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Polish diagnostic and therapeutic recommendations for adrenocortical carcinoma

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Abstract

Advances in the diagnosis and treatment of adrenocortical carcinoma (ACC), along with the development of new therapeutic and diagnostic methods, have prompted a team of experts to formulate the first Polish guidelines for managing ACC. This article presents the diagnostic and therapeutic recommendations resulting from the discussion of specialists from various medical specialities, who participated in a series of online meetings aimed at developing consistent and effective recommendations under the National Oncology Strategy. These guidelines aim to optimise ACC treatment in Poland through coordinated efforts of multidisciplinary specialist teams, ensuring an effective and modern approach. **(Endokrynol Pol 2024; 75 (4): 339–358)**

Key words: *adrenocortical carcinoma; adrenal gland; carcinoma; cancer; diagnostic recommendations; therapeutic recommendations*

Introduction

These recommendations represent Poland's first guidelines for the diagnosis and treatment of adrenocortical carcinoma (ACC). They were prepared by a team of experts in endocrinology, clinical oncology, surgery, diagnostic imaging, and molecular biology under the National Cancer Strategy. The recommendations incorporate US guidelines [1] and European guidelines [2, 3], adapting them to the epidemiological context in Poland, local experiences in ACC management, and reimbursement options.

These guidelines target physicians across all specialties involved in the care of patients with ACC. Given the frequent detection of incidental adrenal gland lesions during radiological exams, particularly computed tomography, the authors limit detailed information on this aspect, directing readers to other studies for biochemical and radiological diagnostics of incidental adrenal nodules.

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Table 1. *Assessment of quality of evidence and strength of recommendations*

Quality of evidence according to the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO)	
I	Evidence from at least one large, randomised trial, a randomised controlled trial (RCT) of high methodological quality (low risk of bias), or a meta-analysis of properly designed RCTs without significant heterogeneity
II	Small RCTs or large RCTs with risk of bias (lower methodological quality) or meta-analyses of such studies or RCTs with significant heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without a control group, case reports, expert opinions
Strength of recommendations according to the National Comprehensive Cancer Network (NCCN)	
1	Recommendations based on high-quality evidence on which unanimity or a high level of consensus of the expert panel has been reached
2A	Recommendations based on lower-quality evidence on which unanimity or a high level of consensus of the expert panel has been reached
2B	Recommendations based on lower-quality evidence on which a moderate level of expert panel consensus was reached
3	Recommendations based on evidence at any level of quality for which expert panel consensus has not been reached

The recommendations were evaluated based on the quality of evidence and the strength of recommendations (Tab. 1). The authors consented to the publication after completing a 7-item questionnaire assessing the acceptance level of each chapter (Tab. 2). The expert group commits to periodic updates every 2 years to reflect evolving medical knowledge.

1. Epidemiology

Adrenocortical carcinoma is an aggressive malignancy with poor prognosis. In 30–40% of cases, diagnosis is typically driven by clinical symptoms of excess adrenal cortical hormones (most commonly cortisol — Cushing's syndrome, less commonly androgens, and rarely mineralocorticoids). Hormonally inactive tumours manifest through mass effect symptoms (pain, gastrointestinal issues). ACC is discovered incidentally in 10–15% of cases during imaging for other reasons.

Due to its poor prognosis and low incidence, adrenocortical carcinoma requires meticulous registration under International Classification of Diseases (ICD) code C74.0. It is crucial to differentiate it in the registry from other adrenal malignancies, particularly pheochromocytoma (C74.1).

The incidence of adrenocortical carcinoma in Poland is 1 per 1,000,000, mirroring rates in other countries. The disease exhibits a bimodal age distribution, with incidence peaks before age 5 and between ages 60 and 69 years [4].

Adrenocortical carcinoma typically presents as a unilateral lesion. Bilateral lesions on imaging, especially in patients with malignancy, may indicate distant metastasis to the adrenal glands.

Most adrenocortical carcinomas are sporadic, but 5–10% of cases are linked to germline mutations, such as those seen in Li-Fraumeni syndrome.

Given its rarity, poor prognosis, and limited therapeutic options, patients diagnosed with adrenocortical

Table 2. *Authors' concurrence on each recommendation issue*

	I agree with all recommendations	I do not agree with 1–2 recommendations	I disagree with 3–5 recommendations	I do not agree with > 5 recommendations
Biochemical examinations	27	3	–	–
Molecular diagnostics	30	–	–	–
Imaging examinations	29	1	–	–
Pathomorphological examinations	30	–	–	–
Surgical treatment	30	–	–	–
Systemic and locoregional treatment	28	2	–	–
Follow-up	30	–	–	–

carcinoma should be treated in centres with a multidisciplinary team experienced in managing the disease. This team should include endocrinologists, surgeons, oncologists, pathologists, clinical geneticists, and laboratory diagnosticians. A treatment plan should be established within 3 months post-surgery.

