The authors recommend considering the additional use of p27 as an

optional marker for distinguishing benign adrenal cortex tumors from malignant ones [Pereira S.S., Morais T., Costa M.M. et al., 2013]. However, it should be noted that immunohistochemical methods have not yet fully resolved the problem of differential diagnostics of benign and malignant adrenal neoplasms. Further comprehensive studies are needed, including both radiation and biochemical and immunohistochemical methods [Britvin T.A., Krivosheev A.V., Beloshitsky M.E., 2015].

Thus, the incidence of incidentally discovered adrenal masses has increased significantly in recent years due to the widespread use of various imaging techniques. In patients without a known extra-adrenal primary malignancy, most incidentalomas are benign, hormonally inactive adenomas. The results of various imaging studies of incidentalomas should be interpreted with caution, as the sensitivity and specificity reported in the overall number of studies may not apply in a given case. The size, hormonal activity, and imaging characteristics should be taken into account when formulating a subsequent management plan. Due consideration should also be given to the cost-effectiveness of the investigations and treatments ordered [Panchani R., Goyal A., Varma T., et al. 2012].

# Chapter 2

## General characteristics of materials and research methods

### 2.1 Study materials.

The study included data from 264 patients with adrenal incidentalomas admitted to the Endocrine Surgery Department of the N.I. Pirogov Clinic of High Medical Technologies, St. Petersburg State University for elective surgical treatment from 2007 to 2015. Among them, there were 203 women and 61 men aged 18 to 75 years (mean age 52.89±12.73 years). In all cases, the tumor was detected incidentally in other medical institutions or in related departments of the N.I. Pirogov Clinic of High Medical Technologies, St. Petersburg State University during ultrasound, MRI or CT scans performed due to suspected pathology in the abdominal cavity or retroperitoneal space, or during routine medical examination. The proportion of patients with incidentally detected neoplasms among the total number of patients operated on for adrenal tumors (359 people) was 73.54%, the remaining 26.46% (95 people) were detected hormonally active tumors (tables 1 and 2). The localization and histological structure of incidentalomas are presented in table 3.

Table 1

General distribution of patients by age and gender

| Gender | Age, years | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | 19 and under | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-78 | |
| Women | 1 | 24 | 31 | 52 | 80 | 69 | 21 | 278 |
| Men | - | 6 | 12 | 15 | 32 | 11 | 5 | 81 |
| Total: | 1 | 30 | 43 | 67 | 112 | 80 | 26 | 359 |

Table 2

Distribution of patients with adrenal incidentalomas by age and gender

| Gender | Age, years | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | 19 and under | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-78 | |
| Women | 1 | 14 | 16 | 31 | 65 | 58 | 18 | 203 |
| Men | - | 5 | 7 | 10 | 25 | 11 | 3 | 61 |
| Total: | 1 | 19 | 23 | 41 | 90 | 69 | 21 | 264 |

Table 3

Histological structure and localization of accidentally detected formations

| Histological structure of the tumor | | Localization | | | Total | |
|---|---|---|---|---|---|---|
| | | Left | Right | Bilaterally | | |
| Cortical adenoma | Clear cell | 69 | 65 | 1 | 135 | 143 |
| | Mixed cell | 1 | 1 | - | 2 | |
| | Dark cell | 3 | 3 | - | 6 | |
| Cystic formations of the adrenal glands | | 10 | 14 | 2 | 26 | |
| Adrenal cortical cancer | | 15 | 7 | 1 | 23 | |
| Pheochromocytoma (incidentally detected, hormonally inactive) | | 11 | 6 | - | 17 | |
| Myelolipoma | | 5 | 5 | - | 10 | |
| Metastases to the adrenal gland | | 9 | 1 | - | 10 | |
| Hemangioma | | 3 | 2 | - | 5 | |
| Adrenal hyperplasia | | 3 | 1 | - | 4 | |
| Schwannoma | | 2 | 2 | - | 4 | |
| Lymphangioma | | 3 | 1 | - | 4 | |
| Spindle cell tumor | | 2 | 1 | - | 3 | |
| Non-Hodgkin's lymphoma | | 2 | - | - | 2 | |
| Adrenal hematoma with secondary changes | | 1 | 1 | - | 2 | |
| Ganglioneuroma | | 1 | 1 | - | 2 | |
| Angioleiomyoma | | - | 1 | - | 1 | |

| | | | | |
|---|---|---|---|---|
| Angiolipoma | - | 1 | - | 1 |
| Leiomyosarcoma | 1 | - | - | 1 |
| Primary multiple adrenal tumor: clear cell adrenocortical adenoma and composite pheochromocytoma (combination of pheochromocytoma and ganglioneuroma) | - | 1 | - | 1 |
| Neurofibroma | 1 | - | - | 1 |
| Retroperitoneal cyst | 1 | - | - | 1 |
| Undifferentiated tumors | 1 | 2 | - | 3 |
| Total | 144 | 116 | 4 | 264 |

The selection of patients for surgical intervention was carried out by the department staff. The decision on the need for surgical treatment was made after a thorough outpatient or inpatient examination. Among the 7443 patients referred for consultation with the diagnosis of "adrenal neoplasm" during the specified period, 660 were hospitalized for examination.

A total of 360 surgical interventions were performed in 359 patients (2 surgeries were performed in a patient with bilateral pheochromocytoma), including 30 traditional ones (open adrenalectomy) and 330 using endovideosurgical techniques (169 laparoscopic adrenalectomies and 159 retroperitoneoscopic ones). It should also be noted that when performing retroperitoneoscopic access, the operation was performed through one port in 55 patients [Fedotov Yu N., Krasnov LM, Fedorov EA, Sablin I. V., Malyugov Yu N. et al., 2017] and through one port with subsequent forced installation of an additional trocar in 5. In 2 cases, retroperitoneal tumors located above the upper pole of the kidney were diagnosed during the operation. Neoplasms were removed using laparoscopic and retroperitoneoscopic approaches with preservation of the adrenal glands [Krasnov L. M., Rusakov V. F., Fedorov E. A. et al., 2015].

The work was carried out in the N.I. Pirogov Clinic of High Medical

Technologies of St. Petersburg State University (Director, MD, Shkarupa D.D.). Surgical interventions were performed at the endocrine surgery department (Head of the department, MD, Chernikov R.A.) of the N.I. Pirogov Clinic of High Medical Technologies of St. Petersburg State University.

2.2 Research methods.

The clinical stage of the examination was standard for all patients. It included, first of all, a physical examination, which allowed us to suspect or exclude clinical manifestations of the hormonal activity of the formation. This was followed by laboratory diagnostics: general clinical and biochemical tests, a study of the level of steroid hormones, their precursors and metabolites, and the excretion of metanephrines. A separate group of patients underwent a study of the steroid profile of urine using gas chromatography-mass spectrometry (GC-MS) for the purpose of differential diagnostics of benign and malignant neoplasms. To determine the localization of the tumor and its radiation characteristics, we most often used ultrasound and CT, less often MRI. All removed formations were subjected to histological and, in some cases, immunohistochemical studies.

Most of the biochemical studies were performed in the laboratory of the North-West Center for Evidence-Based Medicine. The concentration of potassium, sodium and ionized calcium in blood plasma was studied by ion-selective analysis on an Easy Lite Calcium semiautomatic analyzer (USA) with programmed normal values. The spectrum of steroid hormones and their precursors in blood plasma (cortisol, cortisone, corticosterone, 11-deoxycorticosterone, 11-deoxycortisol), cortisone, adrenaline, noradrenaline, dopamine, and total metanephrines in daily urine was studied by high-performance liquid chromatography (HPLC) on a Shimadzu chromatograph (Japan) using a diode matrix and a spectrofluorometric detector. The components were separated in the gradient elution mode on a column with a C18 sorbent. Quantitative

determination of cortisol in daily urine, renin, aldosterone, angiotensin 1, dehydroepiandrosterone sulfate (DHEA-S), neuron-specific enolase (NSE) and chromogranin A in blood serum was performed by chemiluminescent immunoassay (CLIA) using LIAISON and LIAISON XL automatic analyzers from DiaSorin (Germany, Italy). Salivary cortisol was determined by manual enzyme-linked immunosorbent assay (ELISA) on a system from DRG Instruments GmbH (Germany). Quantitative determination of adrenocorticotropic hormone (ACTH) in blood plasma with ethylenediaminetetraacetic acid (EDTA) (after freezing) was performed by chemiluminescent immunoassay (CLIA) using a LIAISON analyzer from DiaSorin (Germany, Italy). General urine analysis was performed on a semi-automatic urine analyzer AUTION MAX AX-4280 by ARKRAY (Japan) using the dual-wave and single-wave reflection method. Clinical blood analysis was performed on a multichannel automatic hematology analyzer Sysmex XT-1800i by Sysmex Corporation (Japan) using the methods of flow cytofluorometry, specific lysis, conductometry, and hydrodynamic focusing.

The sample of patients for determination of the urinary steroid profile (USP) was 67 people. Of these, 23 were diagnosed with ACR, the remaining 44 had hormonally inactive formations: adenomas (37 patients), pheochromocytomas (6 patients) and one patient with a solitary adrenal cyst. All patients completed informed consent for scientific research with their biological samples.

All patients had their daily urine collected with diuresis monitoring, 20 ml samples were taken and frozen at -72°C. The samples were then defrosted and a 2 ml aliquot was taken for the study.

The next steps of sample preparation were re-extraction of free steroids and derivatization. A 2% solution of methylhydroxylamine (Sigma-Aldrich, Germany) was used at +60°C for 1.5 hours. Cyclohexane (Sigma-Aldrich, Germany) was used to

remove soluble derivatives. After removing cyclohexane under nitrogen, the remaining steroid solution of 0.4 ml was ready for GC-MS measurement.

The GC-MS study was conducted using equipment and materials from the laboratory of the Chromatography Research Laboratory of the Endocrinology Research Institute of the North-West State Medical University named after I.I. Mechnikov (Head, Doctor of Biological Sciences, Professor L.I. Velikanova) and the Steroid Laboratory of King's College Hospital, London, UK (Head, PhD, Norman Taylor).

Statistical processing of the obtained data was carried out using standard Microsoft EXEL XP tools.

Ultrasound examination (US), computed tomography (CT) and magnetic resonance imaging (MRI) were used to determine the nature of morphological changes in the adrenal glands.

Ultrasound of the adrenal glands was performed on an Accuvix V10 ultrasound scanner from Samsung Medison (Republic of Korea) using a standard technique with a convex sensor with a frequency of 3-7 MHz. The neoplasms were assessed according to the following criteria:

1. Number of neoplasms.

2. The location of the tumor in the structure of the adrenal gland (in the body, in the lateral or medial peduncle).

3. Form of the formation; contours of the formation (clear, fuzzy); tumor echogenicity (hypoechoic, isoechoic, hyperechoic, anechoic); presence of a visible capsule; presence of cysts, calcifications, decay zones; echostructure (homogeneous, heterogeneous); invasion into surrounding tissues or organs.

4. Variant of neoplasm vascularization (avascular, perinodular, mixed types of blood flow).

Magnetic resonance imaging was performed on various magnetic resonance imaging machines in outpatient settings in various medical and diagnostic institutions in St. Petersburg.

Computer tomography was performed for most patients on an Aquilion 64 CT scanner by Toshiba (Japan) with the ability to obtain 0.5 mm thick slices with the construction of multiplanar reformations in native conditions. In 117 patients, the study was performed with intravenous "enhancement" of a non-ionic, monomeric, triiodinated, water-soluble radiopaque agent with a concentration of 350-370 mg iodine/ml, pH 6.8-7.6 with the introduction of a contrast agent in a volume of 100 ml with an automatic syringe at an injection rate of 3.5-4 ml/s with obtaining images in the arterial, venous and delayed (after 10 minutes) phases. The main criteria for evaluating CT scans were: the size of the detected formation, its shape, contours, structure, the presence of a capsule, densitometric density in different phases of the study, the presence of inclusions and enlarged lymph nodes, the relationship to other organs.

Histological and immunohistochemical studies were performed in the laboratory of the National Center for Clinical Morphological Research (Director, PhD, S. L. Vorobyov). After adrenalectomy, a macroscopic examination of the surgical material was performed. The following characteristics were assessed: adrenal gland size, tumor size, presence of tumor capsule, tumor color and consistency, presence of inclusions and cysts, and condition of the adrenal tissue outside the tumor. The surgical material selected for histological examination was fixed in 10% buffered formalin solution (pH 7.0-7.2) for 18-24 hours, after which the fragments were embedded in paraffin. Immunohistochemical examination was performed on paraffin sections using the biotin-streptavidin immunoperoxidase method. Sections 3-4 μm thick were deparaffinized and rehydrated according to the standard scheme using isopropyl alcohol.

During histological examination, the tumor was assessed in accordance with the

international histological classification of adrenal tumors (WHO, 2004) [De Jellis R. A., Lloyd R. V., Heitz P. U., 2004].

The tumors were examined for structural and cellular-nuclear polymorphism, nuclear hyperchromia, the presence and characteristics of nucleoli, necrotic component, calcifications, and the number of mitoses in 10 fields of view at x400 magnification. The tumor and adrenal capsules were carefully examined for invasion, vessels outside the tumor for tumor emboli, and periadrenal adipose tissue. The presence or absence of distant metastases was assessed based on the data of radiation examination methods and/or morphological examination of the surgical material.

Histological features of adrenocortical tumors were assessed according to the Weiss system (1989).

According to the Weiss (1989) system, the following factors were evaluated: mitotic activity (more than 5 mitoses in 50 visual fields with a magnification of x400), presence of atypical mitoses, large nuclei, number of eosinophilic cells, nature of necrosis, and diffuse architectural pattern of the tumor. Capsular sinusoidal and venous invasion were also taken into account. Each positive factor was counted as one point. Based on this system, if a tumor scored 3 or higher, it was considered malignant. Tumor size was measured by the maximum length of the formation using a metric system.

Monoclonal antibodies to vimentin, pancytokeratin AE1/AE3, β-catenin, inhibin a, melan-A, polyclonal antibodies to Ki-67, p21, p53, CD1, CD34 were used for immunohistochemical studies. The working dilutions of antibodies were selected empirically using positive controls. The intensity of expression was evaluated for cytoplasmic and membrane markers: in the complete absence of expression or expression, less than 5% of cells are negative, 5-24% are weakly positive, 25-74% are moderately positive, and more than 75% are pronounced. The expression of Ki-

67,p21,p53,and CyD1 was evaluated quantitatively; the index of proliferative activity of Ki-67-positive nuclei in the field of view of a microscope (magnification x400) in the study of 2000 cells. Light microscopy, digital imaging, and quantitative software evaluation of morphological features were performed on a Nikon Ni microscope (Japan).

When processing the results of histological and immunohistochemical studies, numerical dimensional indicators were examined for consistency with the Gaussian distribution using the Shapiro-Wilk criterion. In the present work, there were no sample distributions consistent with the normal one. Therefore, the Mann-Whitney rank criterion was used to test hypotheses when comparing indicators in groups, and descriptive statistics represented the median and two percentiles of the 25th and 75th.

Non-numeric indicators were processed by comparing the proportions of values in subgroups. The chi-square test was used to test statistical hypotheses. A significance level of 0.05 was assumed for all tests.

The statistical analysis was carried out using the IBM SPSS 20.0 program.

# Chapter 3

## Concomitant diseases in patients with incidentally diagnosed neoplasms of the adrenal glands

Concomitant diseases were observed in the vast majority of patients with randomly identified adrenal neoplasms. They were detected in 256 (96.96%) of the 264 patients who underwent surgery. As a rule, two, three, or more diseases were found in each patient (in 251 of the 256 patients). The absence of any concomitant disease was found only in eight people (3.04%). A list of various pathological conditions is provided in tables 4, 5, 6, 7, 8, 9 and 10.

Table 4

The structure of concomitant diseases in patients with adrenal incidentalomas

| Concomitant diseases | Number of patients | % of the total number of patients with incidentalomas | The number of patients with a combination of several diseases of this organ system | % of the total number of patients with diseases of this organ system |
|---|---|---|---|---|
| Diseases of the cardiovascular system | 207 | 78,4 | 132 | 63,79 |
| Gastrointestinal diseases | 172 | 65,15 | 92 | 53,49 |
| Diseases of the endocrine system | 112 | 42,42 | 10 | 8,93 |
| Diseases of the urinary system | 74 | 28,03 | 13 | 17,56 |
| Diseases of the | 34 | 12,88 | 15 | 44,12 |

| | | | | |
|---|---|---|---|---|
| respiratory system | | | | |
| Diseases of the reproductive system | 28 | 10,6 | - | - |
| Malignant tumors | 22 | 8,33 | 1 | 4,55 |
| Diseases of the spine associated with degeneration and degeneration of tissues. | 93 | 35,23 | - | - |
| Obesity I,III or III stages | 71 | 26,89 | - | - |
| Varicose veins of the lower extremities. | 60 | 22,72 | - | - |
| Encephalopathy | 32 | 12,12 | - | - |
| Mild chronic iron deficiency anemia | 12 | 4,54 | - | - |
| A common form of psoriasis | 5 | 1,89 | - | - |
| Umbilical hernia | 4 | 1,51 | - | - |
| Chronic viral hepatitis C | 3 | 1,13 | - | - |
| Non-Hodgkin's follicular lymphoma stage 2 A | 1 | 0,38 | - | - |

Diseases of the cardiovascular system were diagnosed in 207 patients. Hypertension affected 188 of them (90.82%), and 111 people (59.04%) had hypertension combined with coronary heart disease (CHD). Coronary heart disease without hypertension was detected in 14 patients (6.76%).

Table 5

The structure of concomitant diseases in the cardiovascular system

| Concomitant disease | Number of patients | % |
|---|---|---|
| Hypertension | 77 | 37,19 |
| Coronary heart disease | 14 | 6,76 |
| Hypertension + coronary heart disease | 111 | 59,04 |
| Postinfarction cardiosclerosis | 9 | 4,35 |
| Dysmetabolic cardiomyopathy | 4 | 1,93 |
| Dysmetabolic cardiomyopathy + coronary heart disease and/or hypertension | 10 | 4,83 |
| Reciprocal paroxysmal AV tachycardia | 1 | 0,48 |

Diseases of the gastrointestinal tract were diagnosed in 172 patients. Of these, 92 had a combination of two or more diseases.

Table 6

The structure of concomitant gastrointestinal diseases

| Concomitant disease | Number of patients | % |
|---|---|---|
| Gallstone disease | 11 | 6,39 |
| Gallstone disease + other gastrointestinal pathology | 37 | 21,51 |

| | | |
|---|---|---|
| Chronic non-calculous cholecystitis + other gastrointestinal pathology | 14 | 8,14 |
| Biliary dyskinesia | 14 | 8,14 |
| Chronic pancreatitis | 4 | 2,32 |
| Chronic pancreatitis + other gastrointestinal pathology | 35 | 20,35 |
| Gastroesophageal reflux disease | 25 | 14,53 |
| Chronic gastritis | 34 | 19,77 |
| Chronic gastritis + other gastrointestinal pathology | 48 | 27,91 |
| Chronic gastroduodenitis | 17 | 9,88 |
| Chronic gastroduodenitis + other gastrointestinal pathology | 42 | 24,42 |
| Peptic ulcer of the stomach | 6 | 3,49 |
| Duodenal ulcer | 11 | 6,39 |
| Peptic ulcer of the stomach + duodenal ulcer | 3 | 1,74 |
| Non-alcoholic obesity of the liver | 6 | 3,49 |
| Polyps of various parts of the stomach | 4 | 2,32 |
| Polyps of various parts of the intestine | 3 | 1,74 |
| Diverticulum of the stomach arch | 1 | 0,58 |
| Diverticulosis of the sigmoid colon | 1 | 0,58 |

| | | |
|---|---|---|
| Liver hemangioma | 3 | 1,74 |
| Liver cysts | 5 | 2,9 |
| Pancreatic cysts | 1 | 0,58 |
| Nonspecific ulcerative colitis (Crohn's disease) | 1 | 0,58 |

In 112 patients (42.42% of the total number of patients), pathology of the endocrine system was one of the concomitant diseases, and 10 of them (8.93%) had a simultaneous combination of two nosological forms. Thyroid diseases were diagnosed in 64 patients, parathyroid glands in 6 people, diabetes mellitus and impaired carbohydrate tolerance in 49.

Table 7

The structure of concomitant diseases of the endocrine system

| Concomitant disease | Number of patients | % |
|---|---|---|
| Diabetes mellitus + diffuse non-toxic goiter | 3 | 2,68 |
| Diabetes mellitus + nodular non-toxic goiter | 2 | 1,79 |
| Diabetes mellitus + diffuse toxic goiter | 2 | 1,79 |
| Diabetes mellitus + papillary carcinoma of the thyroid gland | 1 | 0,89 |
| Violation of fasting glycemia + autoimmune thyroiditis | 1 | 0,89 |
| Nodular non-toxic goiter + papillary carcinoma of the thyroid gland | 1 | 0,89 |
| Nodular non-toxic goiter | 24 | 21,43 |
| Multi-nodular non-toxic goiter | 6 | 5,36 |
| Diffuse non-toxic goiter | 4 | 3,57 |

| | | |
|---|---|---|
| Diffuse nodular non-toxic goiter | 3 | 2,68 |
| Diffuse toxic goiter | 2 | 1,79 |
| Autoimmune thyroiditis | 16 | 14,29 |
| Polynodose euthyroid goiter | 1 | 0,89 |
| Follicular adenoma of the thyroid gland | 1 | 0,89 |
| Papillary carcinoma of the thyroid gland | 7 | 6,25 |
| Parathyroid adenoma | 1 | 0,89 |
| Primary hyperparathyroidism | 4 | 3,57 |
| Secondary hyperparathyroidism | 1 | 0,89 |
| Type II diabetes mellitus | 36 | 32,14 |
| Type I diabetes mellitus | 1 | 0,89 |
| Violation of carbohydrate tolerance | 12 | 10,71 |

Diseases of the respiratory system were detected in 34 people (12,88%).

Table 8

The structure of concomitant diseases of the respiratory system

| Concomitant disease | Number of patients | % |
|---|---|---|
| Bronchial asthma | 9 | 26,47 |
| Chronic obstructive pulmonary disease + bronchial asthma | 3 | 8,82 |
| Chronic obstructive pulmonary disease + chronic bronchitis | 13 | 38,24 |
| Chronic bronchitis | 7 | 20,59 |
| Allergic alveolitis | 1 | 2,94 |

| | | |
|---|---|---|
| Sarcoidosis of the lungs | 1 | 2,94 |

Diseases of the urinary system were diagnosed in 74 people (28,03%), 13 of them had a combination of two diseases.

Table 9

The structure of concomitant diseases of the urinary system

| Concomitant disease | Number of patients | % |
|---|---|---|
| urolithiasis | 24 | 32,43 |
| chronic pyelonephritis | 17 | 22,97 |
| cysts of one or both kidneys | 17 | 22,97 |
| chronic tubulointerstitial nephritis | 12 | 16,22 |
| nephroptosis | 5 | 6,76 |
| violation of mineral metabolism in the kidneys | 4 | 5,41 |
| nephroangiosclerosis | 3 | 4,05 |
| angiolipoma of the kidney | 3 | 4,05 |
| chronic glomerulonephritis | 1 | 1,35 |
| hypertensive nephropathy | 1 | 1,35 |

Table 10

The structure of concomitant diseases of other organs and systems

| Concomitant disease | Number of patients | % |
|---|---|---|
| **Encephalopathy** (32 people)**:** | | |
| Cerebrovascular disease, dyscirculatory encephalopathy | 27 | 84,38 |
| encephalopathy of mixed origin | 4 | 12,5 |
| post-traumatic encephalopathy | 1 | 3,12 |
| **Diseases of the reproductive system** (28 people)**:** | | |
| For men (10 people): | | |
| prostatic hyperplasia | 5 | 50 |
| chronic prostatitis | 5 | 50 |
| For women (18 people): | | |
| uterine fibroids | 12 | 66,66 |
| ovarian cysts | 2 | 11,1 |
| ovarian adenoma | 1 | 5,56 |
| fibroids of both ovaries | 1 | 5,56 |
| endometriosis | 1 | 5,56 |
| fibroadenomatosis of the mammary glands | 1 | 5,56 |
| **Malignant neoplasms** (22 people)**:** | | |
| kidney cancer | 6 | 27,27 |
| lung cancer | 5 | 22,72 |

| | | |
|---|---|---|
| stomach cancer | 3 | 13,63 |
| colon cancer | 1 | 4,55 |
| rectal cancer | 2 | 9,09 |
| breast cancer | 2 | 9,09 |
| melanoma of the eye | 1 | 4,55 |
| giant cell tumor of the rib | 1 | 4,55 |
| cardioesophageal cancer + hypernephroid kidney cancer | 1 | 4,55 |

We paid special attention to patients with a crisis course of arterial hypertension and an identified neoplasm of the adrenal glands. They were usually referred for consultation to endocrinologists with suspected pheochromocytoma. Upon further examination, according to radiation and laboratory research methods, this diagnosis was not confirmed. Histological examination after surgery in all cases established the presence of adrenal cortex adenoma in patients. Apparently, such a crisis course of arterial hypertension was caused by other factors. During the examination by neurologists before and after surgery, these patients were diagnosed with somatoform dysfunction of the autonomic nervous system (SDANS), which requires special treatment. This group of patients consisted of 44 people (39 women and 5 men), which accounted for 16.66% of the total number of operated patients with randomly identified adrenal gland formations. We specifically studied the literature data on this issue and compared the features of clinical manifestations in patients with SDANS and in patients with pheochromocytoma.

According to the literature, somatoform disorders are a group of psychogenic diseases characterized by pathological symptoms resembling somatic disease, but there

are no morphological manifestations against the background of nonspecific functional disorders that cannot be explained by known pathophysiological mechanisms [Khodarev N.V., Zhemchuzhnova N.L., Olempieva E.V., et al.,2013]. Somatoform dysfunction of the autonomic nervous system is a condition characterized by a violation of the neurohumoral regulation of the activity of internal organs (cardiovascular system, gastrointestinal tract, respiratory organs, endocrine glands). In ICD-10, its code is F45.3, the prevalence of this disease among somatic patients is on average 30% [Antonen E.G., Hyanikainen I.V., 2014; Popov Yu.V., Vid V.D., 2002]. With SDANS, due to dysregulation of vasomotor centers with a tendency to sympathicotonia with insufficient inactivation of catecholamines, cerebral vasospasm of a functional nature develops, which leads to insufficient adaptability and inadequacy of cerebral circulation of a regional nature in violation of tissue systems of lipid peroxidation and dyslipidemia in combination with hypercortisolemia [Luria A.R., 2002]. According to the psychopathological characteristics, premorbidity and mode of behavior in the disease of persons with SDANS can be divided into two types: anxiety-phobic disorders dominate in 65% of patients, pathological bodily sensations (conenesthesiopathy) prevail in the rest [Las E.A., Albantova K.A., 2011].There is no generally accepted classification of SDANS, the most commonly used classification is Belokon N.A. et al. (1987)[Atsel E.A., Gazizov R.M., 2008]:

– primary or secondary (arising on the background of chronic somatic disease) SDANS.

– the leading etiological factor: (residual organic damage to the central nervous system (CNS), neurotic state, puberty, post-traumatic or constitutional autonomic dysfunction, etc.);

– variant SDANS: vagotonic, sympathicotonic, mixed;

– the leading organ localization or the nature of changes in blood pressure

that require correction: biliary dyskinesia, intestines, arterial hyper- or hypotension, functional cardiopathy;

Severity: mild, moderate-severe, severe;

Course: permanent or paroxysmal.

The concepts of somatoform autonomic dysfunction (SAD), as well as neurocirculatory dystonia (NCD), originally arose in connection with the problems of military medicine. The forerunner of SAD was the "irritable heart syndrome" (synonyms "heart neurosis", "soldier's heart", "neuro-circulatory asthenia"), described in the United States in the late nineteenth century in young soldiers [Abdueva F.M., Kamenskaya E.P., 2012].

This manifestation of SDANS, in which changes from the cardiovascular system primarily attract attention, has been called "neurocirculatory dystonia" (NCD) or "neurocirculatory asthenia" (NCA) [Acel E.A., Gazizov R.M., 2008]. The term NCD was introduced by academician N.N. Savitsky. in 1952, fulfilling the social order of the Central Military Medical Directorate of the Ministry of Defense of the USSR, since after the Great Patriotic War, during the medical examination of conscripts, doctors increasingly began to identify people with fluctuations in blood pressure and heart pain and it was necessary to distinguish these changes from organic diseases of the cardiovascular system, primarily from hypertension and ischemic heart diseases [Kulikov A.M., 1999]. Electrophysiological data indicate that pathological anxiety disrupts the autonomic control of heart rate regulation. Anxiety conditions are characterized by activation of the sympathetic nervous system and a change in vagal control with a possible increase in heart rate variability during physical activity, and then outside it [Starostina E.G., 2006; Sloan R.P., Shapiro P.A., Bagiella E. et al., 1999].

In the etiology of SDANS, hereditary and constitutional features of the activity of the autonomic nervous system, the unfavorable course of pregnancy and childbirth

play a role; of the acquired factors, central nervous system damage, psycho-emotional stress, personality traits, mental and physical overstrain, hormonal imbalance, infections, somatic diseases, osteochondrosis of the cervical spine, surgeries, regular alcohol consumption, smoking, overweight, physical inactivity, prolonged computer work, prolonged watching of television programs, etc. are important [Acel E.A., Gazizov R.M., 2008]. The complex socio-psychological situation in the modern world due to negative changes in the human environment, interpersonal relationships, microsocial environment, and an increase in the level of neuroticism exceeding human adaptive capabilities form the risk of vegetative, and subsequently cardiovascular disorders [Antonen E.G., Hyanikainen I.V., 2014].

Complaints in patients with SDANS are always numerous and extremely diverse, they can be divided into two groups:

1. Complaints about any particular organ system. For example, an increase in blood pressure under the influence of emotional factors, an increase in pulse rate, arrhythmia, dizziness, indicates the manifestation of SDANS in the form of complaints about the **cardiovascular system**;

nausea, vomiting, diarrhea (not related to diseases of the gastrointestinal tract or food poisoning, dry mouth, belching, hiccups, bloating, abdominal pain - these may be complaints about the **gastrointestinal tract**;

a feeling of lack of air, a feeling of incomplete inhalation ("dissatisfaction" with inhalation), shortness of breath, cough unrelated to diseases of the respiratory system - these are typical complaints about the system of **respiratory organs**;

on the **urinary system**:frequent urination (unrelated to diseases of the genitourinary system), increased urine formation (more than 2 liters / day), a feeling of a full bladder that does not pass after urination, sudden, irresistible urge to urinate.

2. Complaints indicating chronic damage to the autonomic nervous system (palpitations, sweating, tremor, redness, feeling of heat, anxiety, panic attacks, fear of confined spaces, feeling of fleeting pain, burning, heaviness, tension, feeling of bloating or stretching in any part of the body, etc.).

It was noted that patients with SDANS have a combination of complaints from both groups presented above. In addition, patients tend to behave excessively emotionally, take great care of their health, and often cry. They are often hypochondriacs, prone to self-blame, complain of sleep disorders, a feeling of fear. Such patients are characterized by persistent dermographism. Dermographism is the reaction of the skin vessels to mechanical irritation, which is caused by streaking irritation of the skin with a blunt object. With weak pressure, a white stripe appears (due to spasm of small vessels), with strong pressure — red (with expansion of the capillaries of the skin). If white dermographism occurs with both weak and strong pressure, this means that the activity of the sympathetic nervous system prevails, if red dermographism occurs, the tone of the parasympathetic nervous system prevails. A number of patients have "spotty" redness of the upper half of the chest, especially at the moment of emotional stress, marbling of the skin (symmetrical spotting of the skin of the trunk and limbs, resembling marble, is determined), hyperemia of the skin of the face and neck, hypothermia of the skin, hyperhidrosis and acrocyanosis of the hands.

In patients with SDANS, the so—called non-infectious subfebrility sometimes occurs - an increase in body temperature in the range of 37-37.9 ° C, detected throughout the day (or only at any time of the day) for several weeks, months, less often years. This duration distinguishes subfebrility from the short-term observed subfebrile fever, which occurs in acute diseases. Moreover, such a body temperature is not accompanied by chills, a feeling of heat, does not normalize under the action of antibiotics, and sometimes antipyretic drugs. A "perverted" body temperature is also

characteristic (with SDANS, the temperature under the tongue is equal to the temperature in the armpit or even lower, although normally the temperature under the tongue is 0.2 ° C higher than under the armpit) and temperature asymmetries - different body temperature when measured in different armpits.

An objective examination often reveals: lability of blood pressure with a tendency to hypertension, there is a tendency to tachycardia that occurs spontaneously and inadequately to the situation, respiratory disorders in the form of respiratory arrhythmia (an increase in the number of heart contractions during inhalation, with a decrease in the frequency of its contractions on exhalation), dyspnea, tachypnea, the so-called "dreary sighs" (the need to periodically take deep breaths of air).

During auscultation, non-rough (functional) cardiac sounds are often heard.

During instrumental examination, non-dangerous sinus arrhythmias, mild and rare extrasystoles are most often detected on the ECG, there are no signs of myocardial ischemia, although some minor deviations from the norm are still noted when assessing myocardial nutrition. With bicycle ergometry, there is more often a decrease in physical performance and tolerance of the cardiovascular system to physical activity. If more serious violations are detected, the necessary pharmacological tests, Holter ECG monitoring, etc. are carried out. Echocardiography reveals circulatory disorders, rheovasography and capillaroscopy – a violation of vascular tone, thermography – a violation of thermoregulation of the body.

With SDANS, consultations with a neurologist, psychotherapist, and psychiatrist are important. According to the indications, consultations with an ENT doctor, an optometrist, an endocrinologist are prescribed. Differential diagnosis is required to exclude diseases that have symptoms similar to SDANS. For example, if a patient complains about the work of the heart, ischemic heart disease, hypertension, symptomatic hypertension, systemic heart lesions, rheumocarditis, congenital heart

defects, non-rheumatic carditis, etc. are excluded. Febrile manifestations require the exclusion of infectious and systemic pathology, cancer, and a comprehensive examination with a preliminary diagnosis of "fever of unknown origin". And so on, according to the organ systems, depending on the complaints presented to the patients.

Approximately one third of patients with randomly identified adrenal neoplasms had previously undiagnosed hypertension, presumably interpreted as symptomatic. In most cases, it was transient in nature and did not cause a noticeable deterioration in well-being, however, in a number of cases, its crisis course was noted. As a rule, this course of hypertension was typical for patients with pheochromocytoma or somatoform dysfunction of the autonomic nervous system. The difference between the course of a hypertensive crisis in SDANS and the course of a crisis in pheochromocytoma was that in the first case, headache first appears or increases, numbness and cold of the extremities occur, and only then there is an increase in blood pressure to 150/90 - 180/110 mm Hg, pulse increases to 110-140 beats / min, pain in the area is noted the heart, there is excitement, motor restlessness, sometimes the body temperature rises to 38-39 ° C. In the second case, with pheochromocytoma, the crisis develops suddenly, without precursors. A crisis can be provoked by mechanical irritation of the tumor (palpation of the abdomen), hyperventilation, the use of alcoholic beverages and foods containing tyramine (some varieties of cheese, certain brands of red wines), taking medications with pronounced vasodilating properties (histamine, magnesium sulfate, euphyllin, papaverine, etc.).The clinical picture during the hypertensive crisis in pheochromocytoma is due to the release of a large amount of catecholamines into the blood. Blood pressure rises instantly to 250/130 - 300/150 mmHg. Pallor, acrocyanosis, sweating (sometimes profuse), body trembling, tachycardia, vision and hearing may be impaired. Body temperature rises, leukocytosis and hyperglycemia are detected, sugar can be detected in the urine. There are various rhythm disturbances on the ECG. The crisis may be complicated by a violation of cerebral circulation, pulmonary edema. The

crisis stops suddenly. The exit from the crisis is characterized by a rapid decrease in blood pressure, often accompanied by orthostatic hypotension; tachycardia stops, pallor of the face is replaced by redness, a feeling of warmth in the body appears, patients are extremely exhausted. The duration of the attack varies from a few seconds to several days; the frequency of attacks varies from 1-2 within a few months to 5-10 within an hour. Crises with pheochromocytoma are not accompanied by loss of consciousness. The exceptions are "adrenaline" pheochromocyotomas in young people. In these patients, the crisis begins with pronounced tachycardia ("the heart wants to jump out of the chest"). This is due to the effective effect of adrenaline on the β1 receptors of the heart. The one-time and minute heart rate increases, leading to an increase in blood pressure, which is accompanied by pulsating headaches. At the same time, the total peripheral resistance decreases, which is associated with the effect of adrenaline on the β2 receptors of resistive vessels. Against the background of increased blood pressure, if the patient assumes an upright position, then an orthostatic collapse occurs. This is due to the expansion of resistive vessels under the influence of β2 receptors and the resulting temporary discrepancy in the capacity of the vascular bed to the volume of circulating blood. In the future, the total peripheral resistance, as a rule, increases, apparently due to the stimulation of α1 receptors, the release of vasopressin and angiotensin 2.

When analyzing the nature of hypertension crises in patients with pheochromocytoma, two phases of the crisis can be distinguished. The first phase is conventionally called "sympathetic". Patients consistently develop the following symptoms: pronounced tachycardia with throbbing headaches and pallor of the skin. Then there is a feeling of cooling of the lower extremities, "creeping goosebumps", internal trembling and chills. It is known that catecholamines do not penetrate the hemato-encephalic barrier [Gardner D., Shobek D., 2011], but during this period they act on the receptors of unprotected subcortical centers (hypothalamus, pituitary gland,

epiphysis), an inexplicable feeling of anxiety and fear of death arises. The second phase is "parasympathetic". It is associated with the activation of the parasympathetic centers of the autonomic nervous system and a decrease in the release of catecholamines into the bloodstream, as well as their metabolism. The face turns red, there is profuse sweating, there may be bradycardia. Due to the dilation of the renal vessels (reactive hyperemia), renal blood flow and filtration of primary urine are increased, and polyuria is observed in patients.

We have never seen such frequency during a crisis in patients with randomly identified adrenal neoplasms and SDANS. Symptoms of arousal of the sympathetic and parasympathetic parts of the autonomic nervous system were observed in them, as a rule, simultaneously and randomly. The crisis began with tachycardia, but at the same time there was hyperemia of the skin of the face, which never happened with pheochromocytoma. These patients complained of feelings of anxiety and fear, sometimes turning into a panic state. But unlike patients with pheochromocytoma, they also had a feeling of fear outside the crisis. Crises with SDANS were provoked by stressful situations, being in a confined space, in the subway, in crowded transport, which was not observed in any patient with pheochromocytoma. The fear of confined spaces in these patients often came out on top, or this symptom was easily detected even with a cursory survey of the patient.

Another sign of arousal of the parasympathetic system is polyuria. In all patients with pheochromocytoma, it was observed at the end of the crisis, in patients with SDANS it could be at any stage of its course, and in some of them it occurred long before the development of the crisis and was regarded by us as a harbinger. It should also be noted that when analyzing our material, we were convinced that there are no precursors of a crisis in pheochromocytoma at all. Patients with randomly identified neoplasms and SDANS may have such precursors. Polyuria could be one of them. It is

associated with the formation of a focus of inhibition in the hypothalamic region, the processes that occur in this case lead to suppression of the production of antidiuretic hormone, which, in turn, is the cause of polyuria (hypothalamic crisis). Conversely, when aroused, vasopressin (antidiuretic hormone) production increases dramatically, which leads to temporary urinary retention, which can also be a symptom of a precursor to a crisis. We have never seen such a symptom in patients with pheochromocytoma. It should also be noted that when such precursors appear, patients usually know that a crisis will occur in a few hours.

There are also indications in the literature that patients with pheochromocytoma may have loss of consciousness and seizures [Nikolaev O.V., 1965]. None of our patients had seizures. They were found in 2 patients with hormonally inactive adrenocortical adrenal adenomas with SDANS. According to the literature, they occur if the excitation from the hypothalamic focus spreads to the stem structures. It is worth noting that the occurrence of convulsive syndrome is possible in patients with a combination of epilepsy and pheochromocytoma.

In half of the patients with incidentalomas, nonspecific clinical manifestations were noted (moderate weakness, changes in body weight, etc.). At the same time, some of these manifestations – such as a sharp decrease in body weight, fever of unknown origin, pain syndrome in the lumbar region of varying severity – forced, first of all, to think about the malignant nature of the neoplasm. Usually, pain syndrome was observed with tumor sizes exceeding 6 cm in diameter, and was caused by compression or invasion of nearby tissues and organs. Approximately 20% of the patients had no complaints.

Analyzing the clinical manifestations in patients with hypertension, we came to the conclusion that in these patients they usually have their own differences [Sablin I. V., Krasnov L. M., Fedorov E. A., Rusakov V. F., 2018]. Hypertensive crises in them

were not accompanied by pronounced vegetative symptoms as in patients from the other two groups. The main data is presented in table 11.

Table 11

| Manifestation | The crisis period | SDANS | Pheochromocytoma | Hypertension |
|---|---|---|---|---|
| Factors provoking a crisis | Before the start of the crisis | Stressful situation | Mechanical irritation of the tumor, alcohol intake, etc. | Emotional arousal |
| The presence of "harbingers" of the crisis | Before the start of the crisis | Are | Missing | Missing |
| Tachycardia | Beginning | It is noted | It is noted | It is noted |
| Bradycardia | Beginning | Perhaps it will be noted | Not typical | Not typical |
| Skin discoloration | Beginning | Redness of the face | Pallor of the face | Redness of the face |
| | The end | Pallor may be noted | Redness of the face | Redness of the face |
| Polyuria | Beginning | It can be marked as a harbinger | Not typical | Not typical |
| | The end | Perhaps it will be noted | It is noted | Not typical |
| Diarrhea | During a crisis | Perhaps it will be noted | Not typical | Not typical |
| Anxiety, fear of death | Beyond the crisis | It is noted | Not typical | Not typical |
| | During a crisis | It's getting stronger | It is noted | It may occur |
| Fear of confined spaces | Beyond the crisis | It is noted | Not typical | Not typical |

We did not specifically study the long-term results of surgical treatment of patients in the framework of this work, however, upon further observation of patients,

we noted that the manifestations of SDANS persisted after surgery, which confirms the absence of conditionality of this clinical picture by the presence of an adrenal tumor.

# Chapter 4

## Radiation methods in the differential diagnosis of benign and malignant neoplasms of the adrenal glands

Adrenal gland incidentalomas are detected using radiation research methods, which are usually carried out before determining the hormonal activity of these tumors. Therefore, the data obtained using these methods are of great value for the differential diagnosis of adrenal tumors.

In our study, a retrospective analysis of the results of an ultrasound, MRI and CT examination was carried out in a group of 264 patients, which included patients with adrenal gland incidentalomas. The final diagnoses were established on the basis of postoperative histological and immunohistochemical studies. We compared the results of ultrasound, MRI and CT scans in patients with hormone-inactive adenomas with data obtained in patients with randomly identified pheochromocytomas, myelolipomas, cysts, adrenocortical carcinomas and adrenal metastases.

As already described above, due to the availability, lack of radiation exposure and cost-effectiveness, ultrasound is a screening method in the topical diagnosis of randomly identified adrenal neoplasms. According to the literature, it is possible to assume the malignancy of a neoplasm based on its size. According to research results, among randomly identified adrenal tumors, only about 2% of carcinomas have a size of less than 4 cm in diameter, sizes from 4 cm to 6 cm had 6% of neoplasms, about 90% have a size of more than 6 cm [Mansmann G., Lau J., Balk E., et al., 2004; Schteingart D.E., Doherty G.M., Gauger P.G., et al., 2005; Nawar R, Aron D., 2005].

On ultrasound, an adrenal adenoma is detected as a hypoechoic tumor with a clear, even contour, usually of a homogeneous internal structure, ranging in size from 1 to 8.5 cm. Tumors with no dorsal effects and causing an acoustic shadow effect are found in approximately equal proportions [Soldatova T. V., 2011]. After analyzing the

data obtained from our patients with randomly identified adenoma (n=143) during ultrasound, it turned out that the adenoma was defined as a hypoechoic tumor with clear, even contours, usually of a homogeneous structure. The maximum size of the adenoma was 8.0 x 7.5 cm, the minimum was 1.0 x 0.9 cm, the median size was 3.47±1.52 cm.

The ultrasound diagnostic method has sufficient information to differentiate pheochromocytoma and adrenocarcinoma from adenoma (sensitivity 93% and 100%, respectively) [Vorontsova S. V., 2002]. A pheochromocytoma is defined as a rounded formation with a thickened capsule. The inner and outer contours of the capsule are smooth and clear. The echogenicity of the tumor is reduced compared to the liver parenchyma. The structure can be very variable: homo- or heterogeneous due to hemorrhages, necrosis and cysts [Farrugia F.A., Charalampopoulos A., 2019]. Moreover, the larger the tumor, the more likely hemorrhages and necrosis are [Gilyazutdinov I.A., Khasanov R.Sh., Kuryanov D.P., 2007]. An important distinguishing feature of pheochromocytoma is the presence of blood flow in the tumor, which has both perinodullary and intranodullary character [Gerdemann C., Deeg K.H., 2013]. A randomly detected pheochromocytoma (n=17) on ultrasound was detected by us as a hypoechoic formation of an oval or rounded shape with clear contours. In tumors whose size exceeded 4 cm, the internal structure was heterogeneous, with anechoic sites (decay zones) and hyperechoic inclusions with a clear acoustic shadow (calcinates).

Adrenocortical carcinomas in ultrasound images have inhomogenously reduced echogenicity or differ in alternating zones of increased and decreased echogenicity [Panchani R., Goyal A., Varma T. et al., 2012]. Hormone-inactive cancer of the adrenal cortex usually has a large size, irregular shape, with uneven contours, heterogeneous structure [Papierska L., Cichocki A., Sankowski A.J. et al., 2013], peri- and (or) intranodular blood flow with color and energy Doppler mapping [Smolentseva N.V.,

2004]. The tissue of the affected adrenal gland is not detected on ultrasound. As a rule, difficulties in the topical (mainly ultrasound) diagnosis of primary tumors arise in cases where their size exceeds 12 cm [Fassnacht M., Libй R., Kroiss M, et al., 2011]. At the same time, it is difficult to determine the type of tumor, the possibility of its germination into surrounding organs and tissues, the degree of invasion, metastatic lesion of retroperitoneal and paraaortic lymph nodes. It is possible to establish organ affiliation in 75% of observations of such neoplasms [Remnyakov V.V., 2005].

Adrenocortical carcinomas (n=23) in 18 patients were rounded or oval-shaped formations with smooth contours and a homogeneous structure. In the form of irregularly shaped formations with uneven bumpy contours and heterogeneous structure, they were detected in 5 patients. The size of the tumors ranged from 5.0 x 4.6 cm to 20.2 x 14.9 cm, the median size was 6.87=3.48 cm.

On ultrasound, myelolipoma is revealed as a homogeneous hyperechoic formation of a regular rounded or oval shape, with clear even contours [Fedorov E. A., Sablin I. V., 2014; Nabi J., Rafiq D., Authoy F.N., Sofi G.N., 2013]. Myelolipomas (n=10) were also determined by ultrasound as hyperechoic neoplasms of a rounded shape with clear contours. The presence of predominant fat in the formation of the adrenal gland is pathognomonic for myelolipoma. MRI of the abdominal cavity, compared with ultrasound, is more effective in diagnosing these tumors. Due to the difference in the intensity of T1 and T2 signals, it is possible to differentiate adrenal adenoma from myelolipoma. MRI shows a myelolipoma-specific picture of a fatty tumor. In this case, the pulse sequence of IR (with fat suppression) in the T2 mode of weighted images can be considered diagnostically significant. The loss of the signal from myelolipoma is revealed in comparison with the standard image in T2 mode (FAST SE pulse sequence). This feature of myelolipoma is a characteristic feature that distinguishes it from adrenocortical neoplasia, which "loses" signal intensity during an

MR study in the GE (out of phase) pulse sequence in T1 weighted images (compared with T1 weighted images and the SE pulse sequence) and is well visualized on T2 weighted images in the IR pulse sequence [Fedorov E. A., Sablin I. V., 2014].

The radiation pattern of cysts is most characteristically manifested in MRI and ultrasound, which are the methods of choice in the diagnosis of liquid-containing formations. On ultrasound, cysts look like anechoic volumetric formations with the presence of a capsule, with smooth, clear contours, accompanied by an acoustic effect of "dorsal amplification" [Yemelyanov S.I., Bogdanov D. Yu., 2012]. The adrenal cyst (n=26) on ultrasound had the appearance of a rounded anechoic formation with clear, even contours, with the presence of a capsule and the acoustic effect of "dorsal amplification". In 4 cases, the presence of calcifications in the cyst wall was noted.

Among the currently most common radiation research methods, we preferred computed tomography, due to the fact that this method has more informative value in the study of adrenal neoplasms than MRI [Lafemina J., Brennan M.F., 2012; Arablinsky A.V., Sidorova Yu.V., 2011; Grumbach M.M., Biller B.M., Braunstein G.D., et al., 2003]. MRI was performed on 14 patients (as a rule, during this study, accidental detection of an incident tumor occurred), who subsequently underwent CT with intravenous contrast in order to assess the densitometric characteristics of the tumor in different phases of the study.

The principle of using CT for the differential diagnosis of neoplasms is based on determining the density of substances that make up their composition. The more lipids are included in the tumor, the lower its densitometric density will be. Thus, in lipid-rich tissues, which are characteristic of benign adrenal cortex adenomas [Arnaldi G., Boscaro M., 2012], it is quite low (less than 10-15 units) [Korivi B. R., Else yes K. M., 2013; Sahdev A. et al., 2010]. However, up to 25% of benign adenomas may not have such a low native density [Sundin A., 2012].

According to many modern authors, the small size (less than 4 cm), a clear, even contour, plus a uniform distribution of low density (less than 10 HU), characterize, as a rule, benign neoplasms [Wong K.K. et al., 2012; Sachdev A. et al., 2010; Young W.F. et al., 2007]. Large tumors of the adrenal glands (more than 4 cm) that do not have classical signs of goodness are more likely to be malignant [Korivi B.R., Elsayes K.M., 2013; Lee M.J. et al., 1991]. Another feature of malignant neoplasms is their rapid growth over a short period of time. On the other hand, tumors that are stable for a long period of time are more likely to be benign. Fuzzy and uneven contours of the formation are not reliable signs of malignancy [Sahdev A. et al., 2010].

Signs of pheochromocytoma according to computed tomography, described in the literature — the presence of cystic cavities, calcification, fibrosis, necrosis sites, internal hemorrhages. Pheochromocytoma often looks like a tumor with a densitometric density of up to 30-40 HU with clear contours with areas of reduced density [Farrugia F.A., Charalampopoulos A., 2019].

According to the literature, adrenocortical carcinomas, when examined by computed tomography without intravenous contrast, demonstrate a higher density than adenomas, with a specificity for differentiating adenoma from carcinoma of 100% and 96.9% using a threshold of 10 and 20 HU, respectively [Young W.F.Jr., 2011; Boland G.W.L., Blake M.A., Hahn P.F. et al., 2008; Hamrahian A.H., Ioachimescu A.G., Remer E.M. et al., 2005]. The characteristic features of carcinoma of the adrenal cortex, when visualized using CT, are: large size (>6 cm), a well-defined contour with thin pronounced edges, and the appearance of the so-called "low attenuation stellate" in the center of the tumor in images obtained with enhanced CT. Tumor germination into the inferior vena cava (IVC) with the formation of a blood clot can be detected on CT in about 15% of patients [Boland G.W.L., Blake M.A., Hahn P.F. et al., 2008].

As is commonly believed, the presence of fuzzy contours is often the main sign of the malignant nature of the formation. But this is not always the case. Also, the presence of clearly bounded contours is not necessarily a sign of the goodness of the process [Zhang H.M., Perrier N.D., Grubbs E.G. et al., 2012].

The presence of calcifications, weakening or absence of contrast in the central region, have also been proposed as typical signs of adrenocortical carcinoma [Fishman E.K., Deutch B.M., Hartman D.S. et al., 1987; Dunnick N.R., 1990; Ribeiro J., Ribeiro R.C., Fletcher B.D., 2000]. As shown in their study by Zhang H.M. et al. [Zhang H.M., Perrier N.D., Grubbs E.G. et al., 2012], dotted, spotted or irregularly shaped nodular calcifications were present in 37%, and a low level of contrast in the central zone was determined in all tumors. The stellate pattern in the central region was found in more than half of the tumors [Zhang H.M., Perrier N.D., Grubbs E.G. et al., 2012]. The same picture was described by Ribeiro et al. [Ribeiro J., Ribeiro R.C., Fletcher B.D., 2000] as a pattern resembling a "central scar" in primary liver tumors. However, as noted by Fishman et al. [Fishman E.K., Deutch B.M., Hartman D.S. et al., 1987] similar manifestations are also characteristic of pheochromocytomas, large metastases, and even adenomas, and therefore cannot be used as a hallmark of adrenocortical cancer.

When performing CT scans with intravenous "amplification" and measuring the densitometric density of formation at different phases of contrast agent excretion, data were obtained indicating that adrenal cortex adenomas rapidly decrease density (10 minutes after contrast administration, the absolute percentage of leaching is more than 50), while other adrenal formations tend to contrast agent delay. The measurement of this indicator has a diagnostic value close to absolute values in the differential diagnosis of adenomas, on the one hand, from pheochromocytoma, carcinoma and metastases, on the other [Sablin I. V., Rusakov V. F., Fedorov E. A. et al., 2015; Melnichenko G. A. et al., 2014].

Two methods have been developed to calculate this rate: determination of the absolute percentage of contrast agent leaching (APCW) and the relative percentage of contrast agent leaching (RPCW) [Korivi B.R., Elsayes K.M., 2013].

To determine the APCW, the densitometric density of the formation is first measured in a study without contrast (native density), then at 60 seconds after contrast administration, and 10-15 minutes after drug administration (delayed phase).

The absolute percentage of washout is calculated using the formula:

APCW = [ (Density of formation at 60 seconds after contrast enhancement, HU - Density of formation in the delayed phase, HU) / (Density of formation at 60 seconds after contrast enhancement, HU is the density of formation before contrast, HU) ] Ч 100.

According to the literature, for the diagnosis of adrenal adenoma with a ten-minute delay, the APCW value ≥52% has 100% sensitivity and 98% specificity [Caoili E.M. et al., 2002]. The method using a delay of 15 minutes, with an APCW value of ≥60%, has a sensitivity of about 87% and a specificity of 94% [Low G., Dhliwayo H., Lomas D.J., 2012; Dunnick N.R., Korobkin M., 2002; Korobkin M. et al., 1998].

Parameters reflecting the rate of contrast washout have their diagnostic value for the detection of adrenocarcinomas only in combination with other signs of malignancy, which make it possible to differentiate malignant tumors from other formations [Zhang H.M., et al., 2012].

This is explained by the fact that adenomas remove contrast faster than other adrenal tumors, including malignant ones, which take longer to remove the contrast agent [Low G., Dhliwayo H., Lomas D.J., 2012]. A number of authors draw attention to the fact that the calculation of APCW requires measuring the densitometric density of education without contrast, which in everyday practice does not always work [Korivi

B.R., Elsayes K.M., 2013]. In such patients, it is possible to calculate the relative percentage of washout using the following formula:

RPCW = [( Density of formation at 60 seconds after contrast enhancement, HU - Density of formation in the delayed phase, HU ) / (Density of formation at 60 seconds after contrast enhancement, HU)] × 100.

It has been proven that RPCW ≥50% when using the 10-minute delay parameter is characteristic of adrenal adenoma. It is believed that the sensitivity of this method is 98%, the sensitivity is 100% [Pina S.S. et al., 2000]. When using data obtained 15 minutes after intravenous enhancement, adenoma is characterized by an RPCW value of ≥40%. This technique measures efficiency from 96% to 100% [Danik N.R., Korobkin M., 2002; Low G., Dliwayo H., Lomas D.J., 2012].

In order to differentiate adenomas from other benign tumors, a four-phase CT scan was proposed. During the execution of one study, measurements are performed in the contrast-free, arterial, venous phases and measurement of the density of formation with a delay of 5 minutes after administration of the drug. A comparative analysis of calculations of absolute and relative percentages of washout showed the diagnostic accuracy of the method at 97.1%. RPCW is the most accurate diagnostic indicator of the contrast washout rate. There is clear information that as a method of visualization of translators, they are completely new and experienced, he can use in his activities from abroad a long scanning period of 5 minutes, the average scanning volume is from 10 to 15 minutes [Foti G. et al., 2012].

In our study, the main criteria for evaluating computed tomograms were: the size of the identified formation, its shape, contours, structure, the presence of a capsule, densitometric density in various phases of the study, the presence of inclusions and enlarged lymph nodes, and the relationship to other organs. In 117 patients (77 adenomas, 23 ACC and 17 pheochromocytomas), quantitative densitometric parameters

were evaluated with four-phase CT: in the native phase, with intravenous "enhancement" by radiopaque agent with imaging in the arterial, venous and delayed (after 10 minutes) phases. The results of a comparative analysis of computed tomograms of patients with diagnosed clear cell adrenocortical adenomas, pheochromocytomas and carcinomas are presented in Table 12.

Table 12

The results of the comparative analysis of computed tomography

| **CT Criteria** | | **Adenoma** | **Carcinoma** | **Pheochromocytoma** |
|---|---|---|---|---|
| Number of observations | | 77 | 23 | 17 |
| Location | right | 37 (48,05%) | 7 (30,43%) | 6 (35,29%) |
| | left | 39 (50,65%) | 15 (65,22%) | 11(64,71%) |
| | bilateral | 1 (1,3%) | 1 (4,35%) | 0 |
| Minimum size, cm | | 1,0 x 0,9 | 5,0 x 4,6 | 1,6 x 1,0 |
| Maximum size, cm | | 8,0 x 7,5 | 20,2 x 14,9 | 4,8 x 4,3 |
| Median size, cm | | 3,47±1,52 | 6,87±3,48 | 3,36±0,87 |
| Form | oval | 38; (49,35%) | 9; (39,13%) | 7 (41,18%) |
| | rounded | 31; (40,26%) | 9; (39,13%) | 10 (58,82%) |
| | irregular, bumpy | 8; (10,39%) | 5; (21,74%) | 0 |
| Contours | clear | 77; (100%) | 18; (78,26%) | 17 (100%) |
| | fuzzy | 0 | 5; (21,74%) | 0 |
| | smooth | 74; (96,1%) | 18; (78,26%) | 17 (100%) |

| | | | | |
|---|---|---|---|---|
| | uneven | 3; (3,9%) | 5; (21,74%) | 0 |
| Capsule | determine | 5; (6,5%) | 3; (13,04%) | 17 (100%) |
| | not defined | 72; (93,5%) | 20; (86,96%) | 0 |
| Presence of inclusions | necrosis | 2; (2,6%) | 4; (17,39%) | 6 (35,29%) |
| | calcinates | 5; (6,49%) | 3; (13,04%) | 0 |
| Minimum densitometric density in the native phase, HU | | -29-(-17) | +13-(+17) | +17 |
| Maximum densitometric density in the native phase, HU | | +35 | +37- (+45) | +47 |
| Median densitometric density in the native phase, HU | | -0,39±13,28 | +27,32±8,6 | +31,82±8,64 |
| Maximum increase in densitometric density | Arterial phase | 66; (85,71%) | 11; (47,82%) | 17 (100%) |
| | Venous phase | 10; (12,99%) | 6; (26,09%) | 0 |
| | Delayed phase | 1 (1,3%) | 6; (26,09%) | 0 |

The minimum densitometric density of the adenoma (Fig. 1) in the native phase of the study was - 29-(-17) HU, the maximum density observed in adenoma was +35 HU, the median value is -0.39±13.28 HU.