2. Biochemical eaminations

The detection of an adrenal tumour necessitates urgent answers to 2 critical questions:

1. Is the tumour malignant?
2. Is it hormonally active?

Addressing these questions requires biochemical evaluation for hypercortisolaemia, hyperandrogenaemia, and hyperaldosteronism, alongside the exclusion of pheochromocytoma. It is crucial to emphasise that if adrenocortical carcinoma is suspected, an urgent multidisciplinary team consultation should be scheduled, even if the biochemical diagnosis is not yet complete due to the aggressive nature of the disease.

Hormone excess symptoms are found in approximately 50–60% of patients with adrenocortical carcinoma. Hypercortisolaemia is the most common hormonal disorder, occurring in 50–70% of patients with hormonally active ACC. Excess androgens, often in combination with excess cortisol, are observed in 20–30% of female patients, while excess oestrogens, leading to feminisation symptoms, are seen in 5% of male patients. The rarest hormonal abnormality is mineralocorticosteroid excess [4]. The presence of mixed endocrine function in an adrenal tumour increases the likelihood of it being adrenocortical carcinoma.

The Polish Society of Endocrinology outlined specific objectives for the biochemical diagnosis of patients with incidental adrenal tumours in 2016 [5]. These recommendations highlight the indications and interpretations of the basic biochemical tests that should be performed in patients suspected of having adrenocortical cancer [2, 4].

Hormonal diagnosis prior to planned surgical treatment allows for the following:

1. The administration of blood cortisol-lowering drugs in the preoperative period for patients with severe hypercortisolaemia.
2. The assessment of malignancy risk based on the steroid hormonal profile.
3. Monitoring of treatment effects because elevated hormone levels post-surgery can serve as biochemical markers for adrenocortical cancer metastasis [6].
4. Differential diagnosis with pheochromocytoma is essential because it requires different surgical preparation and poses a risk of other perioperative complications [7, 8].

Obligatory and optional biochemical tests for suspected adrenocortical carcinoma are listed in Table 3.

General recommendations

Investigations: It is recommended that any patient with suspected ACC undergo biochemical investigations to determine endocrine function, specifically for the secretion of glucocorticosteroids, sex hormones, mineralocorticosteroids, or steroid precursors of adrenal cortical hormones.

SoR: 1 QoE: I

Table 3. *Obligatory and optional biochemical tests performed in a patient with suspected adrenocortical carcinoma*

Purpose of designation	Recommended test
Biochemical tests mandatory in all patients	
Assessment of glucocorticosteroid secretion disorders	Inhibition test with 1 mg of dexamethasone (or assessment of salivary cortisol concentration/daily urinary cortisol excretion)
	ACTH level measurements
Assessment of mineralocorticosteroid secretion disorders	Serum potassium level determination
	Aldosterone/renin ratio (in hypertensive patients)
Evaluation of sex hormones and steroid precursors	Determination of DHEA-S, 17OHPG, androstenedione, testosterone (women only), 17β-oestradiol (men and postmenopausal women), 11-deoxycortisol
Exclusion of pheochromocytoma	Daily urinary excretion of fractionated methoxycatecholamines or plasma methoxycatecholamines concentration*
Supporting studies	
Suspected hypercortisolaemia	Determination of DHEA-S in plasma
Steroid profile*	Determination in urine

ACTH — adrenocorticotropin; DHEA-S — dehydroepiandrosterone sulphate; 17OHPG — 17OH-progesterone; *The authors of the recommendation believe that, with wider availability, the survey should become mandatory.

In any patient with suspected ACC, where surgical treatment is planned, it is recommended that the presence of pheochromocytoma be excluded by determining the daily excretion of fractionated methoxycatecholamines in the urine or the plasma concentration of methoxycatecholamines.
SoR: 1 QoE: I

In a patient presenting with a bilateral tumour mass, it is recommended that adrenal insufficiency be excluded to assess the likelihood of metastasis from another primary site.
SoR: 1 QoE: I

Specific recommendations

According to available literature and clinical practice, the diagnosis for excess of specific hormones or their precursors produced by adrenal cortical tumours should be conducted as follows.