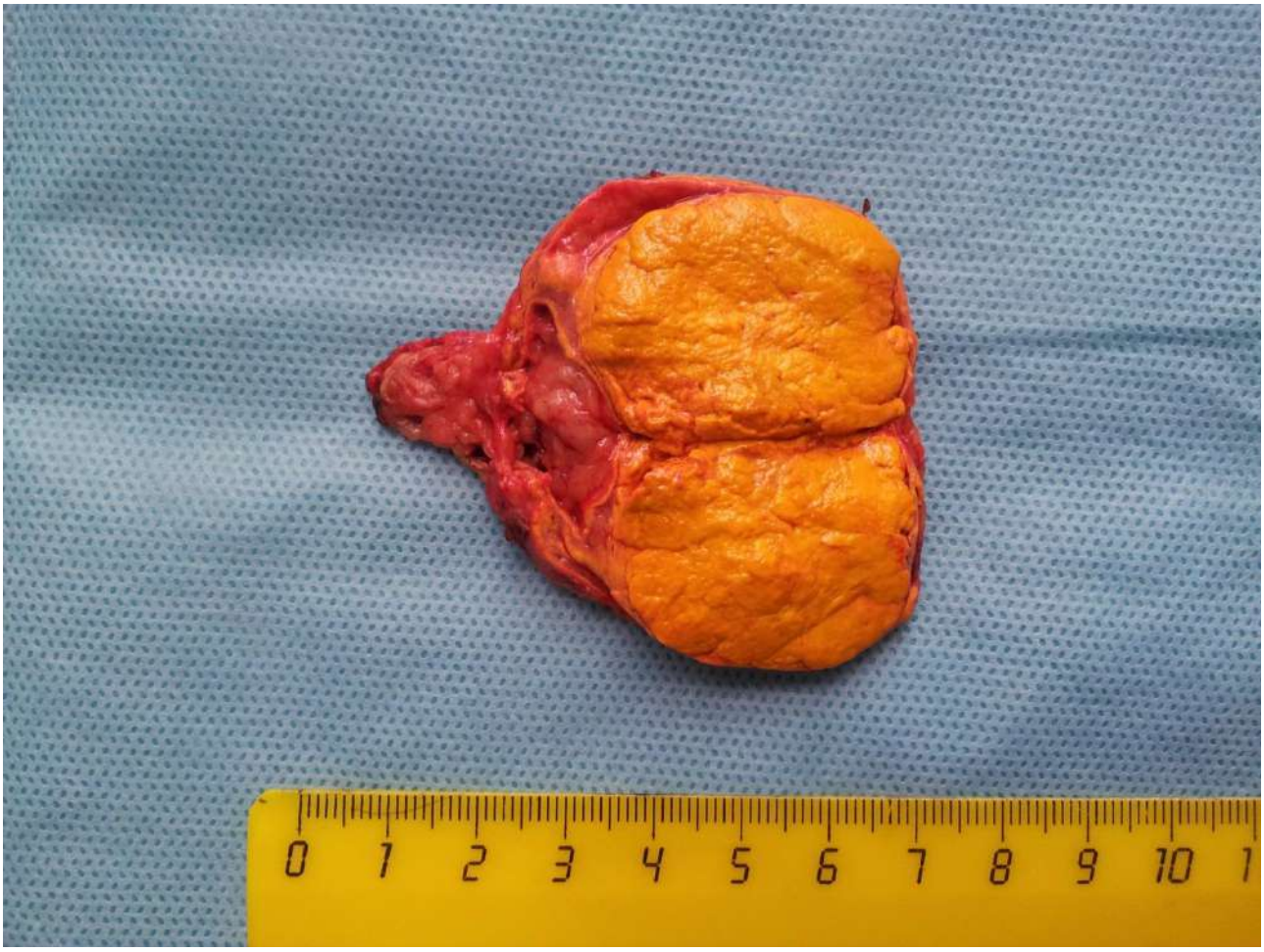


Fig. 1 Clear cell adrenocortical adenoma. Macropreparation.

Adenocarcinomas (Fig. 2) were characterized by an increased native density - the carcinoma with the lowest densitometric density had a value of +13-(+17) HU, with the highest densitometric density - +37-(+45) HU. The median value of densitometric density in the native phase in adrenocortical cancer was +27.32±8.6 HU. It is worth noting that 18 (78.26%) adenocarcinomas had a heterogeneous structure, but 5 (21.74%) ACC were found in our study which , according to the CT description, were homogeneous.

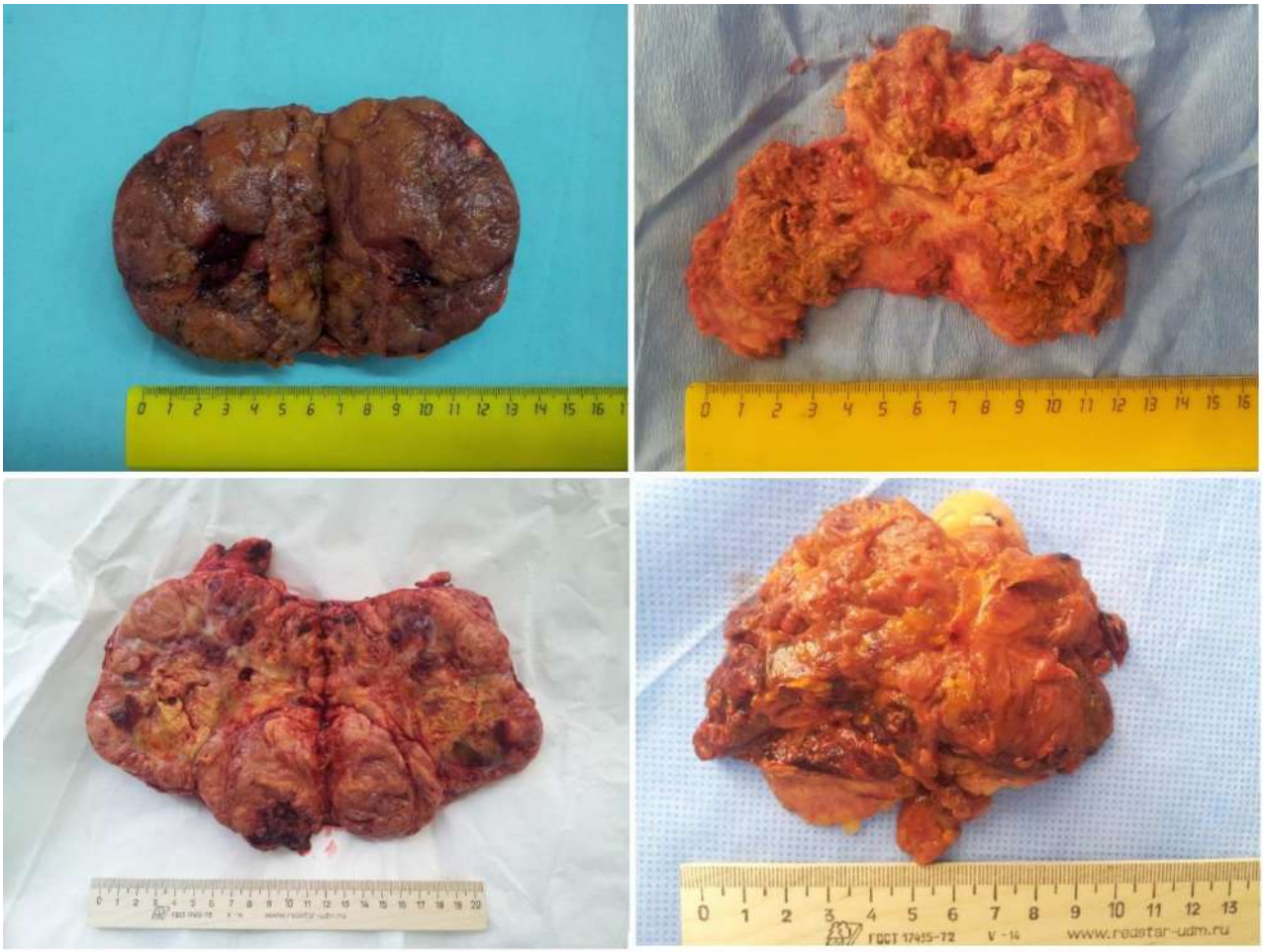

Fig. 2 Adrenocortical carcinomas. Macropreparations.

It was noted that pheochromocytomas also had a fairly high native density - from +17 HU in the tumor with the lowest value, to +47 HU in the formation with the highest densitometric density, with a median value of +31.82±8.64 HU. The size of the randomly detected pheochromocytes based on CT data was 3.36±0.87 cm.

Based on this, it can be concluded that adrenal carcinomas have a higher densitometric density than adenomas, however, it is important to remember that sometimes there may be both heterogeneous adenomas with increased density and adrenocortical carcinomas with a homogeneous structure of small size and low density. When a formation with a high native density is detected on CT, there is a need for differential diagnosis of cancer of the cortical layer and, above all, pheochromocytoma.

CT with intravenous contrast was performed in all patients with randomly diagnosed pheochromocytoma, adrenocortical cancer and 77 patients with adrenal adenoma (53.85% of the total number of patients with adrenocortical adenoma). During this study, carcinomas in 20 cases (86.96%) nonuniformly accumulated contrast agent (Fig. 3). In the venous phase, 26.09% adrenocarcinomas maximized their density (Fig. 4). Also, 26.09% increased their density in the delayed phase (10 minutes after intravenous contrast injection), which indicates a slow leaching of the contrast agent from these tumors.

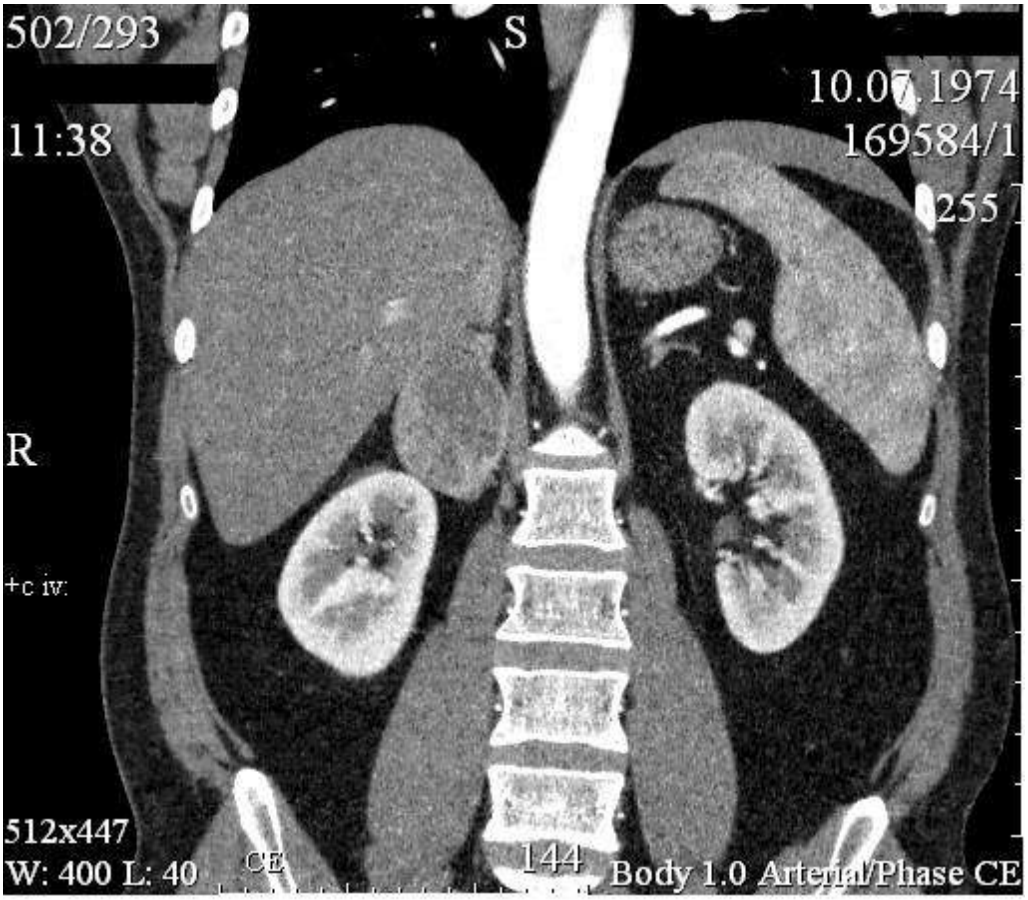


Fig. 3 Carcinoma of the right adrenal gland. Computed tomography, arterial phase of the study.

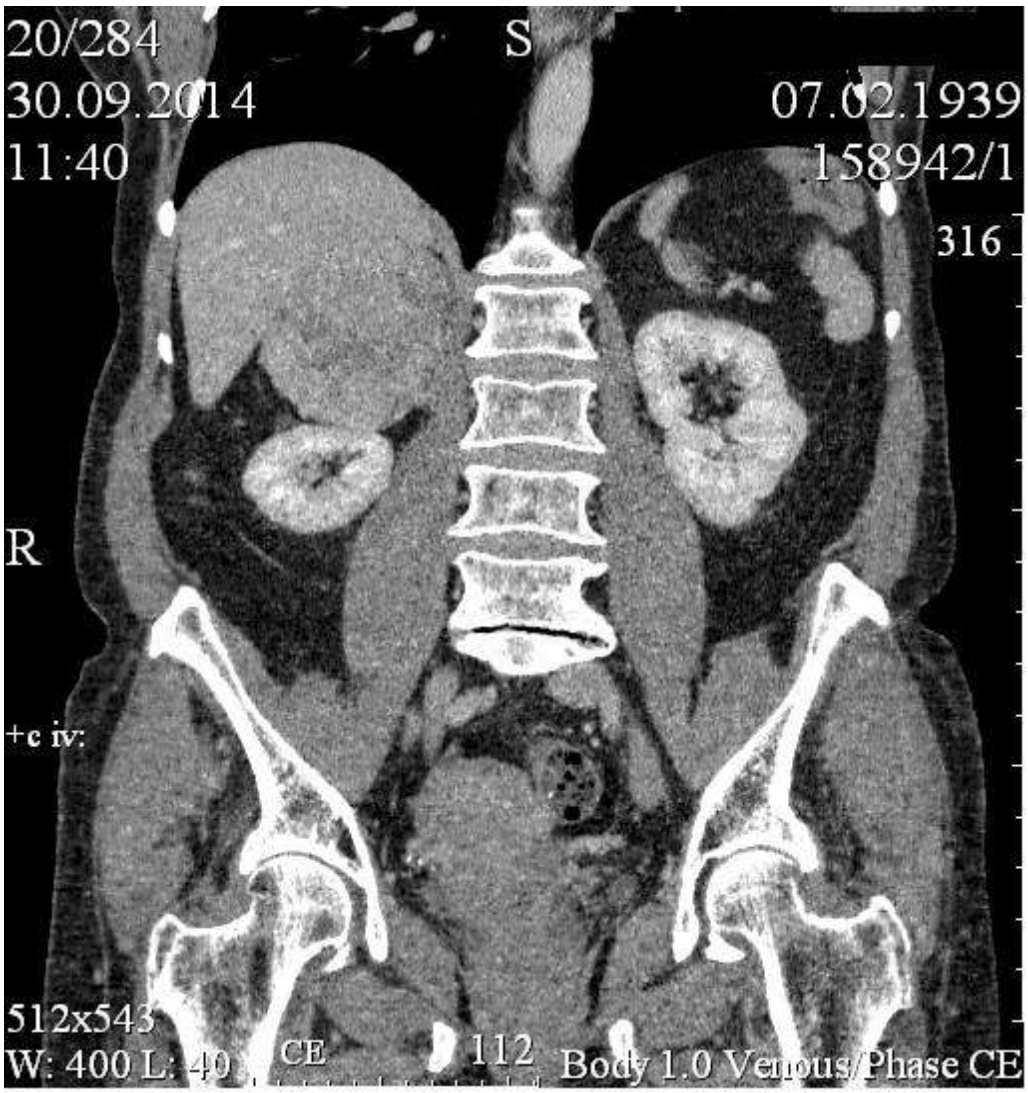


Fig. 4 Carcinoma of the right adrenal gland. Computed tomography, venous phase of the study.

A pronounced accumulation of contrast agent in the central part of the tumor to a lesser extent than in the periphery was noted in 4 (17.39%) carcinomas due to the presence of a decay zone. Inclusions in the stroma in the form of calcinates and necrosis were detected in 7 (30.43%) tumors. Signs of germination into neighboring organs (kidney, vascular pedicle of the kidney, inferior vena cava, pancreas or soft tissues of the lumbar region) were determined in three (13.04%) cases; displacement, compression or deformation of neighboring organs by a tumor - in 10 (43.48%).

Small pheochromocytomas (less than 3 cm in diameter) (n=6), all were homogeneous in structure. Larger tumors were characterized by heterogeneous density due to the presence of necrosis sites and microcalcinates. Nevertheless, all pheochromocytomas, without exception, were characterized by a pronounced accumulation of contrast agent in the arterial phase of the study — the difference between the native density and the density determined in the arterial phase of the study was 105.81±61.69 HU.

The structure of adrenocortical adenomas was homogeneous in 70.45% (Fig. 5), heterogeneous in 29.55%. It was noted that in 57.14% (44 cases), the accumulation of contrast agent was not intense, in 28.57% (22) — intense and in 14.29% (11) — uneven. In the delayed phase, the density of formations decreased by 63.63% (49) compared to their native density, did not change - 32.47% (25), increased - 3.9% (3). This indicates that adrenal adenomas, as a rule, remove the contrast agent well, but among them there are such neoplasms in which excretion is slow. A possible cause of this phenomenon may be a spasm of powerful smooth muscle bundles in the wall of the central vein of the adrenal gland, which, contracting in length, thicken and at the same time approach each other, protrude into the lumen of the vein and narrow it [Sapin M. R., 1961].

In addition to calcifications and necrosis, areas of increased density were also identified in the structure of two tumors (2.6%), thus inclusions in the stroma of formations were determined in 9 adenomas (11.69%).

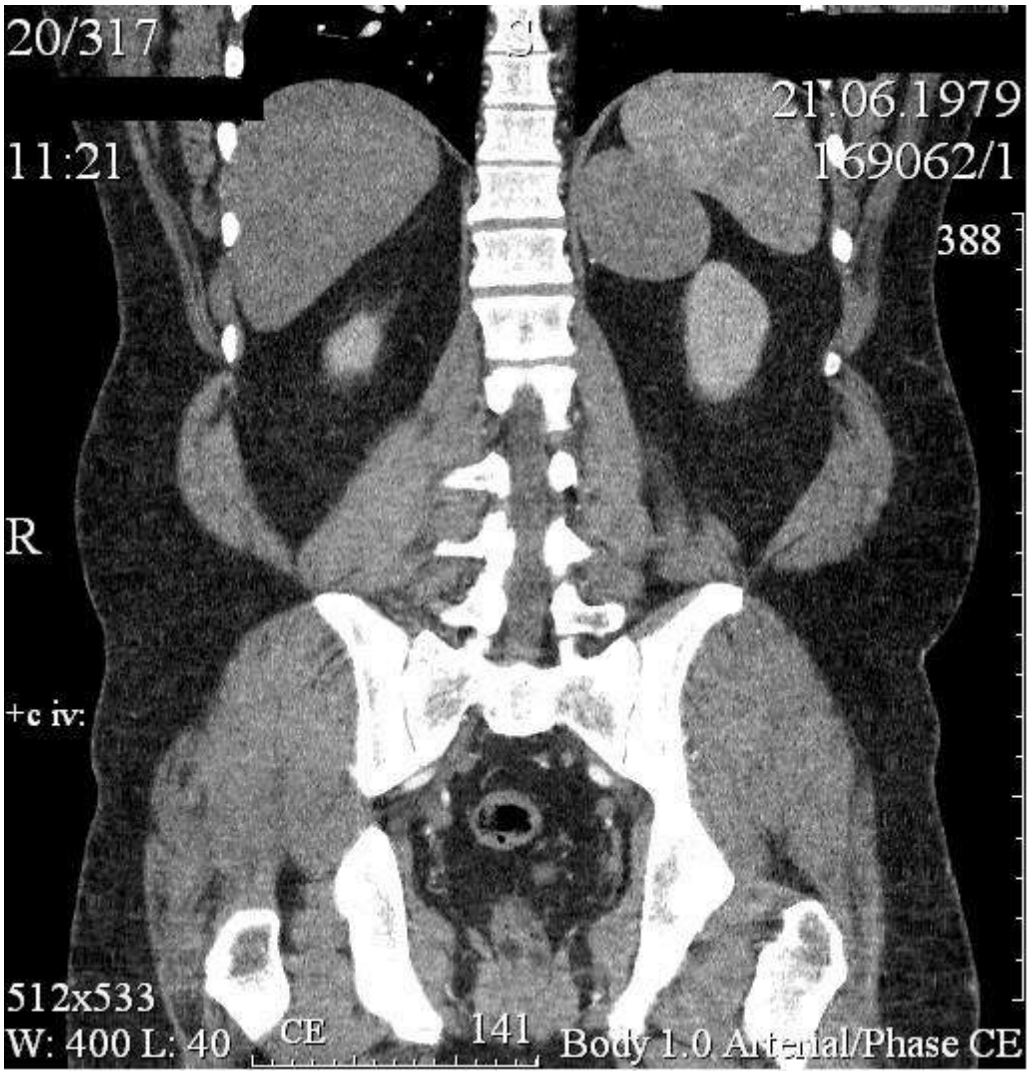


Fig. 5 Adenoma of the left adrenal gland. Computed tomography, arterial phase of the study.

In the course of our work, it was found that formations of small size (up to 4 cm) and having a low densitometric density (up to +10 HU), subsequently, during a histological examination of adenomas that turned out to be, during CT scan in the venous phase, the course of the central vein of the adrenal gland was clearly visualized in the tumor stroma (Fig. 6).

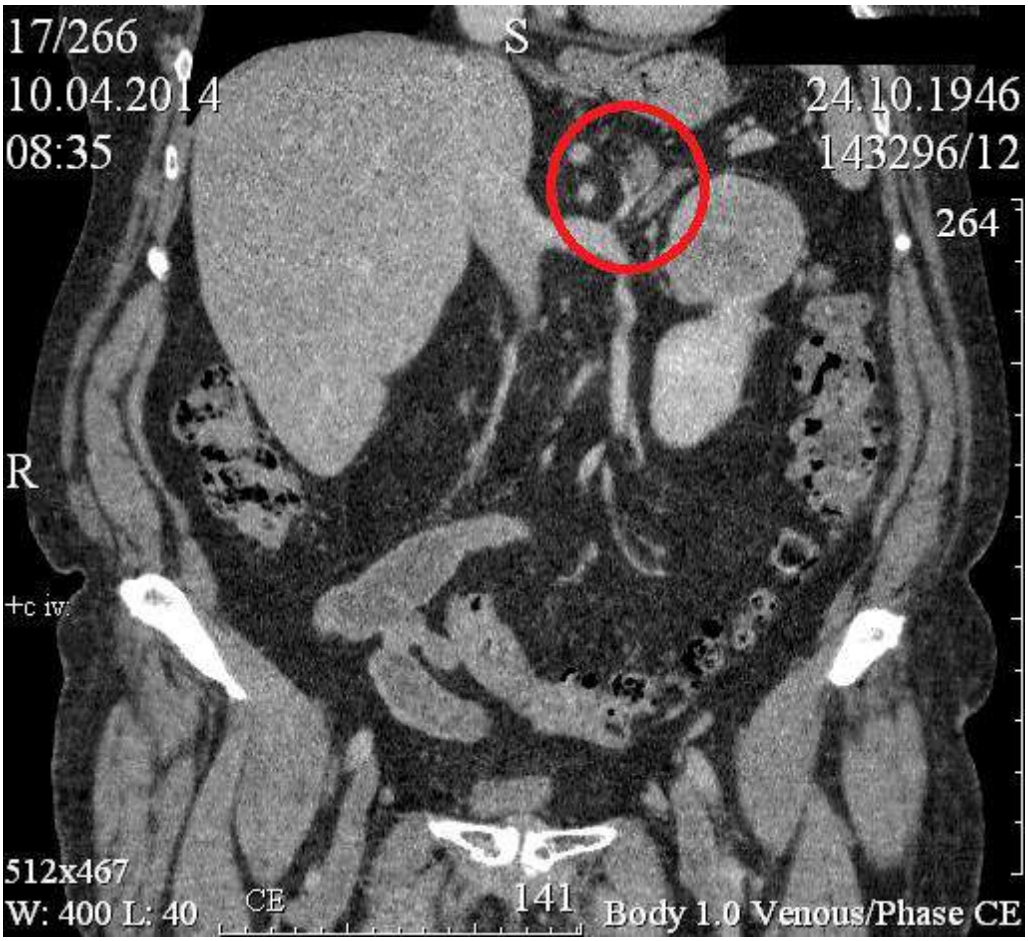


Fig. 6 Adenoma of the left adrenal gland, neoplasm of the left kidney. Computed tomography, venous phase of the study.

According to modern authors, the possibility of visualizing the course of the central vein in the thickness of the adrenal stroma using CT with contrast enhancement is a new distinctive feature that allows differentiating adenoma from other neoplasms of this organ [Vergara Diaz C. L., Pernas J. C., Hernandez D. et al., 2013; Terzolo M., Stigliano A., Chiodini I. et al., 2011; Blake M.A., Cronin C.G., Boland G.W., 2010; Young W.F., 2007]. The authors showed that if during the venous phase of the study it is possible to trace the course of the central vein in the thickness of the neoplasm, then this tumor with a probability close to 100% will turn out to be a benign adenoma. The authors did not identify such a feature in adenocarcinomas, metastases, lymphomas, pheochromocytomas, hemangiomas and myelolipomas.

It is worth noting that during our study, adrenocortical carcinoma was detected (Fig. 7) in which, during CT with contrast, the central vein of the adrenal gland was clearly visualized inside the tumor stroma (Fig. 8). Based on this, it can be concluded that the determination of the central vein of the adrenal gland inside the tumor is not a 100% criterion for the diagnosis of adenomas the adrenal gland.

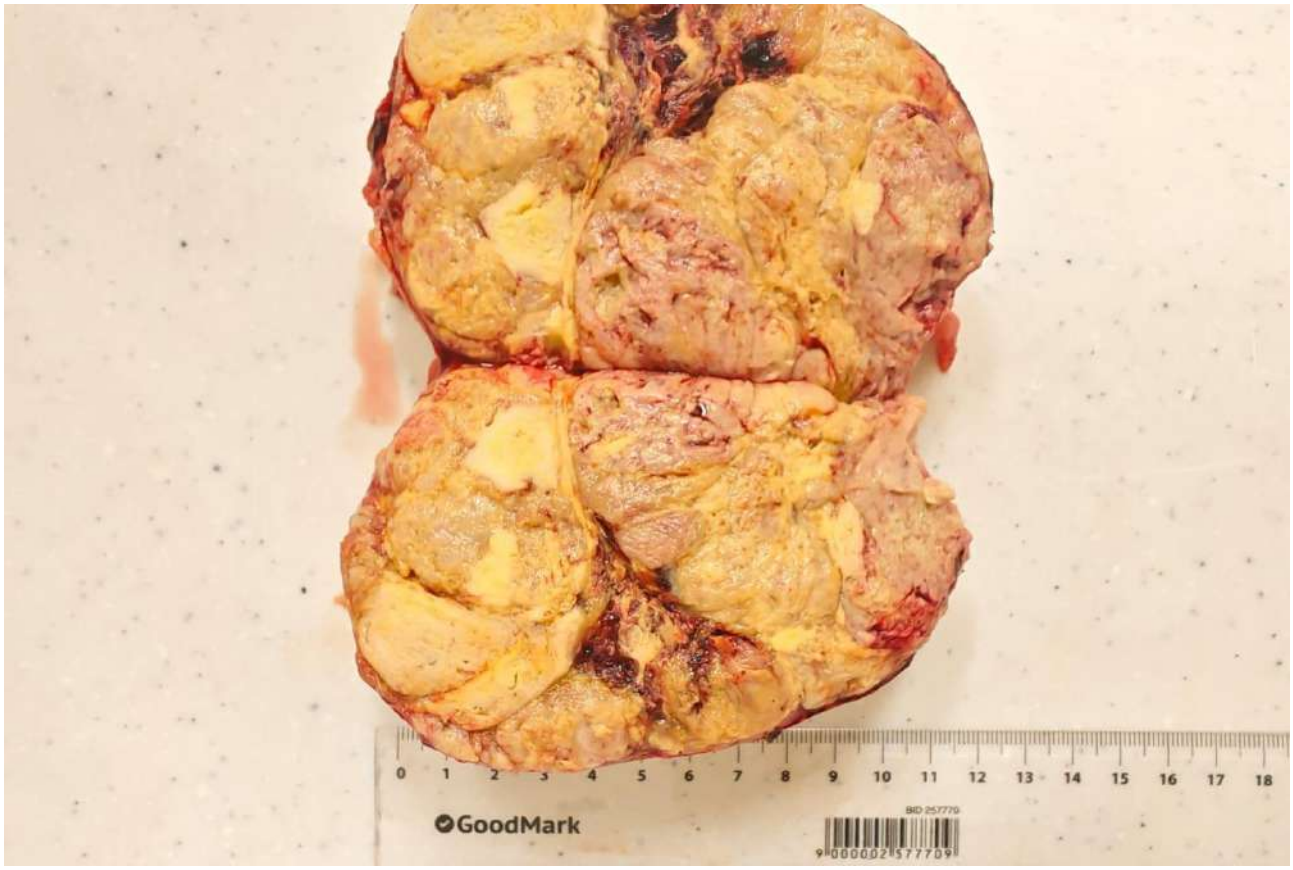


Fig. 7 Adrenocortical carcinoma of the left adrenal gland. Macropreparation.

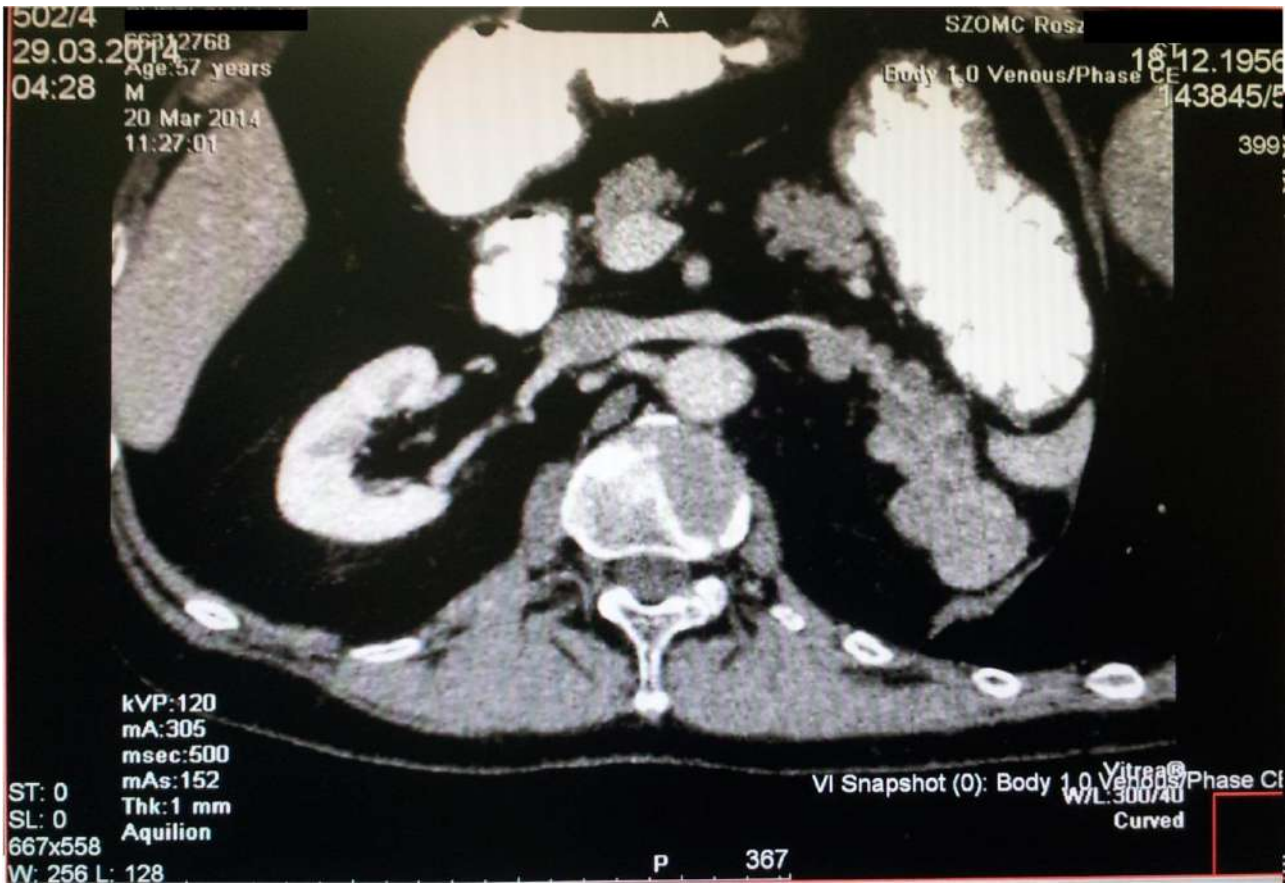


Figure 8 Adrenocortical carcinoma of the left adrenal gland. Computed tomography, venous phase of the study.

In adenomas, signs of germination into neighboring organs, their compression, displacement or deformation were not detected in any of the cases considered. In only one case (1.3%), multiple lymph nodes of the paraaortic and paracaval groups, enlarged in size up to 1.5 cm, and lymph nodes of the small pelvis were visualized.

As a feature of the location of adenomas, we have identified the fact that they can arise both from the body of the adrenal gland and from both of its legs, but these neoplasms are located, as a rule, above the upper pole of the kidney and do not shift to its gates.

According to our study, adenomas, as a rule, were small in size - on average 3.5 cm, adenocarcinomas were most often a large tumor, which was due to the rate of its

growth. Therefore, it must be remembered that an identified adrenal neoplasm larger than 6 cm is more likely to turn out to be a malignant tumor.

In patients with adrenal adenoma, CT with intravenous contrast showed that the accumulation of contrast agent was detected in 100% of adenomas, most often it occurred in the arterial phase (85.71%) and was non-intensive in 57.14%. During the arterial phase of the study, the densitometric density increased by an average of 47 HU. compared with the native phase, 10 minutes after intravenous administration of the contrast agent, the density of formation decreased by 64.29%. These data suggest that adrenocortical adenomas, as a rule, do not intensively accumulate contrast agent, more often this occurs in the arterial phase (moreover, in this phase of the study, adenomas accumulate contrast more intensively than carcinomas) and have a higher rate of contrast agent excretion compared with adrenal cancer. Adrenocarcinomas, in turn, in most cases accumulate contrast heterogeneously and remove it more slowly, which is most likely due to their histological structure.

Adrenocortical carcinomas had an oval or rounded shape, differed in clear, even (78.26%) contours, capsules were not detected in 86.96%, necrosis sites were detected in 17.39% in the central part of the tumor, and small, single calcinates in 13.04%. Thus, 30.43% of tumors had inclusions in the stroma. Signs of germination into neighboring organs were detected in 13.04%; displacement, compression or deformation of neighboring organs by the tumor was detected in 43.48%. Based on this, it can be concluded that these neoplasms are characterized by rapid invasive growth, and tumor growth occurs along the location of the adrenal blood vessels, mainly the central vein.

Adrenal adenomas, as a rule, had an oval or rounded shape and a homogeneous structure with clear (100%) and even (96.1%) contours (Fig. 5). In 93.5%, the tumor did not have a CT-detectable capsule. Calcinates, areas of increased and decreased density in the stroma of formations were determined in 11.69%. We have not detected signs of

tumor germination into neighboring organs, their compression, displacement or deformation, which is due to the small size and slow growth of adenomas.

Pheochromocytoma on CT images is usually characterized by a soft tissue density, 25-70 units. H, clear, smooth contours, rounded shape. The size of the tumor is relatively large: usually more than 40 mm. The structure at large sizes can be heterogeneous, and unlike an adenoma, with areas of necrosis, hemorrhages. Sometimes cystic cavities are found, as well as large and small calcinates [Li J., Yang C.H., 2014]. At the same time, approximately 11% of tumors have a homogeneous structure similar to the structure of the vast majority of adrenal adenomas [Krasnov L.M., 2005]. Sometimes a pheochromocytoma may have a capsule with clear, even contours [Akberov R.F. et al., 2002; Karmazanovsky G.G., Fedorov V.D., 2002].

During our study, it was found that pheochromocytomas occur in the medial pedicle and the body of the adrenal gland (Fig. 9), which may contribute to the displacement of the tumor during its growth to the kidney gate. Analyzing CT images, a feature of the location of pheochromocytes in the retroperitoneal space was also revealed. First of all, this concerned those tumors whose size exceeded 4 cm. Such neoplasms, as a rule, were located near the vascular pedicle of the kidney, thus shifting anteriorly and medially from its upper pole (Fig. 10, 11). This feature of the location, which distinguishes pheochromocytomas from other formations of the adrenal gland, can be useful in the differential diagnosis of neoplasms of this organ.

Hypervascularity, which is not typical for adenomas and aldosteromas and is less pronounced in metastatic lesions of the adrenal glands, makes it possible to diagnose pheochromocytomas with high confidence using CT and MRI. Therefore, the study with intravenous administration of a contrast agent is of great diagnostic importance. When contrasting, pheochromocytoma, unlike other adrenal tumors, actively accumulates contrast agent due to sinusoids in the tumor structure during the

arterial phase of the study [Arablinsky A.V., Sidorova Yu.V., 2011]. Necrosis zones, if present, do not accumulate contrast. CT sensitivity in the detection of pheochromocytomas is high and is 100% [Reginelli A., Di Grazia G., Io A. et al., 2014].

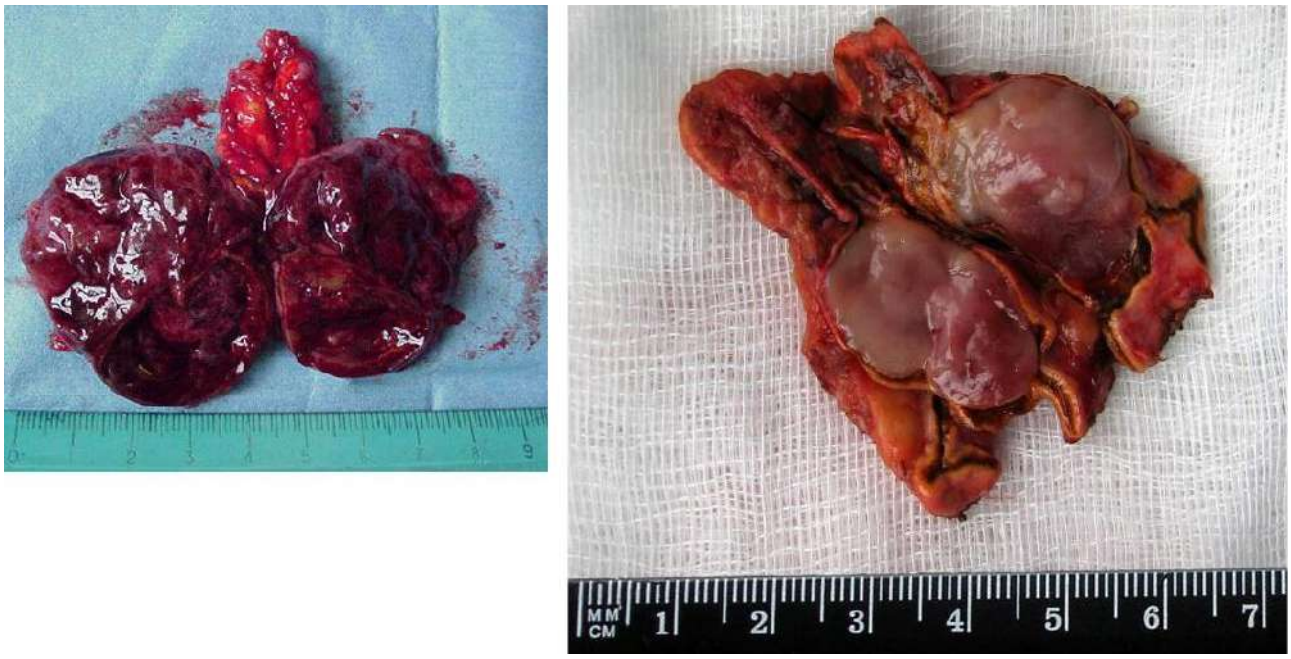


Fig. 9 Pheochromocytoma of the adrenal gland. Macropreparations. The growth of pheochromocytoma is mainly from the medial pedicle.

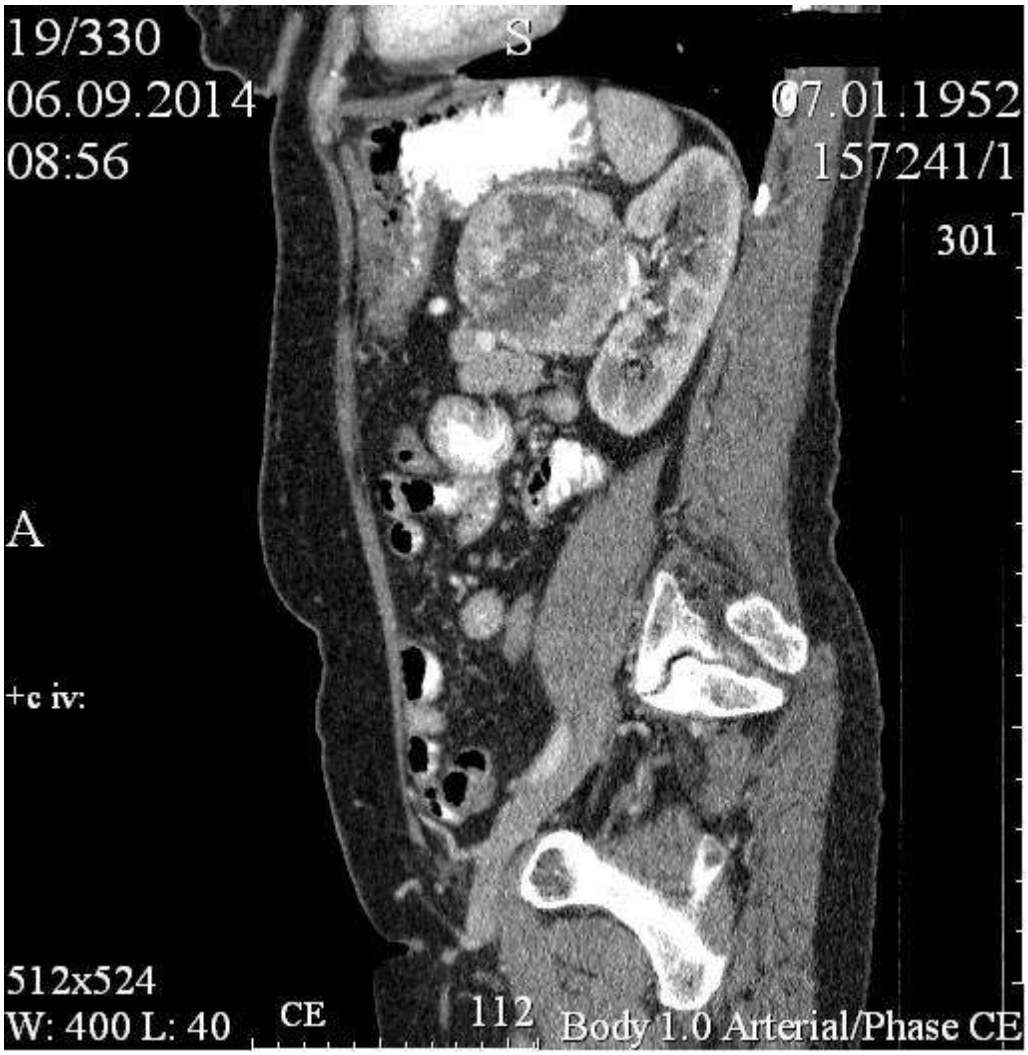


Fig. 10 Pheochromocytoma of the left adrenal gland. Computed tomography, arterial phase of the study.

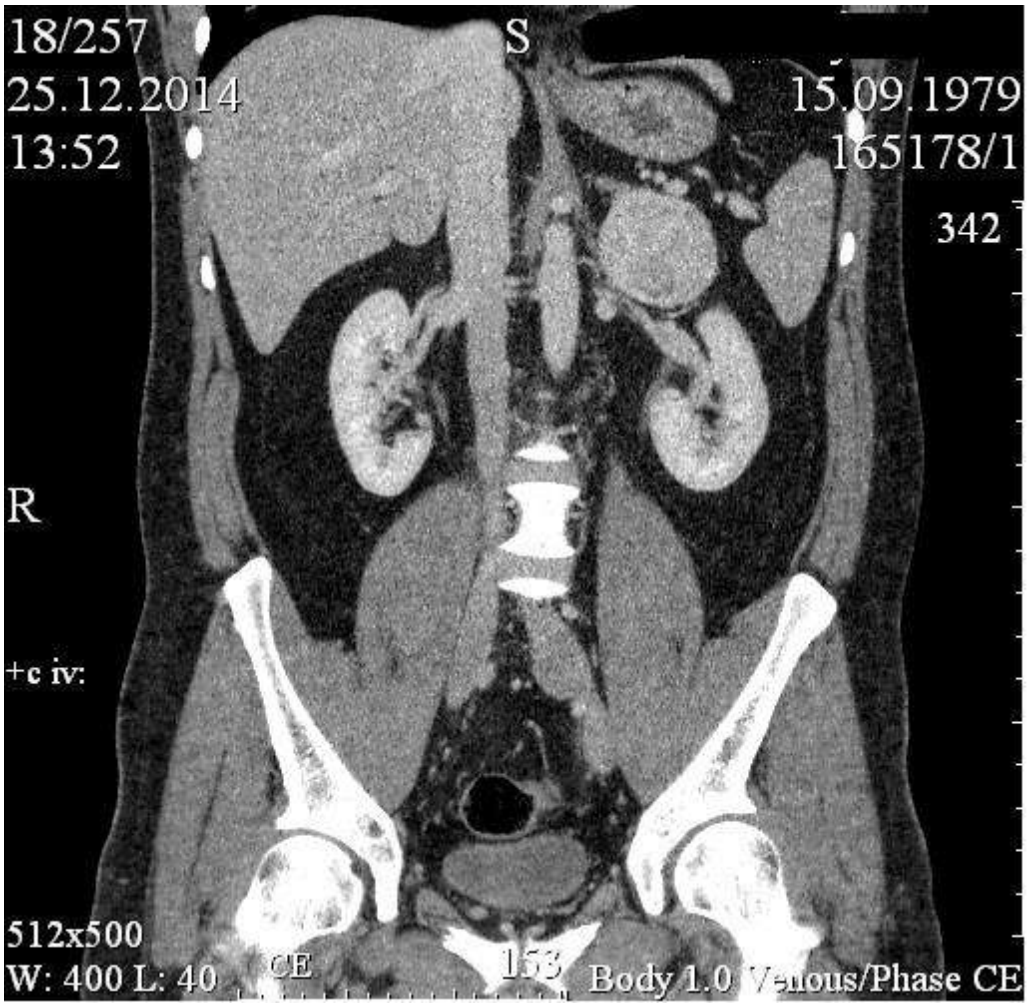


Fig. 11 Pheochromocytoma of the left adrenal gland. Computed tomography, venous phase of the study.

It is not possible to assume the malignant nature of pheochromocytomas in the absence of metastasis by modern methods of radiation diagnosis [Vorontsova S.V., 2002].

In pheochromocytoma, MRI has a very high sensitivity (99-100%), although the specificity does not exceed 88% [Reginelli A., Di Grezia G., Izzo A. et al., 2014]. In an MRI image, an adrenal pheochromocytoma, as a rule, is a large, encapsulated, multi-nodular tumor of fairly large size. The contours of most tumors are clear and uneven. The vast majority of observations show a heterogeneous tumor structure. On T1 VI,

neoplasms have a hypointensive signal, on T2 VI and IP STIR differ in a hyperintensive signal, thus, a long-term hyperintensive signal during MRI in the T2 phase can be considered a characteristic sign of pheochromocytoma [Pappachan J.M., Raskauskiene D., Sriraman R. et al., 2014; Shchetinin V.V., Maistrenko N.A., Egiev V.N., 2002]. Such a "mottled" image of pheochromocytes on T2 VI is probably due to the abundant vascularization of the tumor: vessels with pronounced blood flow velocity have the appearance of irregular lines or rounded foci with signal loss, and areas with high signal intensity are caused by slow blood flow and the tumor cells themselves [Vorontsova S.V., 2002]. The tumor, as a rule, completely replaces the normal adrenal gland tissue, located anteriorly from the upper pole of the kidney and shifting towards its vascular pedicle. Such localization of pheochromocytomas is most clearly revealed during MRI, as a method of multi-plane scanning [Krasnov L.M., 2005]. A bumpy, polycyclic contour may be observed in primary multiple adrenal lesions, and heterogeneity of the internal structure is often revealed [Soldatova T. V., 2011]. In 50% of patients with pheochromocytomas, MRI scans show signs of tumor invasion into surrounding tissues, the inferior vena cava, and the splenic vein. In MRI with gadolinium chelates, the pheochromocytoma has a bright signal [Remnyakov V.V., 2005]. Hypervascularization, which serves as one of the characteristic features of pheochromocytoma, is best detected by angiography [Yemelyanov S.I., Bogdanov D. Yu., 2012].

Positron emission tomography is useful in clarifying the localization of pheochromocytes that do not accumulate methaiodbenzylguanidine. For the same purpose, PET with hydroxyephedrine is used [Shchetinin V.V., Maistrenko N.A., Egiev V.N., 2002].

Pheochromocytoma must be differentiated from corticosteroma, adrenocortical cancer, and metastases. The main signs of pheochromocytoma are high density and good tumor vascularization. This is how it differs from corticosteroma. The most

difficult differential diagnosis is between pheochromocytoma and adrenocortical cancer. Cancer is characterized by rapid growth, a slight accumulation of contrast agent with its bolus administration. In both cases, surgical treatment is necessary in the absence of distant metastases. Metastases are characterized by an irregular shape, low density of formation, and an indistinct, finely rounded contour of the tumor [Remnyakov V.V., 2005].

The occurrence of true adrenal cysts is possible due to hemorrhages, although the lymphogenic origin of these neoplasms is also possible [Karmazanovsky G.G., Fedorov V.D., 2002]. Adrenal cysts of any genesis are well visualized by all methods of radiation examination. With ultrasound, CT and MRI, they have characteristic signs of liquid formation, usually single-chamber [Krasnov L.M., 2005] (multicameral cysts on two-dimensional images are detected in slightly more than 1% of cases [Yemelyanov S.I., Bogdanov D. Yu., 2012]). On CT scans, cysts, as a rule, have the appearance of a round-shaped formation, with the presence of liquid contents, with a density of 0-15 units. H, a thin (1-2 mm) capsule. The characteristic features of cysts are clear, even contours, a pronounced capsule (detected in 100%), and a homogeneous structure [Papierska L., Cichocki A., Sankowski A.J. et al., 2013]. The capsule has a smooth outer and inner contour. Sometimes the capsule is slightly thicker than usual (2-3 mm) with the presence of calcinates in the wall. In this case, it is difficult to differentiate it from the primary solid tumor, the site of central necrosis of which eventually transformed into a cystic cavity. In this case, you can focus on the following signs: the tumor has a thick capsule (3-4 mm), with an uneven inner surface, with calcifications, with the presence of partitions or soft-tissue inclusions in the lumen [Karmazanovsky G.G., Fedorov V.D., 2002]. After administration of the contrast agent, there are no changes in densitometric parameters in adrenal cysts.

When interpreting MR images, adrenal cysts are characterized by a homogeneous hypointensive MR signal on T-1 weighted tomograms and hyperintensive on T-2 weighted tomograms [Jusudov V.V., 2002], however, they may also have the appearance of an isointensive rounded formation [Soldatova T. V., 2011].

In CT, the picture of cysts sometimes turns out to be similar to the native image of adenomas [Vorontsova S.V., 2002]. Usually, the average density of cysts in CT is up to 10 units. N., and after administration of the contrast agent, density indicators do not change significantly [Yemelyanov S.I., Bogdanov D. Yu., 2012].

Pseudocysts (tumor cysts), unlike true ones, are characterized by a heterogeneous structure due to the preserved part of the tumor tissue, thicker walls. An irregular shape of the cavity, an uneven, land-like inner contour [Justisov V.V., 2002].

Cysts differ from adenomas by a well-defined capsule and the absence of accumulation of contrast agent.

Metastases to the adrenal gland occur in 15% of those who die from cancer of other organs. Clinically, they usually do not manifest themselves [Karmazanovsky G.G., Fedorov V.D., 2002] and have a primary localization in the adrenal medulla. On CT, these are irregularly shaped formations, sometimes repeating the shape of the adrenal gland. Metastasis can also be rounded [Akberov R.F. et al., 2002], have a homogeneous structure, which significantly complicates verification and requires additional research [Wagnerova H., Lazurova I., Felsoci M., 2013; Yemelyanov S.I., Bogdanov D. Yu., 2012]. The size of the metastases varies from 2-3 to 6-8 cm in diameter. Their contour is finely rounded, with a density of 20-30 HU (up to 50 HU [Soldatova T. V., 2011]) with decay sites with a density of 15-20 HU or less. With intravenous enhancement, the accumulation of contrast agent with a slight increase in density (by 10-15 HU) [Remnyakov V.V., 2005]. However, the slow removal of contrast media with intravenous "enhancement" of the CT image may be noted as a

characteristic difference in metastases [Reginelli A., Di Grezia G., Izzo A. et al., 2014]. Heterogeneity of the tumor structure is usually observed in tumors larger than 6.0 cm. With tumors over 7.0 cm on CT with contrast enhancement, a thick "gain ring" appears along the edge of the tumor [Akberov R.F., Ziyatdinov K.Sh., Kuryanov D.P., 2009].

With ultrasound in the projection of the adrenal gland, metastasis is visualized as a voluminous formation, with dimensions from 3 to 12 cm, irregular shape, heterogeneous structure [Wagnerova H., Lazurova I., Felsoci M., 2013]. Areas of hyperechogenicity alternate with hypoechoic in about 40% of cases, anechoic zones up to 3 cm in diameter are visualized along the periphery of the formation [Akberov R.F., Ziyatdinov K.Sh., Kuryanov D.P., 2009]. It was noted that in the ultrasound picture, secondary tumors are defined as hypoechoic, irregularly shaped formations with fuzzy contours and a homogeneous structure [Remnyakov V.V., 2005]. Calcifications, hemorrhages and areas of decay in them, as a rule, are not visualized.

On MRI, the contours of the neoplasm are clear, uneven, and the shape is rounded. T2 VI gives a higher intensity of the neoplasm signal [Shchetinin V.V., Maistrenko N.A., Egiev V.N., 2002; Justisov V.V., 2002], allows to determine pseudocysts, necrosis zones in tumor tissue. The sensitivity of ultrasound in detecting adrenal metastases is 86%, CT — 96%, MRI — 100% [Remnyakov V.V., 2005; Akberov R.F., Ziyatdinov K.Sh., Kuryanov D.P., 2009].

Bilateral lesions were noted in about 30%. With metastatic damage to the adrenal glands, which retain their shape, there is a need for differentiation with hyperplasia [Remnyakov V. V., 2005; Kuryanov D. P., 2009].

Lung cancer most often metastasizes to the adrenal glands, less often cancer of the kidney, breast, gastrointestinal tract, pancreas, seminoma, melanoma. Metastases to the adrenal glands can be bilateral and unilateral, single (solitary) and multiple. Bilateral metastases occur in about half of patients and, as a rule, are a reflection of a far-reaching

metastatic process [Wagnerova H., Lazurova I., Felsoci M., 2013]. Metastases to the adrenal glands in most cases are combined with metastases to other organs. Isolated metastases are rare, but the prognosis for their timely detection and treatment is more or less favorable. There are synchronous and metachronous metastases. The former are detected simultaneously or within 6 months after the detection of the primary tumor; the latter — later than 6 months later. A neoplasm of the adrenal gland in a patient with a history of cancer should be considered as potentially metastatic, regardless of the duration of the relapse-free period. Appropriate screening is of great importance in determining the true frequency of metastatic adrenal tumors. The most common histological type is adenocarcinoma, which is noted in 70-90% of cases. Non-epithelial tumors account for 10-30% of cases. Lymphoma and melanoma are more often detected among them, sarcoma, mesathelioma and other tumors are less common. Unlike primary adrenocortical cancer, adrenal metastases are non-encapsulated formations, but their spread is usually limited to the limits of the adrenal capsule. Necrotic changes are characteristic of large metastases to the adrenal glands [Gilyazutdinov I. A., Khasanov R. Sh., Kuryanov D. P., 2007].

Despite the fact that computed tomography has 100% sensitivity for detecting adrenal neoplasms, its use for the purpose of their differential diagnosis does not have 100% specificity. Based on this, in order to verify tumors to determine patient management tactics, indications for surgical treatment and prognosis of the disease, new non-invasive diagnostic methods are currently being proposed, such as determining the steroid profile of urine using the gas chromatography-mass spectrometry method.

# Chapter 5

## Laboratory and morphological methods of differential diagnosis of benign and malignant neoplasms of the adrenal glands

### 5.1. Laboratory methods

One of the most important tasks of modern diagnostic research is the timely identification of an accidentally detected adrenal neoplasm, since this determines the further management tactics of the patient. Hormonal activity should be assessed in all patients with identified adrenal incidentaloma in order to diagnose Itsenko-Cushing syndrome, hyperaldosteronism, pheochromocytoma and androsteroma [Aron D., Terzolo M., Cawood T.J., 2012]. In this case, as a rule, we are talking about subclinical hypercorticism and hyperaldosteronism, non-functioning pheochromocytoma. Less often, clinically non-manifested androsteromas are detected. No such patients were identified among our patients.