2.1. Diagnosis of hypercortisolaemia

The primary test for diagnosing hypercortisolaemia is the 1 mg dexamethasone suppression test. After administering 1 mg of dexamethasone overnight, the next morning's blood cortisol concentration should be below 50 nmol/L (≤ 1.8 μg/dL) to rule out autonomous cortisol secretion (ACS) [3, 9]. Values higher than these thresholds confirm the diagnosis of hypercortisolaemia. Following this, a morning adrenocorticotropin (ACTH) evaluation is recommended. Suppressed ACTH levels indicate an ACTH-independent form of hypercortisolaemia, which is characteristic of adrenocortical carcinoma [1].

Recommendations

2.1.1. Evaluation of autonomous cortisol secretion (ACS):
— conduct an inhibition test with 1 mg of dexamethasone.
— determine serum ACTH concentration under basal conditions. If hypercortisolaemia is excluded, ACTH determination may be omitted.
SoR: 1 QoE: I

2.1.2. Alternative tests for inconclusive results: in patients with an inconclusive result from the 1 mg dexamethasone test or if the test cannot be performed due to interfering factors, one of the following tests may be used as an alternative:
— measure daily urinary free cortisol excretion at least twice. In patients with clinical features of cortisol excess, demonstrating excessive daily urinary cortisol excretion is sufficient for diagnosing hypercortisolaemia;
— determine salivary cortisol concentration in the late evening or night, preferably 2–3 times (while this test is helpful, a single determination is not superior to the 1 mg dexamethasone test).
SoR: 1 QoE: I

2.2. Excess androgens or oestrogens

To date, no single panel of steroid precursors and sex hormones has been developed specifically for diagnosing ACC. Therefore, it is recommended that the androgens and oestrogens be used, as well as the steroid precursors, for which diagnostic methods are available in a given centre [2, 4]. The most commonly assayed hormones include the following:
— 17OH-progesterone (17OHPG);
— dehydroepiandrosterone sulphate (DHEA-S);
— androstenedione;
— testosterone (in women only);
— 17β-oestradiol (in men and postmenopausal women only);
— 11-deoxycortisol [4].

It should be noted that in patients with hypercortisolaemia, DHEAS levels can be significantly reduced. This, along with reduced ACTH levels, holds diagnostic value for confirming hypercortisolaemia.

Recommendations

2.2.1. To exclude excessive sex steroids and steroid precursors, it is recommended that the concentrations of androgens, oestrogens, and steroid precursors be measured using the available methodology at the centre (refer also to R.2.4.1.).
SoR: 1 QoE: I

2.3. Hyperaldosteronism

To confirm or exclude aldosterone secretion by adrenocortical carcinoma, apply the general principles for diagnosing primary hyperaldosteronism [5 ,10]. As part of baseline investigations, it is mandatory to determine serum sodium and potassium concentrations. In most cases of primary hyperaldosteronism, hypokalaemia is not present [10]. In contrast, severe hypokalaemia observed in ACC patients [10] is typically due to very high cortisol secretion.

For patients presenting with hypertension and/or hypokalaemia, the screening test involves calculating the aldosterone-to-renin ratio (ARR) using blood aldosterone concentration and plasma renin activity. An ARR above 30 ng/dL/ng/mL/h (with aldosterone concentrations > 10–15 ng/dL) supports the diagnosis of primary hyperaldosteronism [10].

Recommendations

2.3.1. To evaluate mineralocorticoid excess, it is recommended that serum potassium levels be measured. In patients with hypertension and/or hypokalaemia, evaluating ARR is advisable. The interpretation of ARR results is as follows:
— an ARR activity ratio > 30 supports a diagnosis of primary hyperaldosteronism;
— an ARR above the threshold value calculated at the respective centre supports a diagnosis of primary hyperaldosteronism.
SoR: 2A QoE: II

2.3.2. When an elevated ARR is observed, a confirmatory test(s) is typically recommended to substantiate the diagnosis. The selection of the confirmatory test and its interpretation should adhere to centre-specific guidelines.
SoR: 1 QoE: II

2.3.3. It is suggested that in cases where there is a positive ARR, hypokalaemia, renin concentrations below the detection threshold, and aldosterone concentrations exceeding 20 ng/dL (550 pmol/L), confirmatory testing may be unnecessary.
SoR: (2B) QoE: V