During the work, based on laboratory data, we determined the hormonal activity of the formations, which was detected in 95 out of 359 patients. Of these, 43 patients with pheochromocytoma, 28 with primary hyperaldosteronism and 24 with Itsenko-Cushing syndrome (Tables 13, 14, 15).

Table 13

Distribution of patients with diagnosed hormone-active pheochromocytoma by age and gender

| Gender | Age, years | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | 19 and younger | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-78 | |
| Women | - | 5 | 6 | 8 | 4 | 6 | 3 | 32 |
| Men | - | - | 2 | 3 | 5 | - | 1 | 11 |
| Total: | - | 5 | 8 | 11 | 9 | 6 | 4 | 43 |

Table 14

Distribution of patients with Itsenko-Cushing syndrome by age and gender

| Gender | Age, years | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | 19 and younger | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-78 | |
| Women | - | 3 | 6 | 4 | 4 | 3 | 2 | 22 |
| Men | - | - | - | - | 2 | - | - | 2 |
| Total: | - | 3 | 6 | 4 | 6 | 3 | 2 | 24 |

Table 15

Distribution of patients with primary hyperaldosteronism

by age and gender

| Gender | Age, years | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | 19 and younger | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-78 | |
| Women | - | 3 | 3 | 7 | 8 | - | - | 21 |
| Men | - | - | - | 4 | 3 | - | - | 7 |
| Total: | - | 3 | 3 | 11 | 11 | - | - | 28 |

Laboratory tests aimed at the diagnosis of pheochromocytoma were mandatory when an incident was detected. Therefore, in patients with randomly identified adrenal gland formations, the daily urine content of fractionated methanephrines, the concentration of chromogranin A, neuron-specific enolase (NSE) in blood plasma, and in some cases fractionated methanephrine and normetanephrine in blood plasma were determined. The advantage of metanephrines is that they are constantly secreted by the tumor, unlike catecholamines, therefore, we did not evaluate catecholamines in terms of

hormonal interpretation of the incident.

Among our patients operated on for accidentally detected adrenal neoplasms, 17 people (6.44%) were diagnosed with pheochromocytoma based on the results of histological examination, since these patients did not have a characteristic clinical picture, and laboratory parameters during the examination did not go beyond the reference values - metanephrines are common in daily urine 132.8±25.7 mcg/day at a rate of up to 350 mcg/day; chromogranin A in blood plasma 79.4±15.3 mcg/l at a rate of up to 125 mcg/l; neuron-specific enolase (NSE) in blood plasma is 9.7±2.3 mcg/l at a rate of up to 18.3 mcg/l. This may indicate that the production of catecholamines by the tumor was at a low enough level to detect it using traditional laboratory diagnostic methods. When analyzing the results of CT and histological studies, it was noted that these were mainly small tumors, measuring 3.2 ±1.3 cm.

In the diagnosis of Itsenko-Cushing syndrome, we used the determination of ACTH and cortisol content in blood plasma, cortisol excretion in daily urine, determination of saliva cortisol content at 23 hours and a test with 1 mg dexamethasone. In addition to 24 people with clinical manifestations of Itsenko-Cushing syndrome in whom laboratory data confirmed the diagnosis (ACTH in blood plasma 0.35±0.21 pmol/l at reference values of 1,034 — 10.736 pmol/l; cortisol in blood plasma 691.5±41.8 nmol/l at a norm of 185 — 624 nmol/l; cortisol excretion in daily urine is 1517.76±254.42 nmol/24h at a rate of 160 - 1112 nmol/24h; salivary cortisol at 23 hours is 22.3±5.1 ng/ml at a rate of 1.2 — 14.7 ng/ml; cortisol in blood plasma at 8 a.m. 163.6±42.8 nmol/l after taking 1 mg dexamethasone at 23 o'clock), among patients with incidentalomas, a group of patients (n=19) was identified who had no suppression of cortisol secretion during the test with 1 mg dexamethasone - cortisol in blood plasma in the morning 96.4±23.6 nmol / l after taking 1 mg of dexamethasone at 23 o'clock at normal plasma cortisol levels - 342.7±72.8 nmol/ l at a norm of 185 — 624 nmol/ l,

salivary cortisol at 23 o'clock 17.8 ±5.1 ng/ml at a norm of 1.2 — 14.7 ng/ml in the absence of obvious clinical manifestations of endogenous hypercortisolism. These patients were diagnosed with "subclinical Itsenko-Cushing syndrome" and underwent surgical treatment. Histological examination revealed the tumor to be adrenocortical adenoma in 14 patients and carcinoma in 5.

In order to identify primary hyperaldosteronism, we determined the concentration of potassium, aldosterone and renin in the blood serum, and calculated the aldosterone-renin ratio (ARR). If, according to the ARR data, the presence of PHA was proven or suspected in a patient with an accidentally detected adrenal gland formation, then the next stage of diagnosis was to conduct a test with saline solution. For the purpose of differential diagnosis of unilateral or bilateral adrenal damage, comparative selective blood sampling from the adrenal veins was performed with determination of plasma concentrations of aldosterone, renin and cortisol. In addition to patients admitted to the department for surgical treatment with an already established and confirmed diagnosis of "Primary hyperaldosteronism" (n=28), among patients with randomly identified adrenal neoplasms examined during hospitalization in our hospital, this diagnosis was established in three more. The clinical picture of PHA in these patients was absent, when analyzing laboratory parameters, a decrease in serum potassium concentration of 3.1±0.23 mmol/l was noted at laboratory reference values of 3.5 — 5.3 mmol/l and direct renin of 1,164±0.72 μm/ml with a standing norm: 4.4 — 46.1 μm/ml, lying: 2.8 — 39.9 microns/ml, an increase in serum aldosterone of 606.2±47.4 pg/ml at a standing norm: 25.6 — 445 pg/ml, lying down: 19.7- 260 pg/ml and an aldosterone-renin ratio above 12.5.

The study of the concentration of dehydroepiandrosterone sulfate (DHEA-S) in blood plasma in all patients with adrenal incidentalomas was aimed at diagnosing ACC. In 19 patients (82.6%) with a histologically confirmed diagnosis, there was an increase

in the plasma content of dehydroepiandrosterone sulfate - 15.7±5.3 mmol/l at a norm of 0.32 - 3.61 mmol/l.

5.2. Determination of the steroid profile of urine by gas chromatography-mass spectrometry

As mentioned in the previous chapter, the determination of the malignancy of adrenal tumors is currently largely based on CT characteristics, which are highly sensitive but insufficiently specific [Grumbach M.M. et al., 2003; Hamrahian A.H et al., 2005; Nieman L.K, 2010]. According to radiation research methods, it is not always possible to make a correct diagnosis with sufficient confidence. In such cases, it is of great importance to study the features of tumor synthesis of hormones, their precursors and metabolites. It is known that about 60% of patients with ACC have clinical signs of excessive secretion of steroid hormones. However, even if there are no pronounced clinical signs, the process of steroidogenesis in neoplasms is still carried out with varying degrees of intensity (Fig. 12).

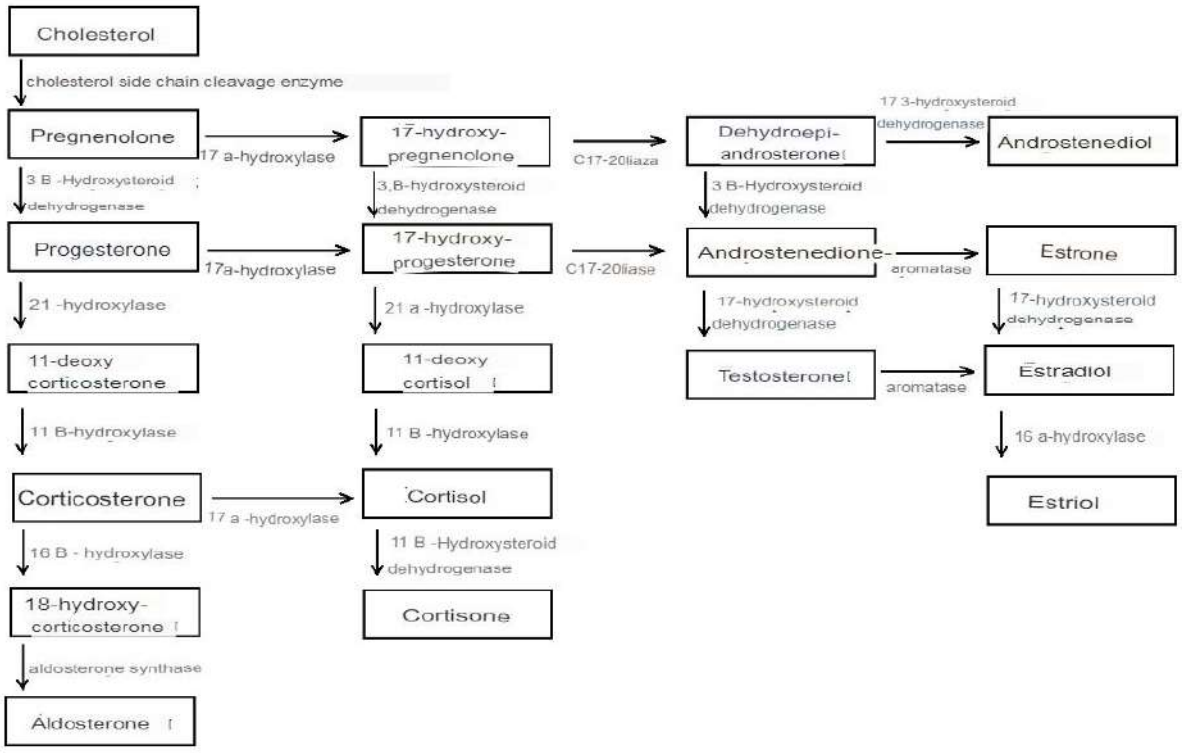


Fig. 12. The scheme of steroidogenesis.

Signs of malignancy of an adrenal tumor are considered to be high plasma levels of dehydroepiandrosterone sulfate [Terzolo M., Ali A., Osella G. et al., 2000], as well as 11-deoxycortisol and 11-deoxycorticosterone, due to a defect in 21α-hydroxylase and 11β-hydroxylase [Shafigullina Z.R., Velikanova L.I., Vorokhobina N.V. et al., 2022; Shavladze M. D., 2003].Dehydroepiandrosterone sulfate is a metabolite of dehydroepiandrosterone, it is formed by adding a sulfate group to it using the enzymes sulfotransferases SULT1A1 and SULT1E1, and as dehydroepiandrosterone can be transformed into testosterone and estradiol. 11-deoxycortisol— a precursor of cortisol, is formed from 17-hydroxyprogesterone under the action of 21α-hydroxylase. 11-deoxycorticosterone, a precursor of corticosterone, is also formed from progesterone by 21α-hydroxylase.

Among our 23 patients with ACC, 17 people (73.9%) had elevated levels of DHEA-S in blood plasma, 15 (65.2%) had 11-deoxycortisol and 12 (52.2%) had 11-deoxycorticosterone. In four patients (17.4%), no increase in any of the listed substances was detected. In patients with adrenocortical adenomas, an increase in the plasma content of these substances was also not detected. Thus, the increased content of dehydroepiandrosterone sulfate, 11-deoxycortisol and 11-deoxycorticosterone in blood plasma in patients with adrenal tumor confirms the diagnosis of ACC, but their normal content does not exclude the presence of a malignant tumor of the cortical layer. A number of researchers claim that only 85% of patients with hormonally active ACC show an increase in adrenal steroidogenesis precursors [Arlt W., Biehl M., Taylor A. E. et al. 2011; Shafigullina Z.R., Velikanova L.I., Vorokhobina N.V., et al., 2015; Kerkhofs T.M., Kerstens M.N., Kema I.P et al., 2015]. The authors note that patients with ACC who do not have clinical signs of excessive secretion of steroid hormones may have increased production of steroid precursors due to inhibition of steroidogenesis enzymes (defects of 11-β-hydroxylase and 21α-hydroxylase are most often detected [Velikanova L. I., Shafigullina Z. R., Lisitsin A. A.et al., 2016]), but it is a very difficult

task to identify such an increase in the content of these precursors in blood plasma [Arlt W., Biehl M., Taylor A. E. et al. 2011; Stigliano A., Chiodini I., Giordano R., et al., 2015]. In addition, the secretion of these substances by tumors may not be constant or not pronounced. According to a number of researchers, a more reliable method for determining the final and intermediate persistent products of steroid hormone metabolism is to determine their concentration in daily urine, that is, to study the steroid profile of urine (USP) [Krone N., Hughes B.A., Lavery G.G. Et al., 2010; Arlt W., Biehl M., Taylor A. E. et al. 2011; Shafigullina Z.R., Velikanova L.I., Vorokhobina N.V. et al., 2015; Stigliano A., Chiodini I., Giordano R., et al. 2015; Kerkhofs T.M., Kerstens M.N., Kema I.P. et al., 2015].

To assess the violation of steroidogenesis and metabolism of steroid hormones, we selected a method for determining the steroid profile of urine by chromatography-mass spectrometry. This method is a combination of chromatography and mass spectrometry, which proceed independently of each other, allowing the qualitative and quantitative determination of components in complex mixtures. The principle of the method is based on the fact that passing through the chromatograph, the mixture is divided into components, and the mass spectrometer identifies and determines the concentration of the detected substances. There are high-precision liquid chromatography (HPLC) and gas chromatography (GC). Due to the higher accuracy of the method, it was decided to use gas chromatography with mass spectrometric detection to determine the concentration of steroids, their precursors and metabolites. According to a number of authors, gas chromatography-mass spectrometry (GC-MS) is the most sensitive and specific method for differential diagnosis between benign and malignant adrenocortical tumors [Krone N., Hughes B.A., Lavery G.G. Et al., 2010; Arlt W., Biehl M., Taylor A. E. et al. 2011; Shafigullina Z.R., Velikanova L.I., Vorokhobina N.V. et al., 2015; Stigliano A., Chiodini I., Giordano R. et al. 2015; Kerkhofs T.M., Kerstens M.N., Kema I.P. et al., 2015].

This method consists in the fact that after special sample preparation, the test material is placed in the evaporator of the chromatograph, where it instantly transforms into a gaseous form, mixes with an inert carrier gas and is fed into a column under pressure. As mentioned above, passing through the column of the chromatograph, the sample is divided into its constituent components, which are then passed through the spectrometer. To obtain the spectrum, the molecules of the sample components are ionized, a special sensor reads the change in the ion current and a chromatogram is formed based on these changes. Each peak corresponds to a specific molecular cation formed during ionization. The reconciliation of the obtained peaks with previously registered ones using special software allows us to obtain an accurate qualitative and quantitative determination of the substances that make up the test sample.

We studied the results of a study of the steroid profile of urine by GC-MS in 67 patients with randomly identified adrenal neoplasms. The concentration of 65 steroids in the daily urine was determined (Table 16).

Table 16

The list of detectable steroids in daily urine by GC-MS method.

| № | The name of the steroids | Abbreviation |
|---|---|---|
| 1 | 5α-Androstan-3α,17β-diol | 5α AD |
| 2 | 5 β-Androstan-3α,17β-diol | 5 β AD |
| 3 | 5-Androstene-3β,11β,17β -triol | |
| 4 | Androsterone | An |
| 5 | Etiocholanolone | Et |
| 6 | Androstenediol -17α | dA2-17α |
| 7 | Androstenediol -17β | dA2-17β |
| 8 | Dehydroepiandrosterone | DHA |
| 9 | 16α-OH-dehydroepiandrosterone | 16α-OH-DHA |
| 10 | 11-keto-etiocholanolone | 11-oxo Et |
| 11 | 11-keto-dehydroepiandrosterone | 11-oxo-DHA |
| 12 | Testosterone | T |
| 13 | Androstenedione | |
| 14 | 17-OH-pregnenolone | 17P |

| | | |
|---|---|---|
| 15 | 11β-OH-androsterone | 11β-OH-An |
| 16 | 5β-Androstan-3α,11α,17β-triol | A3-3α,11α,17β |
| 17 | 11β-OH-etiocholanolone | 11β-OH-Et |
| 18 | Pregnenolone | P |
| 19 | 16β-OH-dehydroepiandrosterone | 16 β -OH-DHA |
| 20 | Pregnanediol | P2 |
| 21 | 5-Androstene-3β,16β,17α-triol | 17αdA3 |
| 22 | Pregnantriol | P3 |
| 23 | Pregnan-20-OH-3,11,17-triol | THF-21deoxy |
| 24 | Pregnenolone | dP |
| 25 | Pregnendiol | dP2 |
| 26 | 16-oxo-androstenediol | 16-oxo-dA2 |
| 27 | Androstentriol | dA3 |
| 28 | 16-OH-Testosterone | 16-OHT |
| 29 | 5-pregnen-3α,16α,20α-triol | 5Pd3α,16,20 |
| 30 | 5-pregnen-3β,16α,20α-triol | 5Pd3β,16,20 |
| 31 | 5α-Tetrahydro-11-deoxycortisol | 5α-THS |
| 32 | 5 β -Tetrahydro-11-deoxycortisol | 5β-THS |
| 33 | 16-OH-pregnanediol | 16P2 |
| 34 | 5-Pregnen, 3,17-diol,20-OH | 17dP |
| 35 | Tetrahydro-11-deoxycorticosterone | THDOC |
| 36 | 11-oxo-pregnanediol | 11-oxo-P2 |
| 37 | 11-oxo-pregnantriol | 11-oxo-P3 |
| 38 | 11-OH-pregnanediol | 11P2 |
| 39 | 21-OH-pregnantriol (5β) | 21P3 (5β) |
| 40 | 11-OH-pregnantriol | 11P3 |
| 41 | Pregnentriol | dP3 |
| 42 | 16-hydroxypregnenolone | 16dP1 |
| 43 | 6-hydroxypregnenolone | 6OH-dP |
| 44 | Pregnan-3,17,20,21-tetrol(HHS) | 21P3 (5α) |
| 45 | Tetrahydrocortisone | THE |
| 46 | 5-Pregnene,3β,16α,20α-triol | 5dP3β,16,20 |
| 47 | Tetrahydrocorticosterone | THB |
| 48 | Tetrahydrocortisol | THF |
| 49 | allo-Tetrahydrocorticosterone | allo-THB |
| 50 | allo-Tetrahydrocortisol | allo-THF |
| 51 | allo-Tetrahydrocortisone | allo-THE |
| 52 | Tetrahydro-11-dehydrocorticosterone | THA |

| | | |
|---|---|---|
| 53 | α-cortolone | α-cortolone |
| 54 | β-cortol | β-cortol |
| 55 | 21-OH-pregnenolone | 21dP1 |
| 56 | β-cortolone | β-cortolone |
| 57 | 5β-Pregnan-11-oxo-3,20,21-triol | 5β -HHA |
| 58 | α-cortol | α-cortol |
| 59 | 5β-Pregnan-3,11,20,21-tetrol (HHB) | 5β -HHB |
| 60 | 5α-Pregnan-3,11,20,21-tetrol (HHB) | 5α -HHB |
| 61 | 5α-Pregnan-11-oxo-3,20,21-triol | 5α HHA |
| 62 | 5-pregnen-3,11,17,20-tetrol | dP4 |
| 63 | Dihydrocortisone | 20-diHE |
| 64 | Dihydrocortisol | 20-diHF |
| 65 | Estrone | |

Histological examination of the removed tumors in this group of patients revealed adrenocortical carcinomas in 23 patients, adenoma in 37, pheochromocytoma in 6 and solitary adrenal cyst in 6. In patients with randomly identified adenomas, the levels of cortisol, aldosterone and DHEA-S in the blood did not differ from healthy ones, the serum cortisol level during the test with 1 mg of dexamethasone was less than 50 nmol/L.

After analyzing the data of statistical processing of USP obtained by GC-MS, common signs were established for patients with ACC, namely, increased urinary excretion of tetrahydro-11-deoxycortisol— a metabolite of dihydrocortisol, which in turn is a metabolite of cortisol and is formed with the participation of 5α-reductase; 5-pregnen-3α,16α,20α-triol, 5-pregnen-3β,16α,20α-triol and pregnentriol are metabolites of pregnenolone, a precursor of steroid hormones formed from cholesterol by shortening the side chain; and pregnanediol— a metabolite of pregnanolone derived from progesterone, as well as an increase in the ratio of tetrahydrocorticosterone to allotetrahydrocortisol (the heights of their peaks on the chromatogram compared to the norm).

When studying the USP samples, we came to the conclusion that each sample is purely individual (Fig. 13, 14) and it is not worth focusing only on the concentrations of certain steroids, but it is necessary to evaluate the totality of all substances in each specific sample, since the volume of daily diuresis, and, as a result, the concentration of the hormones being determined Their precursors and metabolites are influenced by many different factors.

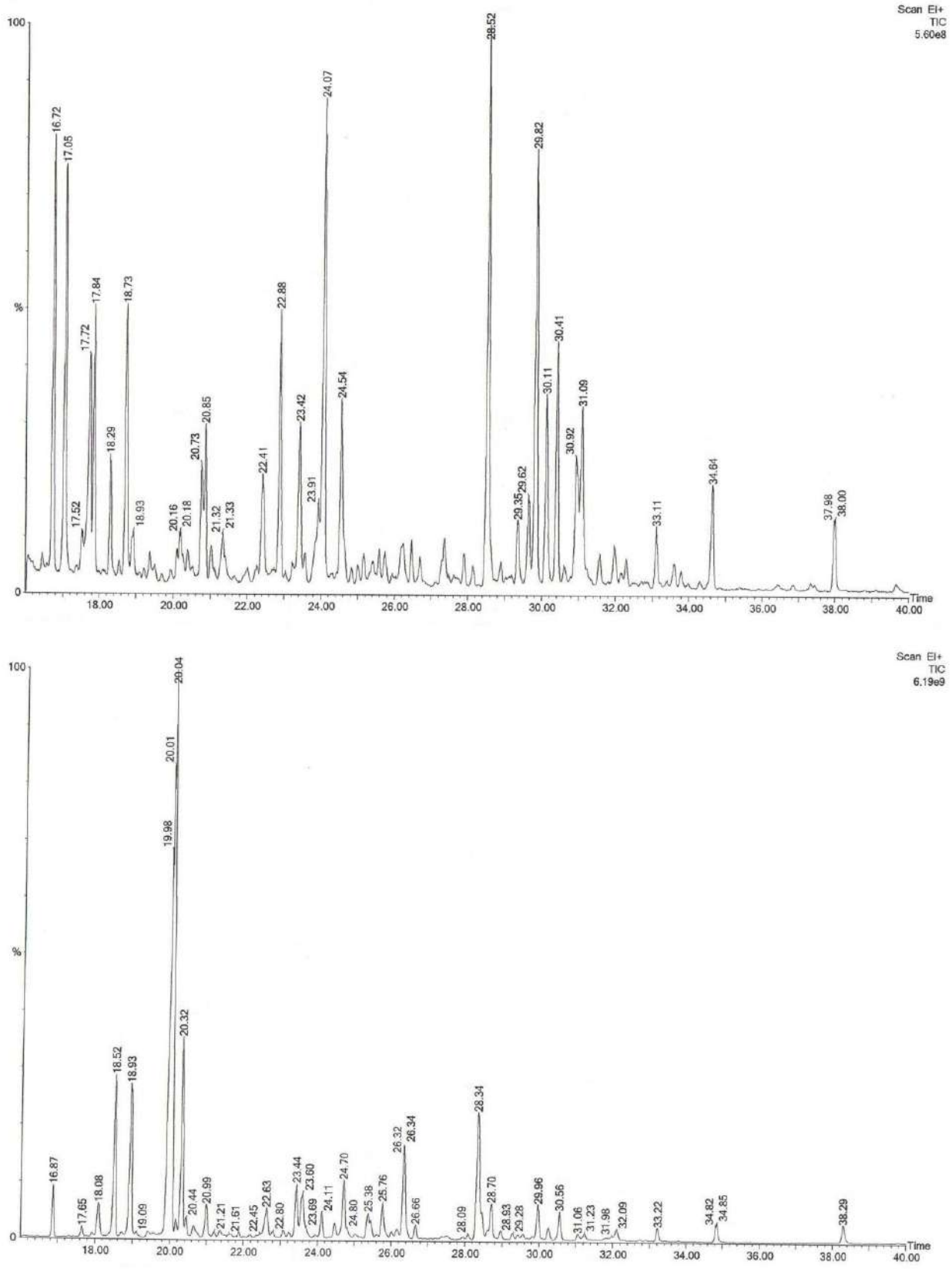


Fig. 13. Steroid profiles of urine of patients with ACC.

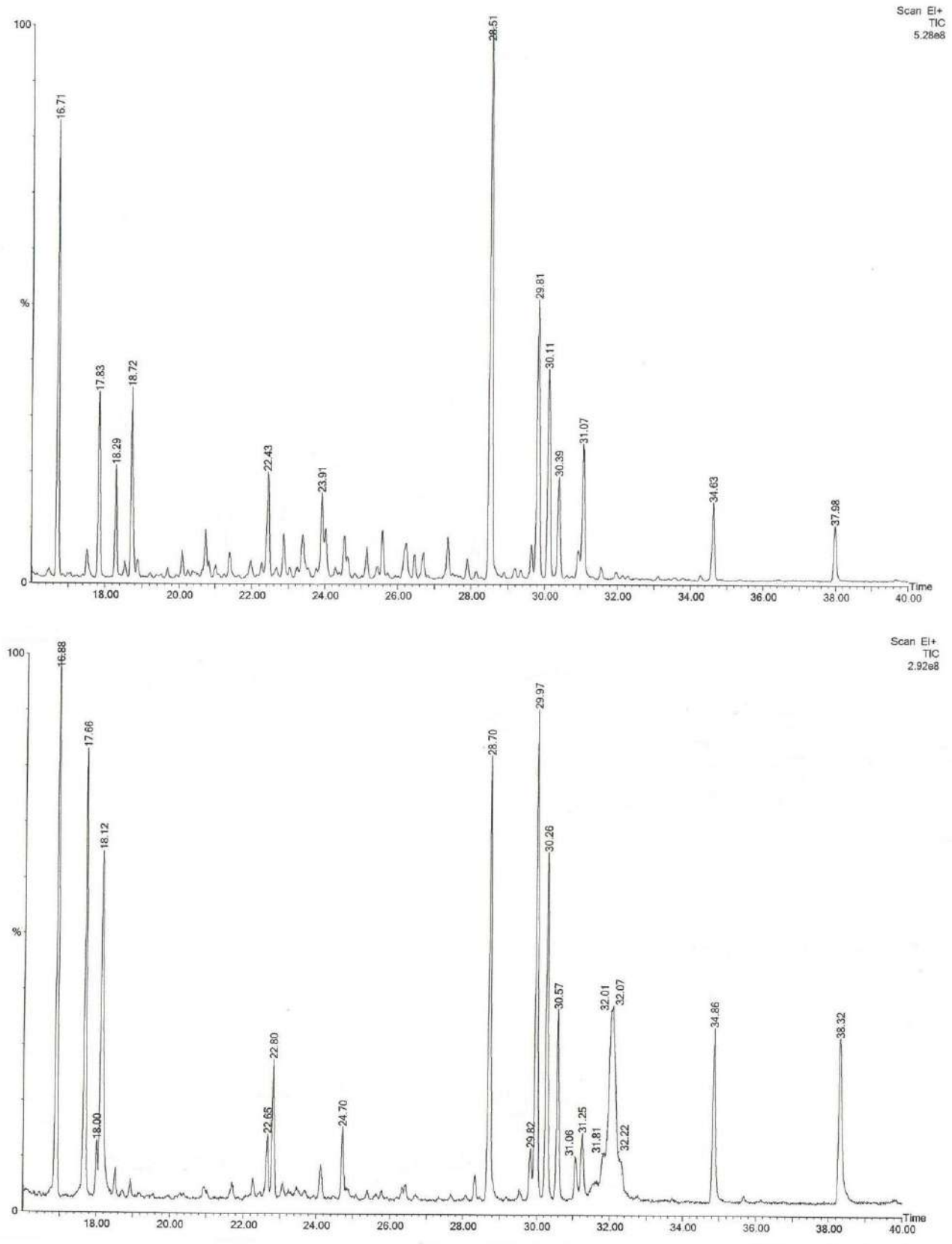


Fig. 14. Steroid profiles of urine of patients with hormone-inactive adrenal neoplasms.

In this work, we established the most informative signs of ACC in the preoperative period using the GC-MS method, comparing the results of statistical analysis in patients with ACC and hormonal inactive adrenal formations. Common signs characteristic of ACC according to GC-MS data are an increase in urinary excretion of tetrahydro-11-deoxycortisol, 5-pregnen-3α,16α,20α-triol, 5-pregnen-3β,16α,20α-triol, pregnanediol, pregnentriol, as well as an increase in the ratio of tetrahydrocorticosterone to allo-tetrahydrocortisol. These signs were not detected in 3 patients with ACC and in all patients with benign cortical formations and pheochromocytomas. The obtained data indicate the importance of using GC-MS in the differential diagnosis of ACC and adrenocortical adenomas, which, in combination with data from imaging research methods, will increase the accuracy of diagnosis of ACC at the preoperative stage. In controversial or doubtful cases of histological assessment of a removed tumor, the determination of USP performed before surgery may be useful in the process of establishing a final diagnosis as an additional diagnostic method.