2.4. Steroid profile in blood and urine

ACC is characterised by disrupted steroidogenesis [11], resulting in the accumulation of steroid hormone precursors and their metabolites in blood and urine. Therefore, it is recommended that a comprehensive steroid profile be determined, including precursors and metabolites, in patients suspected of ACC. Techniques for assessing these compounds include liquid chromatography tandem mass spectrometry (LC-MS/MS), gas chromatography mass spectrometry (GC-MS), and, if unavailable, radioimmunoassays or immunoassays. Determining the steroid profile in blood and urine in patients with a visible adrenal mass can aid in identifying specific types of adrenal tumours and distinguishing between malignant and benign tumours [12–14], although this is currently not readily available in Poland and not reimbursed. However, due to its high sensitivity and specificity, efforts should be made to perform this test in centres offering these capabilities.

A study evaluating 12 serum steroid metabolites using an immunoenzymatic assay demonstrated significantly elevated primary steroid precursors in cortisol-producing ACCs compared to cortisol-producing adenomas. The most effective indicators for detecting cortisol-producing ACCs were 17-hydroxypregnenolone (a glucocorticoid and androgen precursor) and 11-deoxycorticosterone (a mineralocorticoid precursor), along with elevated concentrations of androstenedione and DHEAS [12].

In another study, 2 urine steroid metabolites, namely 5-pregnentriol (5-PT), a metabolite of 17-hydroxy-pregnenolone, and tetrahydro-11-deoxycortisol (THS), a metabolite of 11-deoxycortisol, showed the highest discriminatory value for distinguishing ACC from adrenocortical adenoma [15]. Additionally, urinary steroid metabolite determination has been reported as highly useful in detecting ACC recurrence post-surgical treatment [16].

Recommendations

2.4.1. It is recommended that the serum and urine steroid profile are assessed, encompassing steroid precursors and metabolites, in patients suspected of ACC using available diagnostic methodologies. Liquid chromatography and gas chromatography methods are preferred for this evaluation.
SoR: 1 QoE: I

2.5. ACC in pregnant women — biochemical diagnosis considerations

Stimulation of the hypothalamic–pituitary–adrenal axis and increased levels of cortisol-binding proteins during pregnancy result in physiological hypercortisolaemia, leading to distinct diagnostic considerations for pregnant women suspected of excessive cortisol secretion [17]. Morning serum cortisol concentrations rise notably in the second and third trimesters, but morning and late evening salivary cortisol levels throughout all trimesters do not differ significantly from those in non-pregnant controls [18]. Therefore, assessment of salivary cortisol concentrations using reference values established for healthy non-pregnant women is recommended to confirm or exclude cortisol secretion disorders in pregnant women [18]. Similarly, salivary cortisol determination is advised for women on oral contraceptives suspected of hypercortisolaemia [18].

In urine cortisol testing throughout pregnancy, the physiological increase in adrenal cortisol secretion during the latter half of pregnancy should be considered when interpreting results [17, 19]. ACTH concentration evaluation in pregnant women with ACTH-independent hypercortisolaemia may not provide sufficient suppression, limiting its diagnostic utility [17]. Similarly, the 1 mg dexamethasone suppression test has significant limitations in pregnancy for diagnostic purposes [17].

Diagnosing primary hyperaldosteronism in pregnant women poses challenges due to contraindications to confirmatory tests. Diagnosis is primarily based on

the presence of hypokalaemia, commonly observed despite the progesterone-induced anti-mineralocorticoid effect, along with low renin levels and elevated aldosterone levels. However, the lack of pregnancy-specific reference values complicates interpretation [20].

Recommendations

2.5.1. To exclude or confirm hypercortisolaemia in pregnant women, it is recommended that late evening salivary cortisol concentrations be assessed. If this diagnostic method is unavailable, measuring free cortisol in daily urine is an alternative approach.
SoR: (2B) QoE: II

2.5.2. Use of the 1 mg dexamethasone test is not recommended due to its limited diagnostic value in pregnant women.
SoR: (2B) QoE: II

2.5.3. To exclude or confirm primary hyperaldosteronism in pregnant women, it is recommended that serum potassium levels and the aldosterone-to-renin ratio (ARR) be measured. Confirmatory tests for hyperaldosteronism are not recommended in pregnant women.

3. Molecular diagnostics

Approximately 5–10% of ACC cases are associated with pathogenic germline variants and may be linked to several familial cancer syndromes [21].

In evaluating hereditary predisposition to ACC, particular attention should be given to 2 syndromes: Li-Fraumeni syndrome and Lynch syndrome (see Tab. 4). ACC is an integral part of Li-Fraumeni syndrome and one of the main cancers observed in this syndrome, which, in addition to ACC, is characterised by the early occurrence of a wide spectrum of cancers, particularly soft tissue sarcomas, central nervous system tumours, and early-onset breast cancer in adult women without a family history. Nearly 70% of adult ACC patients carry pathogenic variants in the TP53 gene, with this percentage rising to 80% among patients under 18 years of age [22]. It is estimated that approximately 7% of adults with genetically confirmed Li-Fraumeni syndrome will develop ACC [23]. Notably, at least 20% of TP53 germline pathogenic variants occur as de novo mutations, without a family history [24].

ACC is observed in approximately 3% of patients with Lynch syndrome, predominantly associated with pathogenic variants in the MSH2 [25].

ACC is less frequently observed in other hereditary cancer predisposition syndromes, such as multiple endocrine neoplasia type 1 (MEN1), familial adenomatous polyposis (FAP), Gardner syndrome, Beckwith-Wiedemann syndrome, and neurofibromatosis type 1 (NF1) [4, 21, 26].

Table 4. ***Genetic syndromes predisposing to the development of adrenocortical carcinoma (ACC)***

Team	The most common cancers
Li-Fraumeni	Sarcomas (of bone and soft tissue)
	Breast cancer
	Adrenocortical carcinoma
	Tumours of the central nervous system
	Leukaemia
Lynch	Malignant tumours of the reproductive organs
	Gastric cancer
	Skin cancer
	Renal cell carcinoma

Recommendations

3.1. A medical history for occurrences of other malignant tumours in the patient and their relatives should be taken for every patient.
SoR: (2B) QoE: III

3.2. If Li-Fraumeni syndrome or Lynch syndrome (Tab. 4) is suspected, the patient should be referred to a genetic clinic.
SoR: (2B) QoE: III

4. Imaging examinations

Currently, 3 imaging modalities are used in the diagnosis and characterisation of adrenal tumours: computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography after administration of [^{18}F]-2-deoxy-d-glucose ([^{18}F]FDG-PET). The role of ultrasonography (USG) in the diagnosis of adrenocortical carcinoma is limited due to low resolution, limited penetration, and lack of standardisation in the interpretation of results.

CT and MRI are primarily used to identify benign tumours and exclude malignant tumours of the adrenal glands [27–29]. [^{18}F]FDG-PET is a functional imaging method that allows confirmation of the presence of malignant lesions [30–32]. In a meta-analysis on the importance of imaging studies in the diagnosis of ACC, the level of evidence was found to be low or very low for all 3 imaging modalities [3]. Of the available imaging modalities for adrenal incidentalomas,

only native CT (without *i.v.* CM administration) with assessment of lesion density based on the Hounsfield attenuation coefficient (HU — Hounsfield Units) is recommended. The high sensitivity of this method allows initial differentiation diagnosis (malignant *vs*. benign). If the adrenal lesion is homogeneous and the attenuation factor is ≤ 10 HU on native CT, a malignant process, including ACC, can be excluded. In contrast to benign lesions, usually adenomas, adrenocortical carcinomas are usually large (size > 4 cm), heterogeneous, and have a higher density in native CT > 10 HU [33]. Increasing the attenuation factor to > 20 HU allows for a much higher specificity of the CT result, but at the cost of reduced sensitivity of the examination [3].

Current observations suggest that the second most useful test (after CT) in assessing the nature of indeterminate focal adrenal lesions is PET after administration of [^{18}F]FDG [34–36]. The arguments in favour of using [^{18}F]FDG-PET/CT routinely in ACC patients are the coverage of the whole body and the assessment of the accumulation of the radiopharmaceutical separately in each metastatic focus (which is helpful for monitoring treatment effects/disease progression). There are currently no clearly defined factors arguing against the use of this diagnostic method. Previously raised arguments of the cost of the test, limited access to the test, or increased irradiation of the patient are not justified by the current PET scanners. However, it is noted that the sensitivity and negative predictive value (NPV) are significantly better than the specificity and positive predictive value (PPV) of [^{18}F]FDG-PET/CT. For this reason, testing with [^{18}F]FDG-PET/CT is not recommended for every patient with suspected ACC. Instead, this test is one of the primary imaging modalities in assessing staging and response to treatment, as discussed later in this paper.

An algorithm for the management of adrenal tumours found incidentally on CT/MRI with a size ≥ 1 cm is shown in Fig. 1.