The presented results once again demonstrated the importance of a thorough hormonal examination in patients with randomly identified adrenal gland formations, both with and without a pronounced clinical picture of hormonal activity.

All patients with suspected ACC are recommended to study the steroid profiles of biological fluids using chromatography and spectrometry to identify signs of malignancy of adrenal glands. We note the need for further search for the most informative biochemical markers of ACC [Shafigullina Z.R., Velikanova L.I., Vorokhobina N.V. et al., 2015; Stigliano A., Chiodini I., Giordano R., et al. 2015; Kerkhofs T.M., Kerstens M.N., Kamal I.P. et al., 2015].

The presence of false negative results does not allow us to speak about the predominant use of the method of determining USP as a diagnostic criterion of ACC, but the detection of these specific substances present in patients with histologically

confirmed adrenocortical carcinoma in the preoperative period allows us to use this method in dynamic monitoring of such patients after adrenalectomy in order to assess the effectiveness of the treatment, however, this issue requires further studying.

The absence of these steroidogenesis disorders in patients with randomly identified adrenal neoplasms, who lack malignant potential according to CT with intravenous contrast, suggests that it is inappropriate to use this method to monitor tumor metabolism, since modern scientific data exclude the possibility of malignant degeneration [Lloyd R.V., Osamura R.Y., Klцppel G., Rosai J., 2017].

## 5.3. Histological and immunohistochemical research methods

After the surgical treatment, all patients necessarily underwent a histological examination of the removed tumors with an assessment of drugs on the Weiss L. M. scale. Until 2002, this assessment scale consisted of the following:

Each of the 9 criteria was evaluated at 1 point:

1) High nuclear index,

2) mitotic activity (more than 5% in 50 representative visual fields),

3) atypical figures of mitosis,

4) eosinophilia of the cytoplasm of tumor cells (more than 75% of the cells in the tumor),

5) Diffuse tumor architectonics (33% of tumor tissue),

6) the presence of necrosis,

7) tumor venous invasion,

8) tumor sinusoidal invasion,

9) invasion of the capsule.

When scoring 4 or more points, the diagnosis of "adrenocortical carcinoma" was established.

In 2002, the L.M. Weiss system was modified, while it was proposed to take into account 5 criteria:

1) mitotic activity (more than 5% in 50 representative visual fields) – 2 points,

2) atypical figures of mitosis – 1 point,

3) eosinophilia of the cytoplasm of tumor cells (more than 75% of the cells in the tumor) – 2 points,

4) necrosis – 1 point,

5) invasion of the tumor capsule – 1 point.

When scoring 3 or more points, a conclusion is established - "Adrenocortical carcinoma". Despite the high sensitivity of the L.M. Weiss scale, many researchers recognize the need to develop clearer morphological criteria for the malignancy of adrenal tumors, as well as biomarkers that can be used in mass analyses [Britvin T. A., Krivosheev A.V., Beloshitsky M. E., 2015; Wang C., Sun Y., Wu H. et all, 2014].

In the course of our work, we compared the results of histological and immunohistochemical studies in 66 patients with randomly identified adrenal neoplasms. Histological examination of the removed tumors revealed adrenal adenomas in 44 of them, which had no malignant potential. 22 have adrenocortical carcinomas, having from 4 to 7 points on the L. M. Weiss scale (1989).

After statistical processing of the data, we identified reliable signs that allow us to differentiate adenoma of the adrenal cortical layer from adrenocortical cancer.

Morphological assessment of neoplasia revealed a difference in the size of neoplasms. Thus, the size of adenomas was 4.3±0.4 cm, while the size of carcinomas was 8.2±1.5 cm (Fig. 15).

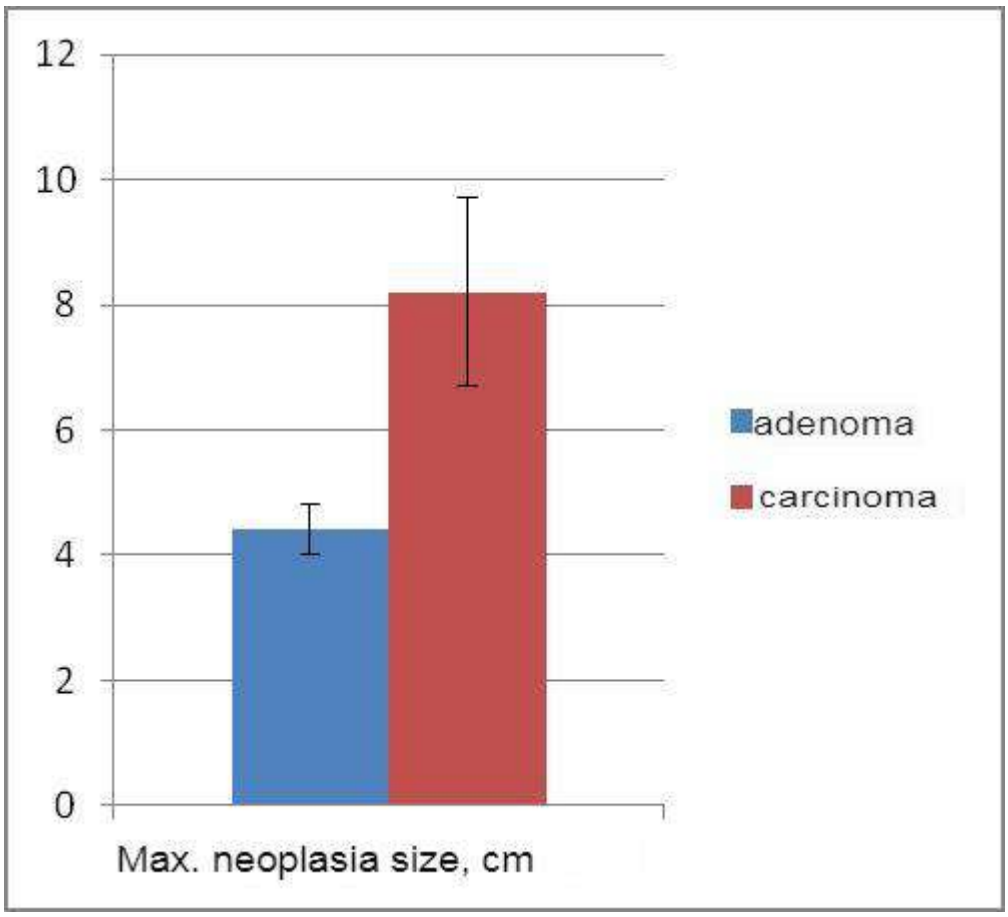


Fig. 15. The maximum size of the removed adrenal adenomas and carcinomas, based on morphological examination data.

Mitotic activity in adenoma cells was not detected in any of the cases. The severity of this indicator in carcinomas is significant – about 36% of the mitotic activity is higher than 20 in 10 fields of vision (Fig. 16).

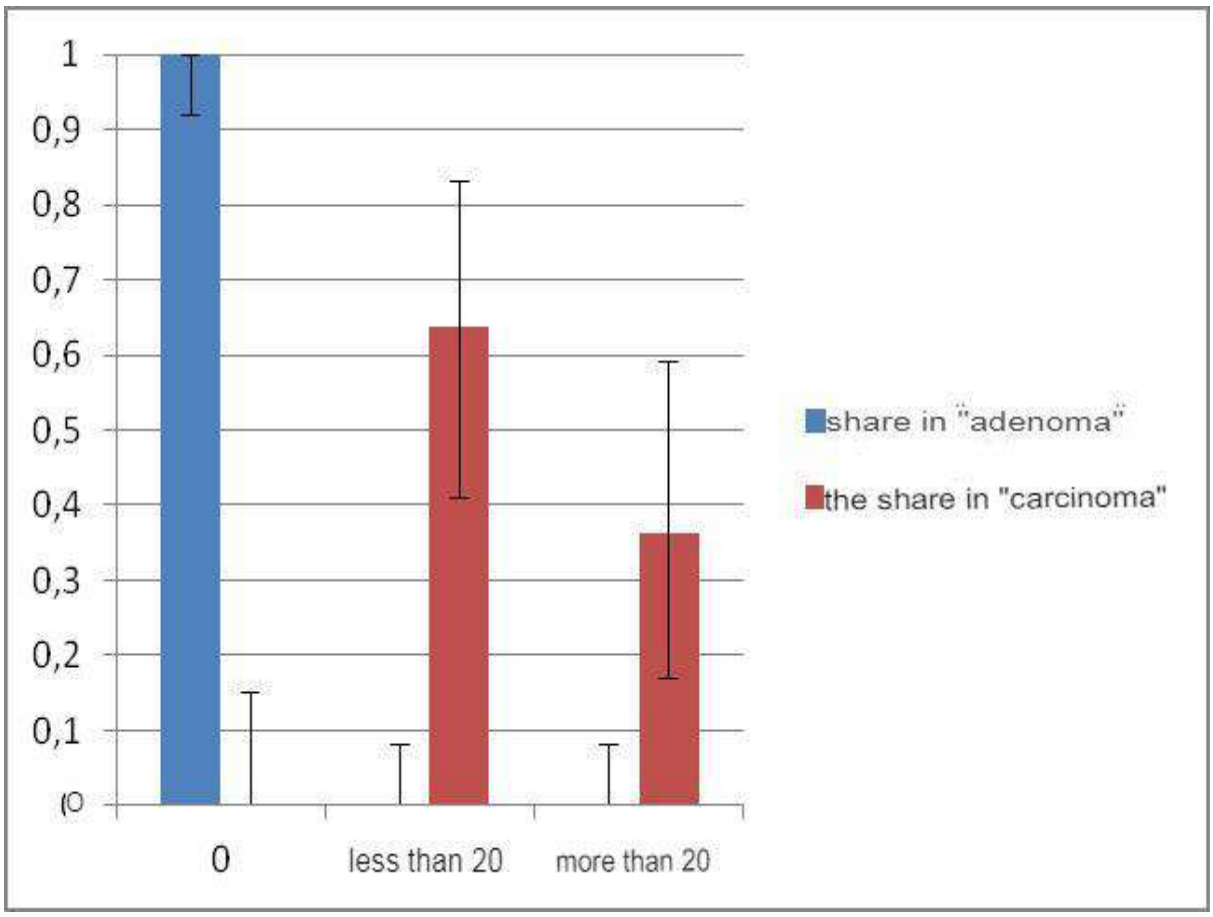


Fig. 16. Mitotic activity. The number of mitoses in 10 visual fields.

When assessing the predominant structure of adenomas, the absence of asymmetry was noted. Monomorphic, "nested" structure is characteristic of adenomas and was found only in 12% of carcinomas. Trabecular and diffuse (structureless) types of structure were found in 88% of carcinomas (Fig. 17).

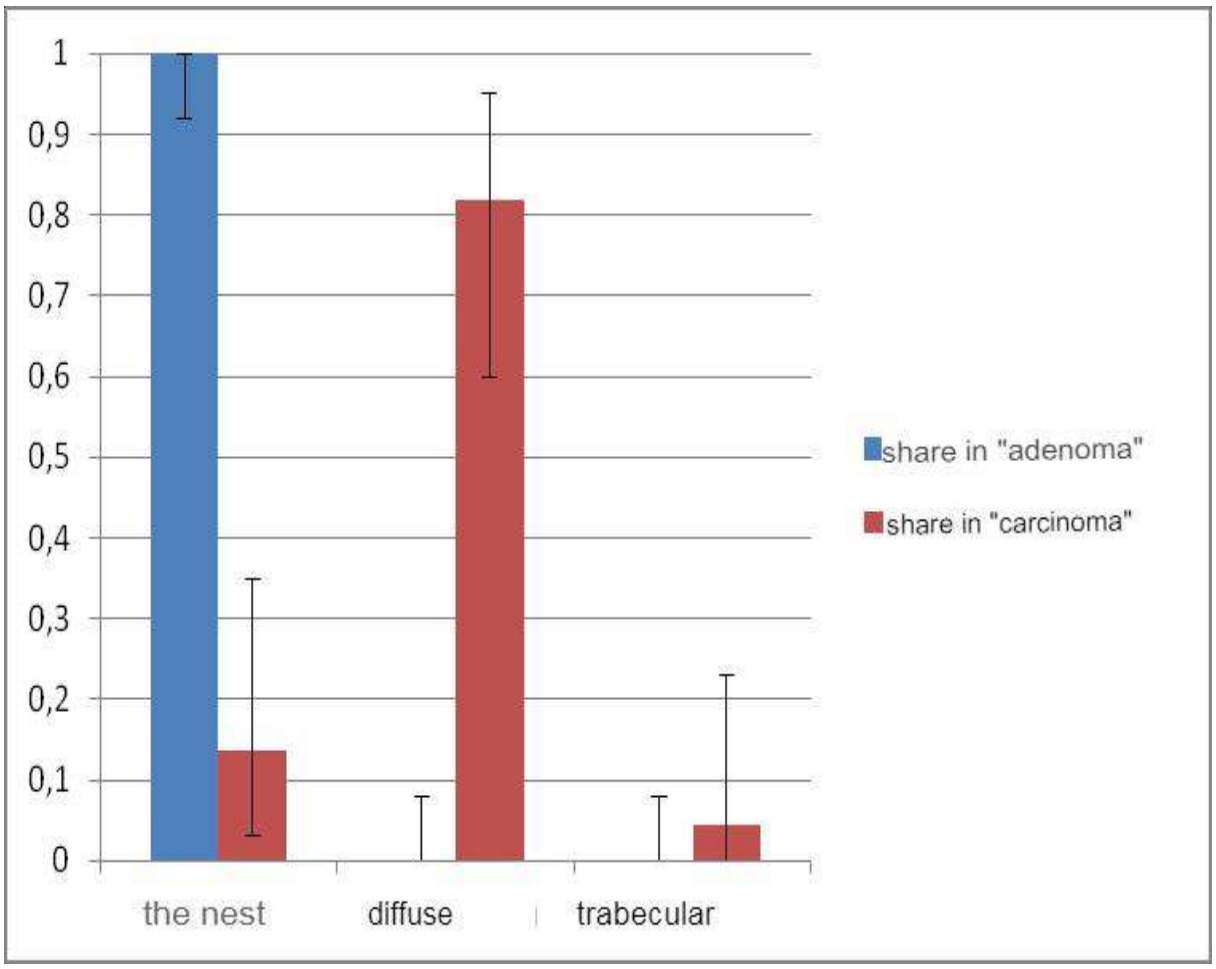


Fig. 17. Predominant cellular structure.

The phenomenon of dark cell endocrinocytes was determined in 45% of adenomas and did not occur in any of the cases of adrenocortical cancer, which is a striking difference in this indicator (Fig. 18).

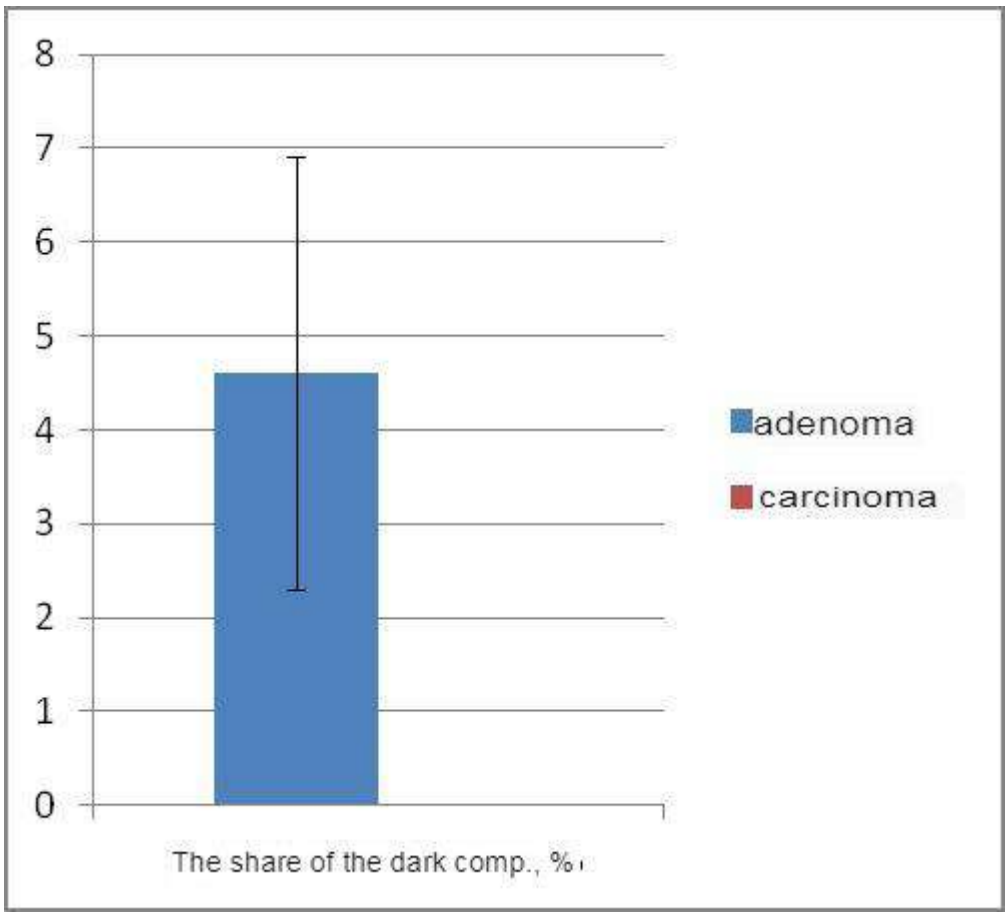


Fig. 18. The proportion of the dark cell component, %.

The described eosinophilic cells as one of the highly specific morphological cellular phenotypes in our study were found in 84% of cases of adrenocortical carcinomas. This type of cell was practically not found in adenomas (8%) (Fig. 19).

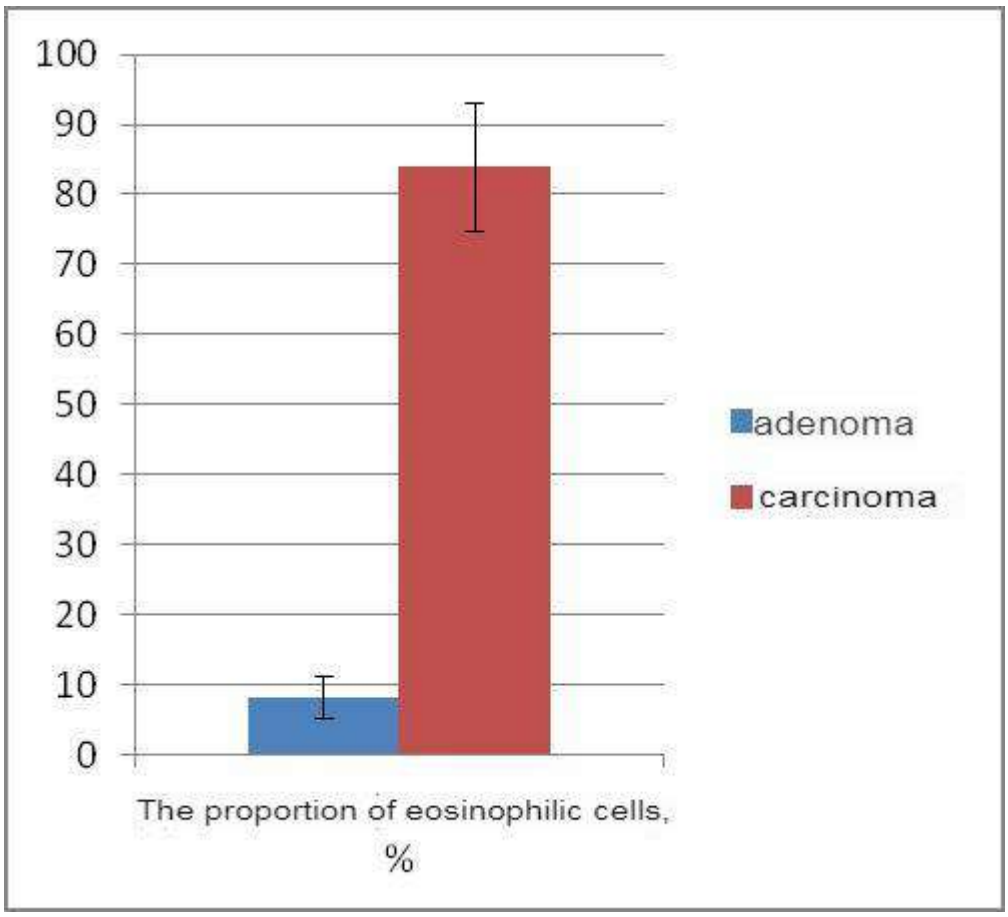


Fig. 19. The proportion of eosinophilic cells, %.

Despite the distinctive signs of adrenal cortex adenomas, in some cases it may be difficult to make a definitive diagnosis, especially if adrenocortical cancer is suspected. Therefore, for the purpose of differential diagnosis of carcinoma of the adrenal cortex from other neoplasms, in addition to light microscopy, an immunohistochemical examination (IHC) method was proposed.

Immunohistochemical examination is a method of identification and determination of localization in cells and tissues of various structures with antigenic properties based on the immunological antigen-antibody reaction. The use of antibodies underlies the research of molecular formations: structural components of the cell, receptors of the cell surface and cellular products (hormones, enzymes, immunoglobulins). There are two types of antibodies — monoclonal and polyclonal.

Monoclonal antibodies are obtained by hybridomic technology. Despite the fact that their preparation is multi-stage and complex, they are highly specific and highly visible antibodies and are directed to a single antigen epitope (a part of the antigen macromolecule that is recognized by the immune system (B lymphocytes, T lymphocytes, antibodies). Polyclonal antiserums obtained during animal immunization contain antibodies to various antigen epitopes. To obtain a polyclonal antiserum, a purified antigen is injected into a laboratory animal along with a non-specific immune response stimulator, an adjuvant. The antigen stimulates many B lymphocytes, each of which gives a clone of plasma cells producing antibodies. The antigen can have several epitopes and the antiserum contains immunoglobulins against each of them, and each clone of plasma cells is able to produce antibodies to only one type of epitopes. As mentioned above, we used monoclonal antibodies to vimentin, pancytokeratin AE1/AE3, β-catenin, inhibin a, melan-A, polyclonal antibodies to Ki-67, p21, p53, CD1, CD34.

Vimentin is a protein of intermediate filaments of connective tissues and other tissues of mesodermal origin, used as a marker of tumors arising from mesodermal tissues.

Inhibin a is a peptide consisting of two chains: the α chain and the β chain, synthesized in the cells of the reproductive system (in women in follicles and placenta, in men in the seminal tubules of the testicles (Sertoli cells), serves to diagnose cancer metastases.

Melan-A is an antigen characteristic of melanocytes, it is also called MART-1 (melanoma antigen recognized by T cells). The Milan/MART-1 gene encodes a protein that is found in the endoplasmic reticulum and melanosomes. The function of this protein is currently reliably unknown. Melan-A is expressed in all normal melanocytes

and melanocyte cell lines, therefore it can serve as a marker of primary melanomas and their metastases.

Pancytokeratin (clone AE1/AE3) is an immunohistochemical marker characteristic of the epithelium, it is present in all cases of cancer and is an indispensable marker of micrometastasis and circulating tumor cells.

p21 (CDKN1A – from English - cyclin-dependent kinase inhibitor 1A, Cip1) is an intracellular protein, an inhibitor of cyclin-dependent kinase 1A, involved in the cellular response to DNA damage. Its level is elevated in differentiated cells.

p53, a protein also involved in the cellular response to DNA damage, is encoded by the TR53 gene located on chromosome 17 (17p13.1) and is expressed in all cells of the body, performs the function of a suppressor of the occurrence of malignant neoplasms – a mutation of the TR53 gene is found in cells of half of cancerous tumors. In the absence of DNA damage, this protein is in an inactive state, and when it is damaged, it activates and starts transcription of a group of genes that contain a nucleotide sequence in the regulatory region called the p53-response element (a section of DNA to which the p53 protein binds). The result of p53 activation is the stopping of the cell cycle and DNA replication, with a strong stress signal — the start of apoptosis. In other words, the function of the p53 protein is to remove from the pool of replicating cells those cells that are potentially oncogenic (hence the figurative name of the p53 protein — English guardian of the genome — keeper of the genome).

CyD1(cyclin D1) is a protein that specifically regulates the G1/S phase transition in the cell cycle. It is encoded by the CCND1 gene located at chromosomal locus 11q13. The content of this protein in a cell depends on the phase of the cell cycle. Cyclin D1 functions as a regulator of cyclin-dependent kinases (forms a complex with cyclin-dependent kinases CDK4 and CDK6 and activates them) and promotes strict temporal coordination of various intracellular signaling cascades during each mitotic

event and the correct course of the cell cycle. The cyclin D1/CDK4 or cyclin D1/CDK6 complex activates (phosphorylates) the retinoblastoma Rb protein (tumor suppressor), which promotes the progression of the cell cycle and the transition from G1 to S-phase. And the expression of the cyclin D1 gene, in turn, is positively regulated by the Rb protein. Mutations, amplification and overexpression of the cyclin D1 gene, which accelerates cell cycle progression and cell division, are often observed in various tumors and can contribute to oncogenesis. Therefore, immunohistochemical staining for cyclin D1 is used to diagnose malignant tumors.

CD34 is a protein located in the cell membrane that serves for intercellular adhesion. Playing a role in the early stages of hematopoiesis, it mediates the binding of stem cells to the extracellular matrix or directly to stromal cells. It serves as a protein framework for attaching specific glycans. CD34 protein is expressed in the early stages of the development of hematopoietic and vascular-associated tissues. It is noted that CD34 is detected in many types of tumors and is involved in the occurrence and development of leukemia.

The Ki-67 antigen is present in the nuclei of all proliferating cells in all phases of the cell cycle, except G0 [Gerdes J., Lemke H., Baisch H. et al., 1984], and attracts the attention of scientists as a marker of rapid proliferation. Ki-67 plays a predictive role for the early stages of cancer. Currently, a link has been identified between the expression of this marker and the risk of tumor recurrence and the likelihood of death in cancer patients. The Ki-67 marker is one of the most in demand for the morphological determination of the malignancy potential of a tumor — the proliferation index of less than 5% is characteristic for adenomas of the adrenal cortex, and more than 5% for carcinomas [Selivanova L.S., Roslyakova A.A., Kovalenko Yu.A. et al., 2019].

A number of labels are used to visualize the binding site of the antigen to the antibody: fluorescent dyes, enzyme labels, metals, metalloproteins, radioisotopes.

There are two most commonly used variants of the IHC method: direct immunofluorescence and indirect peroxidase.

Initially, the visualization of tissue antigens by enzyme immunoassay staining methods was carried out by a direct method using enzymes directly conjugated with antibodies of known antigenic specificity. This method allows the use of a light microscope, but is low-sensitivity. The sensitivity of immunohistochemical staining has been significantly increased with the development of an indirect method in which enzyme-labeled secondary antibodies bind to primary antibodies bound to an antigen. Subsequently, three-stage methods appeared, such as the peroxidase-antiperoxidase method, avidin-biotin complex and others. Modern imaging systems of the antigen-antibody complex belong to a new generation of enzyme-mediated staining methods and allow for immunological studies with high specificity and sensitivity in the presence of only a light microscope. This makes modern research methods available even for laboratories that are not equipped with special equipment.

Imaging systems have a number of advantages over traditional enzyme-mediated methods:

- provide an opportunity to evaluate the immunological profile and morphological features of a cell on a single preparation (in this case, the studied material can be fixed by various methods and allows long-term storage);

- provide high sensitivity and specificity of immunohistochemical studies;

- significantly reduce the analysis time and simplify the procedure, thereby allowing a large number of samples to be processed simultaneously;

- they allow the detection of antigens with weak expression;

- the double staining system allows simultaneous detection of two different antigens on the same drug.

The intensity of expression was evaluated for cytoplasmic and membrane markers: in the complete absence of expression or expression, less than 5% of cells are negative, 5-24% are weakly positive, 25-74% are moderately positive, and more than 75% are pronounced. The expression of Ki-67, p21, p53, and Cid 1 was evaluated quantitatively; the index of proliferative activity of Ki-67-positive nuclei in the field of view of a microscope (magnification x400) in the study of 2000 cells.

After conducting a statistical analysis of the results obtained, we noted several distinctive features characteristic of each type of neoplasm.

When evaluating the expression of pancytokeratin by tumor cells, the differences between adenomas and carcinomas were insignificant (p=0.04). In 5 cases, pancytokeratin expression was detected by adenomas, in 7 – by adrenocortical cancers (Fig. 20).

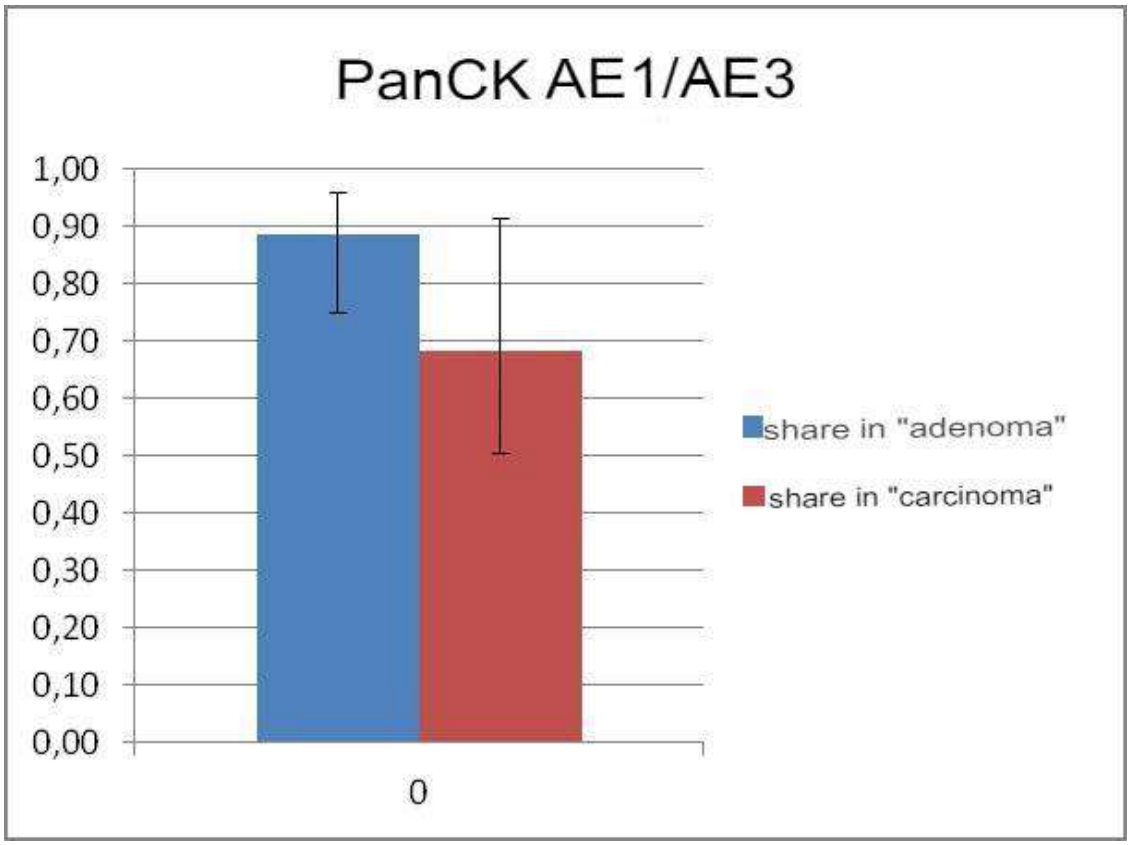


Fig. 20. Expression of pancytokeratin AE1/AE3 by tumor cells.

We noted a significant (approximately three-fold) (p=0.0004) predominance of nuclear expression of B-catenin in adrenal cortical adenoma cells (Fig. 21).

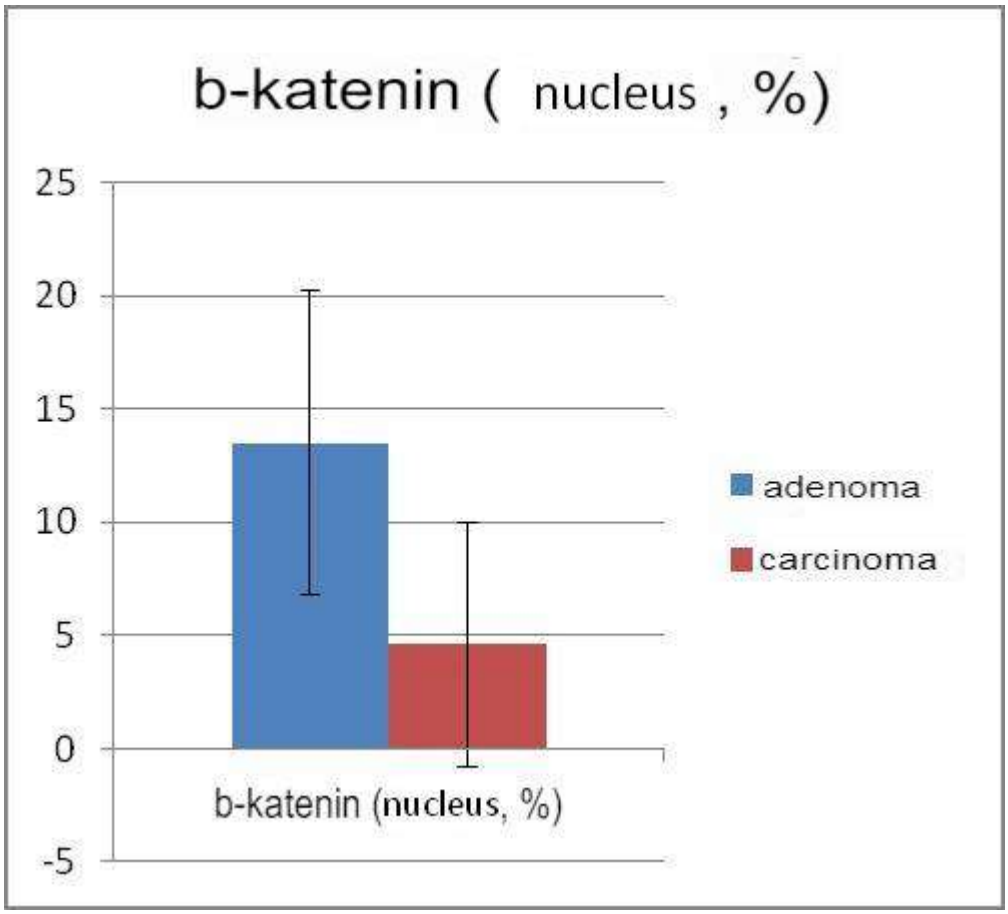


Fig. 21. Expression of B-catenin in the nuclei of tumor cells, %.

The phenomenon of dot-like expression of B-catenin in the cytoplasm was significantly more often detected in adrenocortical cancer cells – 45% versus 15% (p=0.0009) (Fig. 22).

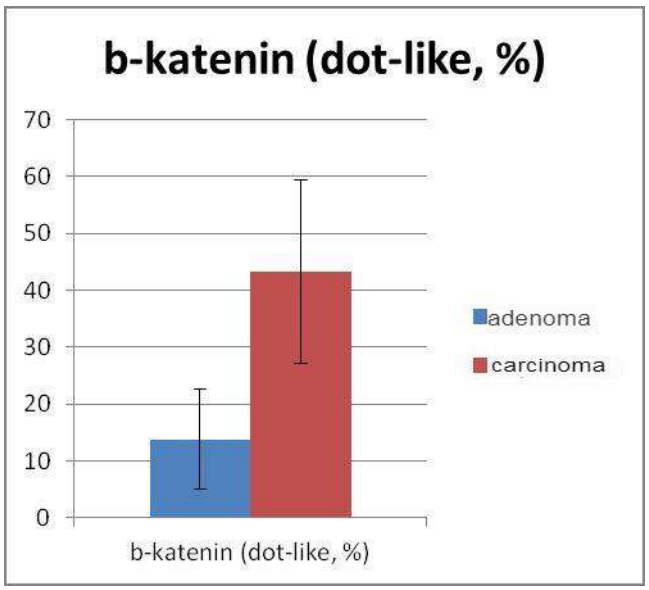


Fig. 22 Dot-like B-catenin expression in tumor cells, %.

The expression of melanin A of varying severity was determined in 100% of adenomas. The degree of expression in carcinomas was "intense" in 40%, "moderate" in 23%, "weak" in 32% (versus 8% in adenomas), and in 5% it was not detected at all (p0.05). We noted a decrease in the severity of melan A expression in carcinomas up to its complete loss (Fig. 23).

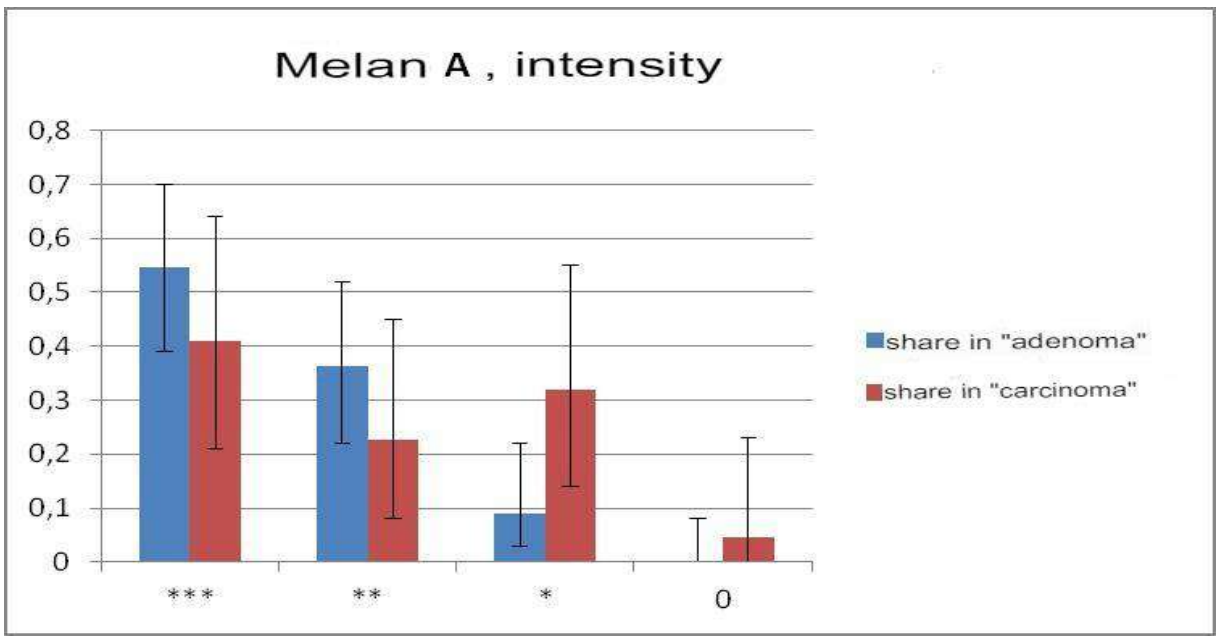


Fig. 23 The intensity of expression of melan A in tumor cells, %.

When assessing the spread and intensity of expression of inhibin a by tumor cells, no significant differences were found between adenomas and carcinomas (p0.01) (Fig. 24, 25).

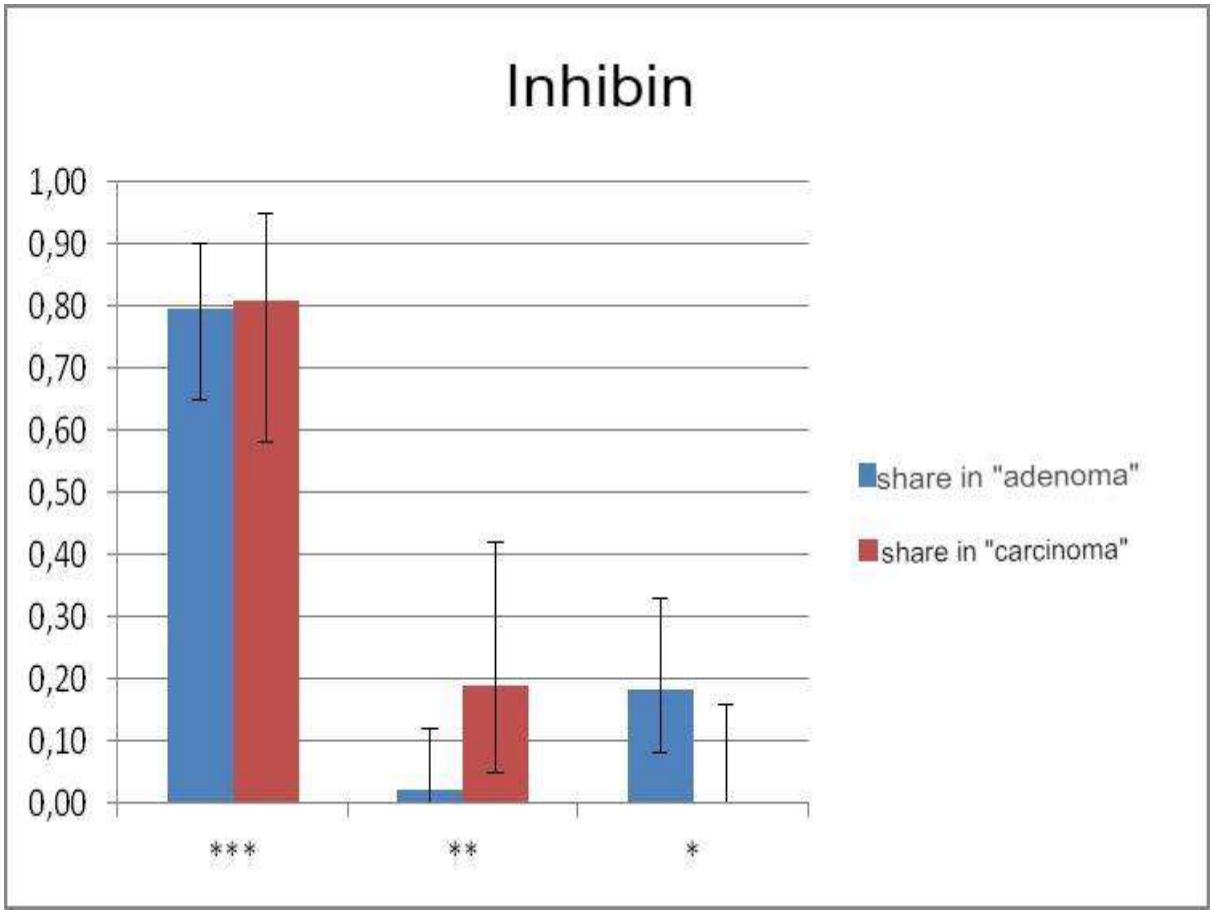


Fig. 24 Expression of inhibin a in tumor cells, %.

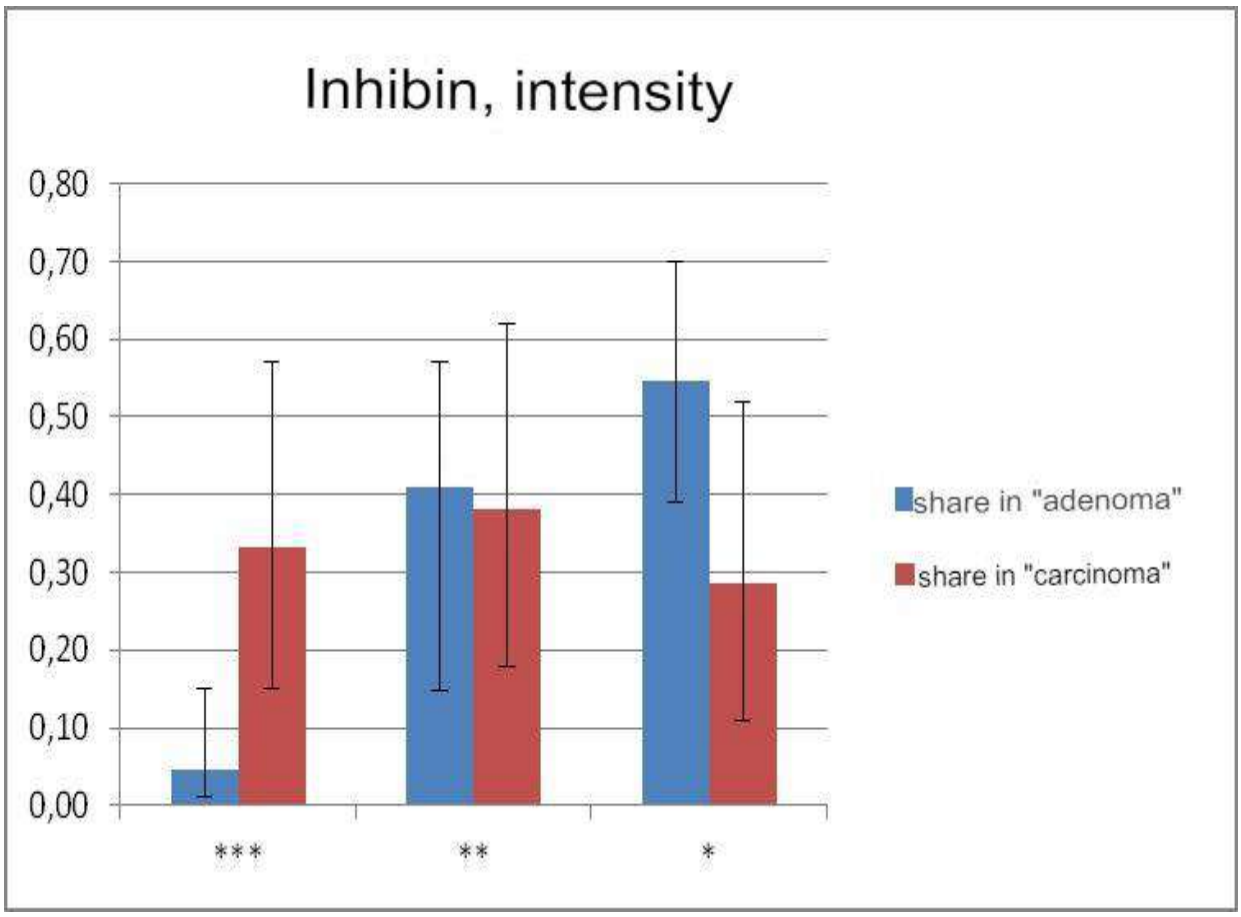


Fig. 25 Intensity of inhibin a expression in tumor cells, %.

Nuclear expression of p21 in carcinomas was found in 35% of cases versus 22% in adenomas, significant differences in this indicator were not revealed ($p<0,01$) (Fig. 26).

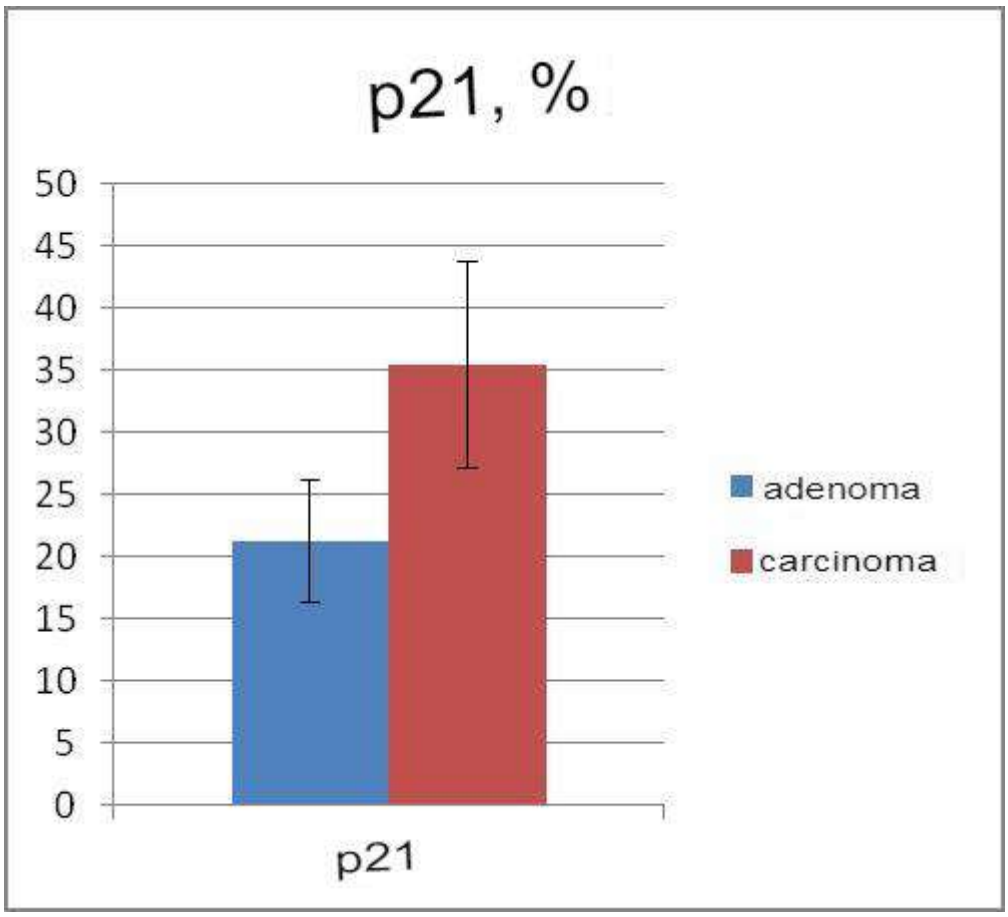


Fig. 26 Expression of p21 in tumor cells, %.

The assessment of the microcirculatory bed by detecting endotheliocytes by determining CD34 expression allows us to identify differences in the nature of the vascular pattern: in adenomas, as a rule, the vascular network was uniform (in 70% of cases), in carcinomas there was pronounced asymmetry, unevenness of the vascular capillary network (p=0.008) (Fig. 27, 28).

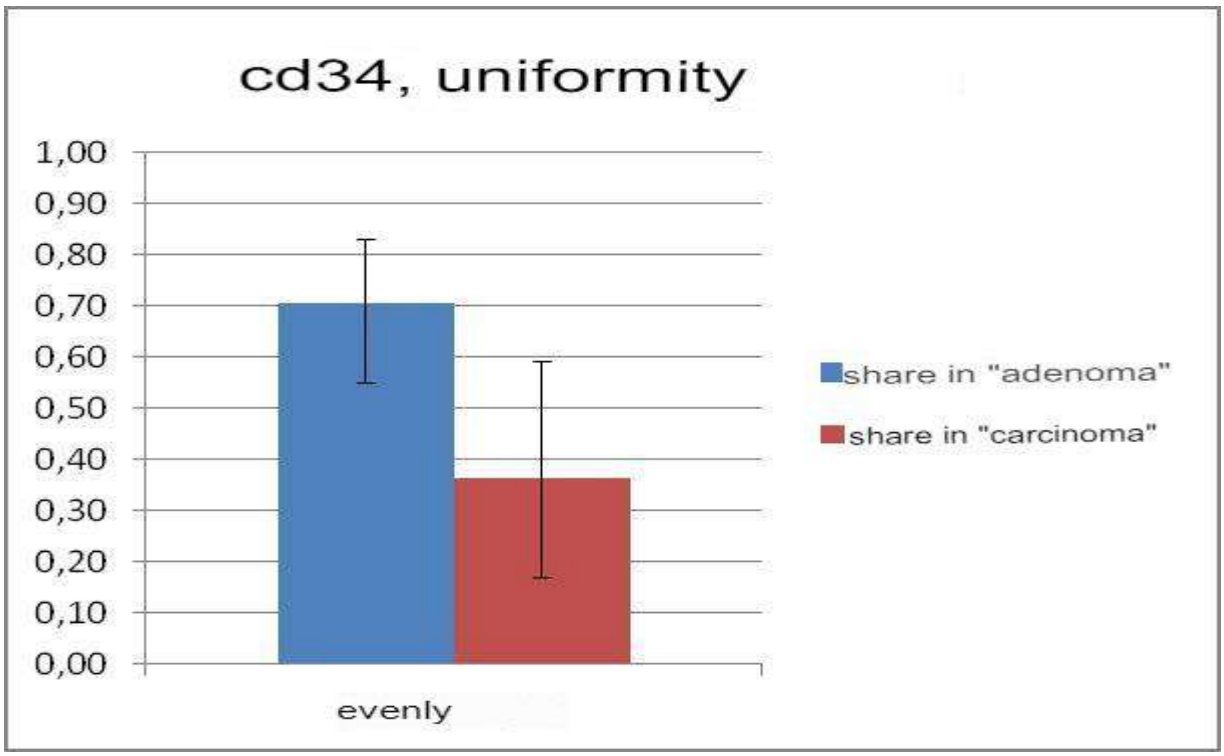


Fig. 27 Uniformity of CD34 expression in tumor cells, %.

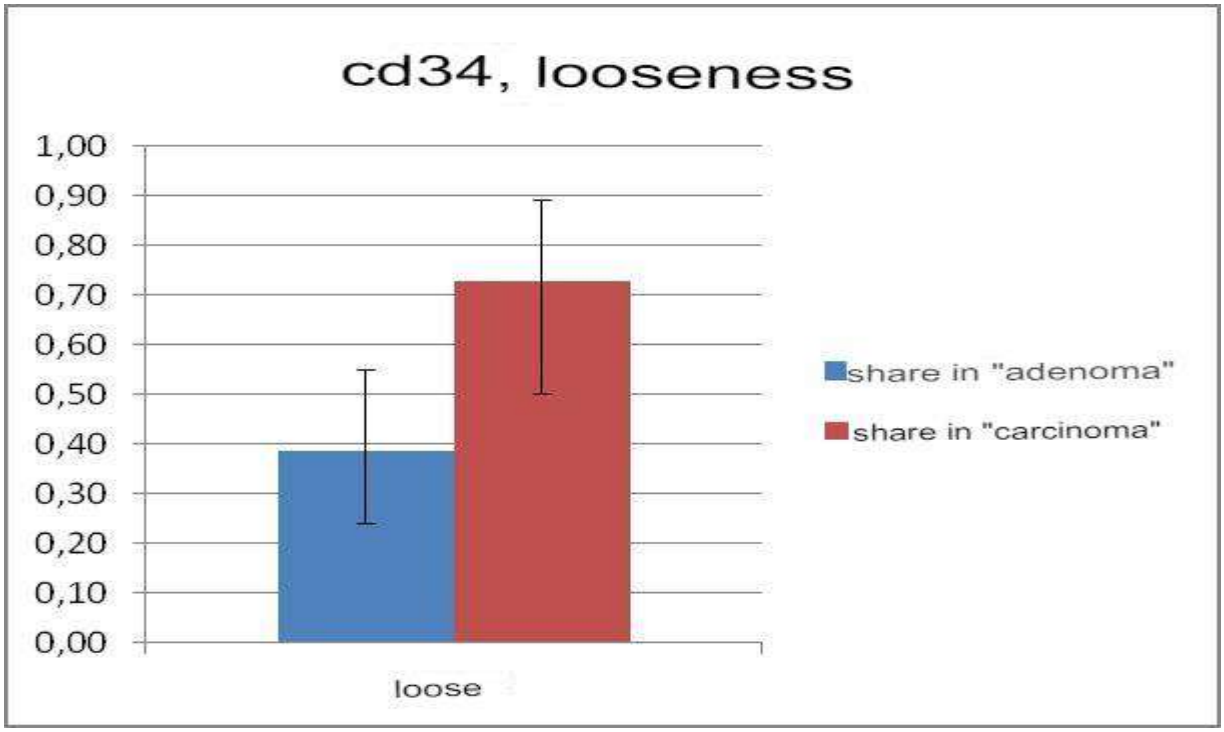


Fig. 28 Looseness of CD34 expression in tumor cells, %.

The expression of Ki-67 by tumor cells corresponds to the indicators of mitotic activity and was determined in 3% of benign tumors and in 23% of adrenocortical cancers, which is the most striking indicator of differences ($p<0,001$) (Fig. 29).

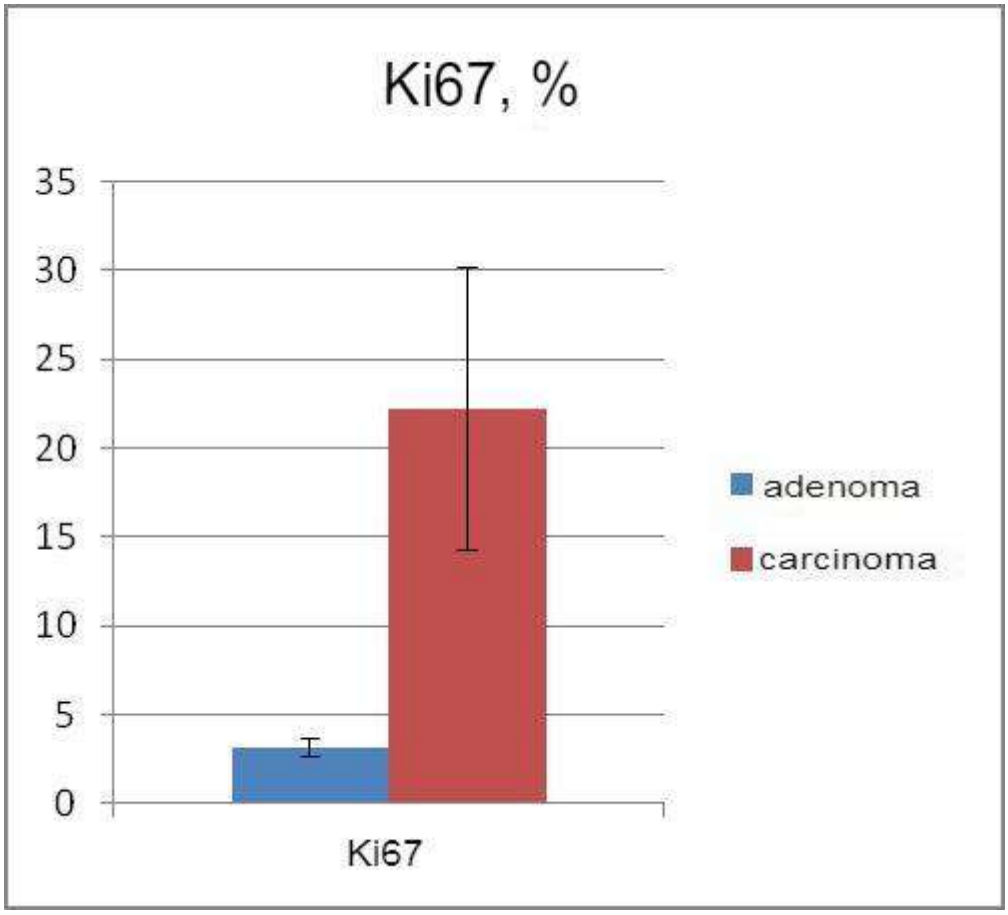


Fig. 29 The expression of Ki-67 by tumor cells, %.