4.1. Principles of CT in ACC

The evaluation of ACC on CT after *i.v.* administration of contrast medium (CM) should take into account the absolute (AWR) and relative (RWR) washout rates of less than 60% (AWR) and less than 40% (RWR), respectively — these values are considered suspicious for determining the nature of the adrenal lesion. To calculate AWR, a CT (naïve) scan without *i.v.* CM administration is performed [4], followed by a veno-venous phase study 60–90 s after CM administration (preferred after 60 s) [3] and in the delayed phase 15 min after *i.v.* administration [3]. RWR does not take into account the native phase. AWR and RWR values should be assessed based on the study protocol outlined above and an available online calculator, e.g. https://radcalculators.org/adrenal-ct-washout-calculator/ or using standard formulas.

Characteristic features of ACC on CT are as follows: large tumour (tumours > 6 cm in diameter are particularly suspicious); irregular tumour shape; density on native CT above 10 HU; areas of necrosis and bleeding visible in the tumour; after *i.v.* administration of CM there is heterogeneous tumour enhancement; visible calcifications in the tumour (found in approximately 30% of ACC); and the presence of infiltration of adjacent structures. In addition, a tumour thrombus may be visible in the renal vein, inferior vena cava, and even in the right atrium of the heart [37]. Difficulties in diagnosing ACC may arise if the tumour is detected incidentally, the lesion is small < 4 cm, and shows no endocrine function. By performing CT without *i.v.* CM it is then difficult to distinguish it from a non-functioning, poor-lipid adenoma [37].

Density measurements not only in the native phase, but also after *i.v.* administration. CM, including the delayed phase with AWR/RWR assessment are therefore key elements for establishing a correct diagnosis. In the case of homogeneous lesions, density measurements should be taken from three-quarters of the tumour area (tumour borders and coverage of tissues adjacent to the lesion should be avoided). For heterogeneous tumours, the measurement should not include areas of necrosis or calcification. An attenuation factor ≤ 10 HU in the native phase indicates a benign lesion, most commonly an adenoma, means no indication for further imaging studies. A radiation attenuation factor > 10 HU in the native phase is an indication for a dynamic CT scan with intravenous contrast administration.

If there is an increased likelihood of a malignant lesion in this ACC based on the CT/MRI findings, local progression of the disease process should be further assessed:

— renal vein involvement (occurs in up to 40% of patients);
— inferior vena cava (IVC) and hepatic vein involvement (relatively common);
— metastases to regional lymph nodes, lung, bone, and liver;
— liver metastases (usually richly vascularised, so a multiphase study including arterial phase (30 s), veno-venous phase (60 s) and delayed phase is required; delayed phase is not required in advanced stage disease [37].

In patients with contraindications to contrast-enhanced CT, or if there is doubt about the nature of the CT lesion, MRI should alternatively be performed before and after *i.v.* CM (dynamic contrast enhance-

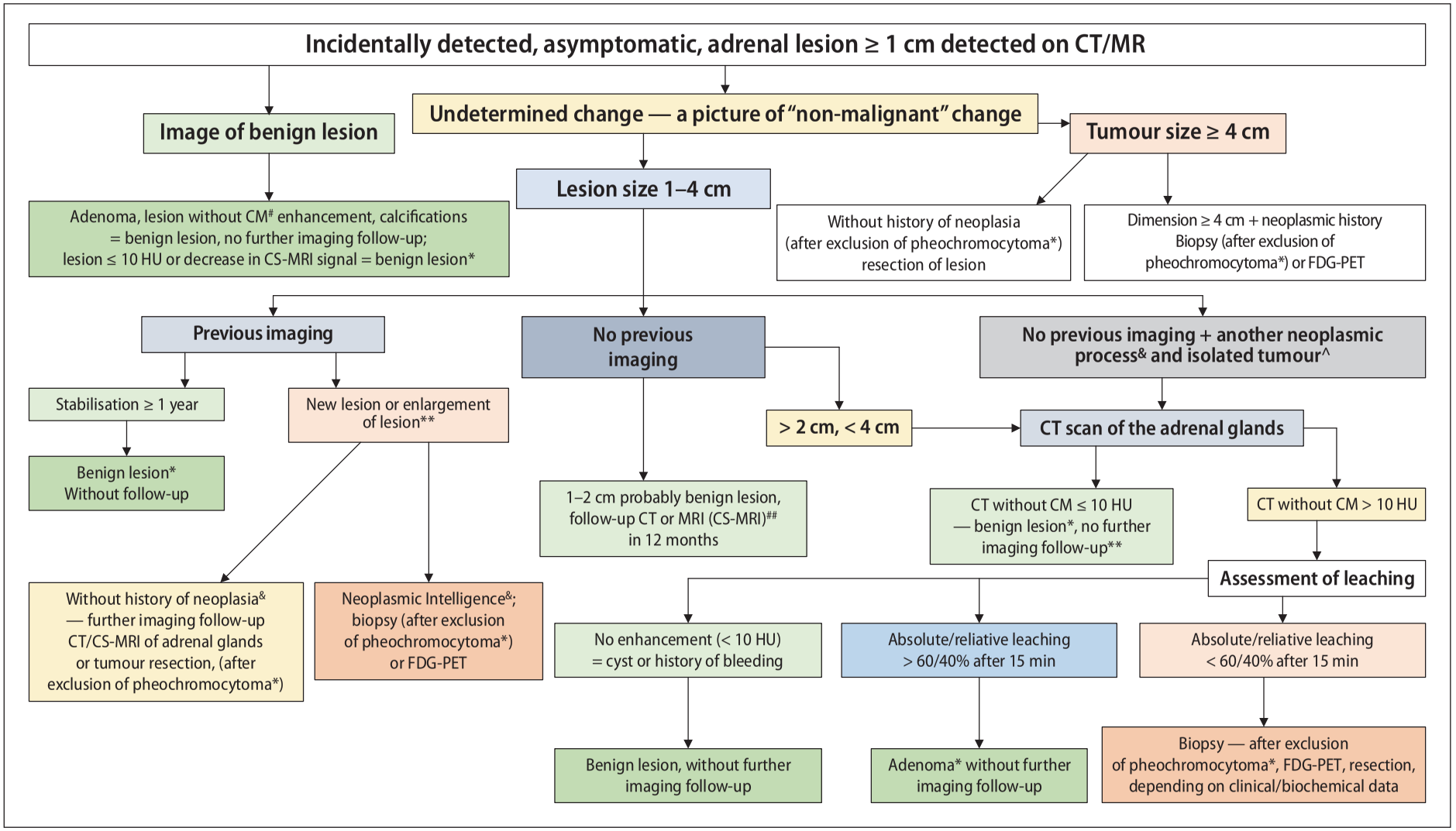

Figure 1. *Algorithm for the assessment of an incidentally detected adrenal mass/tumour. *Consider biochemical testing to determine functional status and rule out pheochromocytoma before biopsy/resection of adrenal lesion; clinical evaluation and plasma fractionated metanephrines required; **Tumour growth rate based on: [38]: benign lesion — < 0.3 cm/year, malignant lesion — > 0.5 cm/year; &meta — or synchronous diagnosis of malignant neoplasm with non-adrenal location; "# of computed tomography (CT) without contrast media (CM) enhancement" applies if a CT scan is available without and with the administration of intravenous (i.v.) CM; ^ "Isolated" defined as the absence of other metastatic disease; ##Chemical shift magnetic resonance (CS-MRI) may be considered; CT without CM — CT examination without administration of i.v. CM; absolute and relative washout of contrast medium after 15 min; calcifications — the presence of calcifications in a tumour; HU — Hounsfield units; FDG-PET — fluorodeoxyglucose positron emission tomography*

ment, DCE). Interpretation of the MRI scan must include an assessment of the presence of areas of bleeding and necrosis in the tumour. The chemical shift (CS) method commonly used in the evaluation of adenomas and the diffusion-weighted imaging (DWI) and ADC maps commonly used in oncology are of little use in the diagnosis of ACC.

A CT scan of the thorax, abdomen, and pelvis after CM *i.v.* administration should be performed to assess the local progression of the disease. For abdominal and pelvic imaging, MRI is an alternative method to CT; for thoracic imaging, CT is the method of choice.

Additional imaging studies may be required to better characterise the tumour or to assess the extent of the disease (thrombus/tumour suppressor in the renal vein, IVC, right atrium).