Based on the above, we have made the following conclusions:

1. The asymmetric structure of the capillary network characterizes tumors with a high potential for malignancy.

2. Detected eosinophilic cells may be a highly specific sign of adrenocortical cancer.

3. The phenomenon of dark cellular endocrinocytes is not found in adrenal carcinomas.

4. There is a decrease in the degree of expression of melanoma expression, up to its complete loss in carcinomas (4%).

5. The phenomenon of don't-like expression of B-catenin in the cytoplasm in adrenocortical cancer is much more common than in adenomas.

6. The expression of Ki-67, as an indicator of the mitotic activity of cells, can be used in the differential diagnosis of benign and malignant neoplasms of the adrenal cortex.

Immunohistochemical examination is a high-tech methodological addition to traditional histological research methods in clinical diagnostics. Currently, the IHC method is widely used for the differential diagnosis of neoplasms, their immunophenotyping (for example, for tumors of the lymphoid system) and assessment of hormonal status, determination of the source of metastasis in an unclear tumor focus, determination of prognostic factors of the tumor process (malignancy potential); identification of various microorganisms (bacteria, viruses); definitions of hormones and their receptors, etc. Since a large number of poly- and monoclonal antibodies with high specificity and avidity are currently available, the number of applied tasks for which IHC methods can be used has become almost unlimited.

## Summary

Over the past many years, the problem of accidentally detected adrenal neoplasms has become increasingly relevant in endocrine surgery. This interest of surgeons and endocrinologists is primarily due to the fact that the widespread use in practice of modern imaging research methods (ultrasound, CT and MRI) conducted for diseases unrelated to the pathology of the adrenal glands, or in the process of medical examination, has led to the massive detection of such tumors. There was even a special term "incidentaloma", emphasizing that the neoplasm was detected accidentally (accidental — accidental). Some researchers are currently writing about an "epidemic" of adrenal tumors.

Randomly identified adrenal gland formations differ significantly in morphological structure. They can be both malignant and benign, secrete hormones and their precursors, or have no hormonal activity. In the current situation, endocrinologists and surgeons are acutely faced with the question of rational examination and choice of management tactics for such patients (dynamic observation or surgical treatment). Meanwhile, the issue of indications for surgical treatment has so far been ambiguously resolved. Surgical treatment is primarily subject to patients with identified hormone-active neoplasms - pheochromocytoma, aldosteroma, corticosteroma, with less common androsteromas and corticoestromas. Surgical removal of all these tumors is indicated regardless of the size of the tumors, since an increase in hormonal activity inevitably leads to irreversible changes in water-electrolyte and fat metabolism, serious disorders in the activity of the cardiovascular system.

Indications for surgical treatment in the presence of undoubted clinical and laboratory signs of a hormone-active tumor are determined quite easily. But, unfortunately, this is not always the case. Adrenal gland formations that have been identified by chance, as a rule, do not have obvious clinical signs of increased hormone

production. Targeted laboratory tests are required to confirm their hormonal activity. According to various authors, adrenal tumors with latent hormonal activity are diagnosed in 7-12%. Meanwhile, timely undiagnosed endocrine disorders caused by neoplasms of the adrenal glands subsequently also lead to changes in metabolism, sometimes very severe.

It often happens the other way around — the patient begins to conduct an examination about the complaints that bother him, which are very characteristic of conditions that can lead to increased secretion of certain adrenal hormones — primarily the crisis course of arterial hypertension. During the course of imaging studies in such patients, neoplasms in the adrenal glands are sometimes detected, however, during laboratory examination, the presence of hormonal activity of the tumor is not confirmed. The question arises — how to deal with such patients? Do they require surgical treatment? Will the operation improve their condition?

Another problem is the detection of malignant neoplasms of the adrenal glands before the operation. The proportion of adrenocortical cancer among randomly detected adrenal gland formations ranges from 2.4% to 4.5%. Various criteria are proposed for the diagnosis of a malignant tumor. Some authors focus on the size of the neoplasm when choosing indications for surgery, and this criterion varies from 2 to 7 cm. A certain progress in the diagnosis of adrenocortical cancer has been the improvement of radiation research methods and, above all, CT with bolus administration of a contrast agent. The study of the native density of formation, density in the arterial, venous and delayed phases made it possible to improve the differential diagnosis of adrenal tumors before surgery so much that using CT with intravenous bolus contrast, it is possible to assume the morphological structure of the tumor with an accuracy of 75 to 99%.

The technique of puncture biopsy for the purpose of morphological verification of the tumor before surgery is currently being developed in detail. However, due to the

high risk of possible complications, it is rarely used and only after biochemical exclusion of a catecholamine-producing tumor. As a rule, a biopsy is used to verify the organ affiliation of metastases in the adrenal glands and diagnose their tuberculous lesion, but only if the expected result of the study is able to change the patient's management tactics.

Certain hopes in the differential diagnosis of benign and malignant neoplasms of the cortical layer are pinned on the study of the steroid profile of urine, a relatively new method and currently rarely widely used.

Uncertainty about the accuracy of the diagnosis leads to an increase in the number of unjustified surgical interventions.

But even after removal of the adrenal neoplasm, the problem of a final diagnosis is not always solved simply. Difficulties often arise in morphological diagnosis. Examination using light microscopy does not always make it possible to make a correct diagnosis. In such cases, it is necessary to use additional techniques, including histochemical, immunohistochemical, electron microscopic and even molecular genetic studies.

All of the above served as the basis for this scientific work. The purpose of this study was to optimize the differential diagnosis of randomly identified adrenal neoplasms to clarify the indications for surgical treatment.

The dissertation work consists of two parts — clinical and diagnostic.

In the clinical part of the study, the task was to identify differences in the manifestations of adrenal diseases and concomitant pathologies with a similar clinical picture. To this end, the data of 264 patients with adrenal incidentalomas who were admitted to the Department of Endocrine Surgery of the Pirogov St. Petersburg State University Clinic of High Medical Technologies for surgical treatment on a planned

basis from 2007 to 2015 were studied. Among them there were 203 women and 61 men aged 18 to 75 years (average age 52.89±12.73 years). In all cases, the tumor was detected accidentally in other medical institutions or in adjacent departments of the clinic during ultrasound, MRI or CT scans performed in connection with suspected pathology in the abdominal cavity or retroperitoneal space, or during routine medical examination. The proportion of patients with randomly identified neoplasms among the total number of patients operated on for adrenal tumors (359 people) was 73.54%, the remaining 26.46% (95 people) were identified hormone-active tumors.

Concomitant diseases were observed in the vast majority of patients with randomly identified adrenal neoplasms. They were detected in 256 (96.96%) operated patients. As a rule, two, three or more pathologies were found in the same patient (in 251 people). The absence of concomitant diseases was found in only 8 people (3.04%).

From the group of patients with randomly identified adrenal neoplasms, a group of patients suffering from a crisis course of arterial hypertension was singled out separately. They were usually referred for consultation with suspected pheochromocytoma. Upon further examination, according to radiation and laboratory research methods, this diagnosis was not confirmed. Histological examination after surgery in all cases established the presence of adrenocortical adenoma in patients. During examination by neurologists before and after surgery, these patients were diagnosed with somatoform dysfunction of the autonomic nervous system (SDANS), requiring special treatment. This group of patients consisted of 44 people (39 women and 5 men), which accounted for 16.66% of the total number of operated patients with randomly identified adrenal gland formations.

A study was conducted, followed by a comparison of complaints and anamnesis of operated patients with randomly identified adrenal gland formations suffering from

SDANS with a crisis course of arterial hypertension, and in patients with pheochromocytoma.

The task of the diagnostic part of the work was to analyze the available laboratory, instrumental and morphological methods of examination of patients with randomly identified adrenal neoplasms in order to determine their advantages and disadvantages. To this end, all patients underwent general clinical and biochemical analyses, a study of the level of steroid hormones, their precursors and metabolites, and the excretion of methanephrines.

The sample of patients for determining the steroid profile of urine (USP) was 67 people. Of these, 23 were diagnosed with ACC, the remaining 44 had hormone–inactive formations: adenomas (37 patients), pheochromocytomas (6 patients) and one patient with a solitary adrenal cyst). All patients filled out an informed consent form to conduct scientific research with their biological samples. Statistical processing of the obtained data was carried out using standard Microsoft EXEL XP tools.

To determine the localization of the tumor and its radiation characteristics, we most often used ultrasound and CT, less often MRI.

Ultrasound of the adrenal glands was performed on an Accuvix V10 ultrasound scanner manufactured by Samsung Medison (Republic of Korea) using a conventional technique using a 3-7 MHz convexic sensor. Magnetic resonance imaging was performed on various magnetic resonance imaging machines on an outpatient basis in various medical and diagnostic institutions in St. Petersburg. Computed tomography for most patients was performed on a Toshiba Aquilion 64 computed tomograph (Japan) with the possibility of obtaining 0.5 mm thick slices with the construction of multiplanar reformations under native conditions. In 117 patients, the study was conducted with intravenous "amplification".

All the removed formations were subjected to histological, and in some cases immunohistochemical studies, which were conducted in the morphological laboratory of the National Center for Clinical Morphological Research (director, doctor of the highest category, Ph.D. Vorobyov S. L.). The results of histological and immunohistochemical studies were compared in 66 patients with randomly identified adrenal neoplasms. Histological examination of the removed tumors revealed adrenal adenomas in 44 of them, which had no malignant potential. 22 have adrenocortical carcinomas.

During the study, the tumor was evaluated in accordance with the international histological classification of adrenal tumors (WHO, 2004). The histological features of adrenocortical tumors were evaluated using the Weiss system. Monoclonal antibodies to vimentin, pancytokeratin AE1/AE3, β-catenin, inhibin a, melan-A, polyclonal antibodies to Ki-67, p21, p53, CD1, CD34 were used for immunohistochemical studies. The working dilutions of antibodies were selected empirically using positive controls.

When processing the results of histological and immunohistochemical studies, numerical dimensional indicators were examined for consistency with the Gaussian distribution using the Shapiro-Wilk criterion. In this paper, there were no sample distributions consistent with the normal one, therefore, the Mann-Whitney rank criterion was used to test hypotheses when comparing indicators in groups, and descriptive statistics represented the median and two percentiles of the 25th and 75th.

Non-numeric indicators were processed by comparing the proportions of values in subgroups. The chi-square criterion was used to test statistical hypotheses. The significance level for all criteria was assumed to be 0.05.

Statistical analysis was carried out using the IBM SPSS 20.0 program.

A clinical study revealed that patients with SDANS usually have a combination of complaints of a violation of the cardiovascular system (most often heart palpitations, blood pressure rises), with complaints indicating chronic damage to the autonomic

nervous system - sweating, tremor, redness, feeling hot, anxiety, panic attacks, fear of confined spaces, a feeling of fleeting pain, burning, heaviness, tension, a feeling of swelling or stretching in any part of the body, and others. As a rule, these patients behaved excessively emotionally, were hypochondriacal, complained of sleep disorders, a feeling of fear. Such patients are characterized by persistent dermographism. In patients with SDANS, the so—called non-infectious subfebrility is sometimes found - an increase in body temperature in the range of 37-37.9 ° C, detected throughout the day (or only at any time of the day) for several weeks, months, less often years. Objective examination often revealed: lability of blood pressure with a tendency to hypertension, there was a tendency to tachycardia that occurs spontaneously and inadequately to the situation, respiratory disorders in the form of respiratory arrhythmia (an increase in the number of heart contractions during inhalation, with a decrease in the frequency of its contractions on exhalation), dyspnea, tachypnea, the so-called "dreary sighs" (the need to periodically take deep breaths of air).

The difference between the course of the hypertensive crisis in SDANS and the course of the crisis in pheochromocytoma was that in the first case, headache first appears or increases, numbness and cold of the extremities occur, and only then there is an increase in blood pressure to 150/90 - 180/110 mm Hg, pulse increases to 110-140 beats / min, pain in the area is noted the heart, there is excitement, motor restlessness, sometimes the body temperature rises to 38-39 ° C. In the second case, with pheochromocytoma, the crisis develops suddenly, without precursors. A crisis can be provoked by mechanical irritation of the tumor (palpation of the abdomen), hyperventilation, the use of alcoholic beverages and foods containing tyramine (some varieties of cheese, certain brands of red wines), taking medications with pronounced vasodilating properties (histamine, magnesium sulfate, euphyllin, papaverine, etc.). Since the clinical picture during a hypertensive crisis when pheochromocytoma is caused by the release of a large amount of catecholamines into the blood, blood pressure

rises instantly to 250/130 - 300/150 mmHg. Pallor, acrocyanosis, sweating (sometimes profuse), body trembling, tachycardia are observed, vision and hearing may be impaired. Body temperature rises, leukocytosis and hyperglycemia are detected, sugar can be detected in the urine. There are various rhythm disturbances on the ECG. The crisis may be complicated by a violation of cerebral circulation, pulmonary edema. The crisis stops suddenly. The exit from the crisis is characterized by a rapid decrease in blood pressure, often accompanied by orthostatic hypotension; tachycardia stops, pallor of the face is replaced by redness, a feeling of warmth in the body appears, patients are extremely exhausted. The duration of the attack varies from a few seconds to several days; the frequency of attacks varies from 1-2 within a few months to 5-10 within an hour. Crises with pheochromocytoma are not accompanied by loss of consciousness.

When analyzing the nature of hypertension crises in patients with pheochromocytoma, two phases of the crisis can be distinguished. The first phase is conventionally called "sympathetic". Patients consistently develop the following symptoms: pronounced tachycardia with throbbing headaches and pallor of the skin. Then there is a feeling of cooling of the lower extremities, "creeping goosebumps", internal trembling and chills, an inexplicable feeling of anxiety and fear of death. The second phase is "parasympathetic". The face turns red, there is profuse sweating, there may be bradycardia, polyuria.

In patients with randomly identified tumors of the adrenal glands and SDANS, such periodicity was not observed during the crisis. Symptoms of arousal of the sympathetic and parasympathetic parts of the autonomic nervous system were observed in them, as a rule, simultaneously and randomly. The crisis began with tachycardia, but at the same time there was hyperemia of the skin of the face, which never happened with pheochromocytoma. These patients complained of feelings of anxiety and fear, sometimes turning into a panic state. But unlike patients with pheochromocytoma, they

also had a feeling of fear outside the crisis. Crises in SDANS were provoked by stressful situations, being in a confined space, in the subway, in crowded transport, which was not observed in any patient with pheochromocytoma. The fear of confined spaces in patients with SDANS often came out on top, or this symptom was easily detected even with a cursory survey of the patient.

Another sign of arousal of the parasympathetic system is polyuria. In all patients with pheochromocytoma, it was observed at the end of the crisis, in patients with SDANS it could be at any stage of its course, and in some of them it occurred long before the development of the crisis and was regarded by us as a harbinger. It should also be noted that when analyzing our material, we were convinced that there are no precursors of a crisis in pheochromocytoma at all. Patients with randomly identified neoplasms and SDANS may have such precursors.

According to the obtained data from the analysis of radiation research methods, as a feature of the location of adenomas, we identified the fact that they can arise both from the body of the adrenal gland and from both of its legs, but these neoplasms are located, as a rule, above the upper pole of the kidney and do not shift to its gates. Adenomas, as a rule, were small in size - on average 3.5 cm, adrenocarcinomas were most often a large tumor. In patients with adrenal adenoma, CT with intravenous contrast showed that the accumulation of contrast agent was detected in 100% of adenomas, most often it occurred in the arterial phase (85.71%) and was non-intensive in 57.14%. In the arterial phase of the study, the densitometric density increased by an average of 47 units compared with the native phase, 10 minutes after intravenous administration of the contrast agent, the density of formation decreased by 64.29%. These data suggest that adrenocortical adenomas, as a rule, do not intensively accumulate contrast agent, more often this occurs in the arterial phase (moreover, in this phase of the study, adenomas accumulate contrast more intensively than carcinomas)

and have a higher rate of contrast agent excretion compared with adrenal cancer. Adrenocarcinomas, in turn, in most cases accumulate contrast heterogeneously and remove it more slowly.

Pheochromocytomas occur in the medial pedicle and the body of the adrenal gland, which may contribute to the displacement of the tumor during its growth to the kidney gate. After analyzing CT images, a feature of the location of pheochromocytes in the retroperitoneal space was also revealed. First of all, this concerned those tumors whose size exceeded 4 cm. Such neoplasms, as a rule, were located at the vascular pedicle of the kidney, thus shifting anteriorly and medially from its upper pole. This feature of the location, which distinguishes pheochromocytomas from other formations of the adrenal gland, can be useful in the differential diagnosis of neoplasms of this organ. Despite the fact that computed tomography has 100% sensitivity for detecting adrenal neoplasms, its use for the purpose of their differential diagnosis, unfortunately, does not have 100% specificity. Based on this, in order to verify tumors to determine patient management tactics, indications for surgical treatment and prognosis of the disease, in addition to radiation diagnostic methods, new non-invasive techniques are currently being proposed, such as determining the steroid profile of urine using gas chromatography-mass spectrometry.

According to the results of the analysis of laboratory data among patients operated on for accidentally detected adrenal neoplasms, 17 people (6.44%) were diagnosed with pheochromocytoma based on the results of histological examination, since these patients did not have a characteristic clinical picture, and laboratory parameters during the examination did not go beyond the reference values - metanephrine total in daily urine is 132.8±25.7 mcg/day at a rate of up to 350 mcg/day; chromogranin A in blood plasma is 79.4±15.3 mcg/l at a rate of up to 125 mcg/l; neuron-specific enolase (NSE) in blood plasma is 9.7±2.3 mcg/l at a rate of up to 18.3

mcg/l. This may indicate that the production of catecholamines by the tumor was at a low enough level to detect it using traditional laboratory diagnostic methods. When analyzing the results of CT and histological studies, it was noted that these were mainly small tumors, measuring 3.2 ±1.3 cm.

In the diagnosis of Itsenko-Cushing syndrome, we used the determination of ACTH and cortisol content in blood plasma, cortisol excretion in daily urine, determination of saliva cortisol content at 23 hours and a test with 1 mg dexamethasone. In addition to 24 people with clinical manifestations of Itsenko-Cushing syndrome in whom laboratory data confirmed the diagnosis (ACTH in blood plasma 0.35±0.21 pmol/l at reference values of 1,034 — 10.736 pmol/l; cortisol in blood plasma 691.5±41.8 nmol/l at a norm of 185 — 624 nmol/l; cortisol excretion in daily urine is 1517.76±254.42 nmol/24h at a rate of 160 - 1112 nmol/24h; salivary cortisol at 23 hours is 22.3±5.1 ng/ml at a rate of 1.2 — 14.7 ng/ml; cortisol in blood plasma at 8 a.m. 163.6±42.8 nmol/l after taking 1 mg dexamethasone at 23 o'clock), among patients with incidentalomas, a group of patients (n=19) was identified who had no suppression of cortisol secretion during the test with 1 mg dexamethasone - cortisol in blood plasma in the morning 96.4±23.6 nmol / l after taking 1 mg of dexamethasone at 23 o'clock at normal plasma cortisol levels - 342.7±72.8 nmol/ l at a norm of 185 — 624 nmol/ l, salivary cortisol at 23 o'clock 17.8 ±5.1 ng/ml at a norm of 1.2 — 14.7 ng/ml in the absence of obvious clinical manifestations of endogenous hypercortisolism. These patients were diagnosed with "subclinical Itsenko-Cushing syndrome" and underwent surgical treatment. Histological examination revealed the tumor to be adrenocortical adenoma in 14 patients and carcinoma in 5.

In order to identify primary hyperaldosteronism, we determined the concentration of potassium, aldosterone and renin in the blood serum, and calculated the aldosterone-renin ratio (ARR). If, according to ARR data, it was proved or suspected

that a patient with an accidentally detected adrenal gland formation had PHA, then the next stage of diagnosis was to conduct a test with saline solution. For the purpose of differential diagnosis of unilateral or bilateral adrenal damage, comparative selective blood sampling from the adrenal veins was performed with determination of plasma concentrations of aldosterone, renin and cortisol. In addition to patients admitted to the department for surgical treatment with an already established and confirmed diagnosis of "Primary hyperaldosteronism" (n=28), among patients with randomly identified adrenal neoplasms examined during hospitalization in our hospital, this diagnosis was established in three more. The clinical picture of PHA in these patients was absent, when analyzing laboratory parameters, a decrease in serum potassium concentration of 3.1±0.23 mmol/l was noted at laboratory reference values of 3.5 — 5.3 mmol/l and direct renin of 1,164±0.72 μm/ml with a standing norm: 4.4 — 46.1 μm/ml, lying: 2.8 — 39.9 microns/ml, an increase in serum aldosterone of 606.2±47.4 pg/ml at a standing norm: 25.6 — 445 pg/ml, lying down: 19.7- 260 pg/ml and an aldosterone-renin ratio above 12.5.

The study of the concentration of dehydroepiandrosterone sulfate (DHEA-S) in blood plasma in all patients with adrenal incidentalomas was aimed at diagnosing ACC. In 19 patients with a histologically confirmed diagnosis, an increase in the plasma content of dehydroepiandrosterone sulfate was noted - 15.7±5.3 mmol/l at a norm of 0.32 - 3.61 mmol/l.

As a result of processing the data obtained in determining the steroid profile of urine by gas chromatography-mass spectrometry, we came to the conclusion that each sample is purely individual and it is not necessary to focus only on the concentrations of certain steroids, but it is necessary to evaluate the totality of all substances in each specific sample, since the volume of daily diuresis, and, as a result, the concentration of detectable hormones, their precursors and metabolites is influenced by many different

factors. The data obtained indicate the importance of using GC-MS in the differential diagnosis of ACC and adrenocortical adenomas, which, in combination with data from imaging research methods, will increase the accuracy of ACC diagnosis at the preoperative stage. In controversial or doubtful cases of histological assessment of a removed tumor, the USP determination performed before surgery may be useful in the process of establishing a final diagnosis as an additional diagnostic method.

The presented results once again demonstrated the importance of a thorough hormonal examination in patients with randomly identified adrenal gland formations, both with and without a pronounced clinical picture of hormonal activity.

All patients with suspected ACC are recommended to study the steroid profiles of biological fluids using chromatography methods to identify signs of malignancy of adrenal glands. We note the need for further search for the most informative biochemical markers of ACC.

The presence of false negative results does not allow us to speak about the preferential use of the method of determining USP as a diagnostic criterion of ACC. But the absence of these disorders in patients with randomly identified adrenal neoplasms, who had no malignant potential, suggests the use of this method to monitor tumor metabolism and eliminate the likelihood of malignant degeneration.

After analyzing the results of histological and immunohistochemical research methods, the following can be noted:

- The asymmetric structure of the capillary network characterizes tumors with a high potential for malignancy.

- Detected eosinophilic cells may be a highly specific sign of adrenocortical cancer.

- The phenomenon of dark cell endocrinocytes does not occur in adrenal carcinomas.

- There is a decrease in the degree of expression of melanin A, up to its complete loss in carcinomas (4%).

- The phenomenon of dot-like expression of B-catenin in the cytoplasm in adrenocortical cancer is much more common than in adenomas.

- The severity of Ki-67 expression, as an indicator of mitotic cell activity, can be used in the differential diagnosis of benign and malignant neoplasms of the adrenal cortex.

Immunohistochemical examination is a highly accurate methodological addition to traditional histological research methods in the diagnosis of malignant neoplasms of the adrenal glands.

Based on the above, we can say that the tasks assigned to this study have been completed.

## Conclusions

1. Adrenal carcinomas have a higher densitometric density (usually more than +25 HU) than adenomas, however, it is important to remember that sometimes both heterogeneous adenomas with increased density and adrenocortical carcinomas with a homogeneous structure of small size and low density can occur. In doubtful cases of diagnosis, the examination of the steroid profile of urine is more important to confirm adrenal cancer than other methods of differential diagnosis of benign and malignant neoplasms of the adrenal glands.

2. Characteristic signs of adrenal cortical adenoma according to CT data are low native density (less than +10 HU), a high percentage of contrast media leaching (more than 50%), clear contours and detection of a central vein passing through the tumor tissue. As a feature of the location of adenomas, it can be noted that they can arise both from the body of the adrenal gland and from both of its legs, but these neoplasms are located, as a rule, above the upper pole of the kidney and do not shift to its gates. Signs of malignancy of an adrenocortical tumor are a high native density, a low percentage of contrast agent leaching (less than 50%) 10 minutes after its administration in the presence of characteristic signs of malignancy according to a study of the steroid profile of urine determined by the GC-MS method.

3. When using radiation research methods, primarily computed tomography with intravenous contrast, according to the characteristic topographic location of the tumor (originates from the medial part of the adrenal gland and is located medial and anterior to the kidney) and densitometric characteristics in different phases of the study (a high-density tumor accumulating contrast agent in the arterial phase more than in the venous), it is possible to assume a pheochromocytoma. Randomly identified pheochromocytomas that do not have hormonal activity do not differ in their densitometric characteristics from functionally active ones. The high content of

methanephrines in blood plasma, their increased excretion in urine, and the absence of signs of a malignant process according to the determination of the steroid profile of urine using GC-MS confirm the diagnosis and make it possible to distinguish pheochromocytoma from adrenocortical carcinoma. In the delayed phase (10 minutes after administration of the contrast agent), the absolute percentage of leaching from these tumors may not differ.

4. The clinical picture of the crisis of arterial hypertension in somatoform dysfunction of the autonomic nervous system in patients with randomly identified hormonal inactive tumors of the adrenal glands has clear differences from the crisis in hypertension and from the adrenal crisis in pheochromocytoma, which, however, does not exclude the need to examine the patient in order to exclude a chromaffin tumor..

5. The most informative sign of ACC according to GC-MS is an increase in urinary excretion of tetrahydro-11-deoxycortisol, 5-pregnen-3α,16α,20α-triol, 5-pregnen-3β,16α,20α-triol, pregnanediol, pregnentriol, as well as an increase in the ratio of tetrahydrocorticosterone to allo-tetrahydrocortisol, this, in combination with data from imaging research methods, increases the accuracy of diagnosis of malignant neoplasms of the adrenal cortex at the preoperative stage.

6. The combination of the asymmetric structure of the capillary network, the predominance of eosinophilic cells, a decrease in the degree of expression of melan A, up to its complete loss, the phonome of dot-like expression of B-catenin in the cytoplasm, an increase in the expression of Ki-67 as an indicator of cell proliferative activity is a reliable complex morphological immunohistochemical sign of adrenocortical cancer. The phenomenon of "dark cell formation" (cytoplasmic basophilia) of tumor cells detected by light microscopy can occur in adenomas of the adrenal cortical layer, but it does not occur in adrenocortical carcinomas.

7. One of the reliable methods of differential diagnosis is the morphological research method, the value of which increases when using an integrated approach — a combination of light microscopy, IHC with an assessment of factors reflecting the biological potential of neoplasia.

## Practical recommendations

1. Metastases of small size (up to 5 cm) to the adrenal glands do not differ in their densitometric characteristics from cancer of the cortical layer. To clarify the diagnosis and the source of metastasis, it is most advisable to use a single-port retroperitoneoscopic adrenalectomy.

2. The detection of a central vein passing through the tumor tissue of the cortical layer according to CT with contrast practically excludes malignant growth and indicates the benign formation.

3. When morphologically examining a removed adrenal tumor, it should be borne in mind that IHC examination is of paramount importance in the differential diagnosis of neoplasms arising directly from the adrenal tissues and metastases to the adrenal gland of tumors of other organs. In controversial or doubtful cases of histological assessment of a removed tumor, determination of the steroid profile of urine using gas chromatography-mass spectrometry performed before surgery may be useful in the process of establishing a final diagnosis as an additional diagnostic method.

4. The use of the method for determining the steroid profile of urine using gas chromatography-mass spectrometry as an independent diagnostic criterion for adrenocortical cancer is ineffective, but the identification of the absence of listed disorders of steroid metabolism in patients with randomly identified adrenal neoplasms, who lacked malignant potential according to CT data, allows us to talk about the use of this method as an additional argument when making a decision in favor of dynamic patient monitoring.

5. Annual CT scan with contrast enhancement is not advisable for patients with tumors of negative native density of small size under dynamic observation. In order to control the size of the tumor, an MRI scan without contrast is sufficient.

## List of conditional abbreviations

ACC - adrenocortical carcinoma

ACTH - adrenocorticotropic hormone

AH - arterial hypertension

APA - aldosterone-producing adenoma

APCW - absolute percentage of contrast agent washout

ARR - aldosterone-renin ratio

BP - blood pressure

CHD - coronary heart disease

CNS - central nervous system

CSBSAV - comparative selective blood sampling from the adrenal veins

CRH - corticotropin-releasing hormone

CT - computed tomography

HPLC - high-precision liquid chromatography

HU - Hounsfield unit

GC - gas chromatography

GC-MS - gas chromatography-mass spectrometry

MEN - multiple endocrine neoplasia

MRI - magnetic resonance imaging

NCA - neurocirculatory asthenia

NCD - neurocirculatory dystonia

NF1 - neurofibromatosis type 1

NF2 - neurofibromatosis type 2

PHC / PG – pheochromocytoma / paraganglioma

PG - paraganglioma

PHA - primary hyperaldosteronism

RPCW - relative percentage of contrast agent washout

SAD - somatoform autonomic dysfunction

SDANS - somatoform dysfunction of the autonomic nervous system

SDHB - succinate dehydrogenase B

VHL - von Hippel-Lindau disease

US - ultrasound

USP - urinary steroid profile

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