Recommendations

4.1.1. It is recommended that all patients suspected of having ACC undergo adrenal-focused imaging, with CT being the standard method. MRI serves as an auxiliary examination and is indicated when CT is not feasible or contraindicated. MRI should be performed using the chemical shift method.
SoR: 1 QoE: I

4.1.2. The imaging study of the highest value to exclude malignancy in a adrenal lesion is the native CT with evaluation of the radiation attenuation factor, which is ≤ 10 HU in benign lesions. For lesions with a radiation attenuation factor of > 10 HU found on CT, an additional full study should be performed after *i.v.* CM with evaluation of AWR or RWR. For 60% AWR or 40% RWR, respectively, the study excludes the presence of ACC.
SoR: 1 QoE: I

4.1.3. In any patient with a high probability of ACC, additional chest CT and structural studies (CT/MRI) of the abdomen and pelvis are recommended.
SoR: 1 QoE: II

4.2. Functional imaging [^{18}F]FDG-PET

The sensitivity and specificity of [^{18}F]FDG-PET range from 92% to 100% and 80% to 100%, respectively. A meta-analysis published in 2015 showed that in the differential diagnosis of adrenal tumours (in particular ACC *vs*. adenoma), the sensitivity and specificity of [^{18}F]FDG-PET/CT is 91% [34]. [^{18}F]FDG-PET demonstrates higher diagnostic efficacy than CT in the diagnosis of ACC (93.4% *vs*. 75%). Due to the frequent localisation of metastases in the adrenal glands, [^{18}F]FDG-PET should be performed in patients with a history of malignancy who present with an indeterminate lesion in the adrenal gland (even smaller than 4 cm in dimension) [39]. PET/CT with [^{18}F]FDG for the indication of adrenocortical carcinoma is currently not reimbursed in Poland.

Recommendations

4.2.1. PET/CT with PET/CT with [^{18}F]FDG in the diagnosis of ACC is indicated for the following:
— assessment of the stage of progression prior to planned surgical treatment;
— in patients with an indeterminate focal lesion in the adrenal gland to exclude metastasis if a malignant neoplasm has been previously diagnosed;
— in cases of suspected recurrence of ACC.
SoR: 2A QoE: III

5. Patomorphological examinations

The diagnosis of adrenal cortex cancer is based on the histopathological examination of postoperative material or, in cases of non-resectable tumours, material obtained through thick needle or surgical biopsy. In cases of large retroperitoneal tumours that do not secrete adrenal hormones, a thick needle or surgical biopsy should be considered to exclude retroperitoneal sarcomas.

The morphological diagnosis of adrenocortical carcinoma is difficult and diagnostic errors are relatively frequent, reaching 9–13%. It is therefore advisable that the pathomorphological diagnosis of adrenocortical carcinoma is confirmed by an experienced pathologist from a reference centre in adrenal pathology.

There are 3 subtypes of adrenal cortex cancer: (1) conventional, (2) oncocytic, and (3) myxoid. Each differential diagnosis towards adrenal cortex cancer should be confirmed by immunohistochemical tests in one of two ways, depending on the experience/capabilities of the facility:
— steroidogenic factor 1 (SF1) antibody, currently recognised as the most sensitive and specific marker of cortical differentiation with a sensitivity of 98% and a specificity of 100%;
— a panel of antibodies: melan-A (MART-1), inhibin-α, and calretinin — recommended when SF1 is not available.

Depending on the histological subtype, appropriate assessment scales are utilised (refer to Tab. 5–7). For the conventional and myxoid subtypes, the Weiss system, reticulin algorithm, and Helsinki system are employed. The Weiss system is the most commonly used and preferred; the others are utilised in ambiguous cases. For the oncocytic subtype, characterised by the pres-

Table 5. *Pathological feature scoring systems according to cancer variant according to World Health Organization (WHO) 2022*

Adrenocortical carcinoma variant	Weiss system	The reticulin algorithm	Helsinki system	Lin-Weiss-Bisceglia system
Conventional	Yes	Yes	Yes	Not
Oncocytic (> 90% of cells oncocytic)	Not	Yes	Yes	Yes
Myxoid	Yes	Yes	Yes	Not

Table 6. *Systems for assessing pathological parameters of adrenocortical tumours (ACC)*

Weiss system parameters	Scoring	Modified Weiss system parameters	Scoring	The reticulin algorithm parameters	Helsinki system parameters	Scoring
Nuclear grade (grade III or IV according to Fuhrman)	1	Mitoses > 5/50 HPF	2	Reticulin fibers interrupted	> 5 mitoses/50 HPF	3
Mitoses > 5 mitoses/50 HPF	1	Atypical mitoses	1	> 5 mitoses/50 HPF	Necrosis	5
Atypical mitoses	1	Clear cells ≤ 25%	2	Necrosis	Ki-67 proliferation index	Numerical value
Clear cells < 25%		Collapsed necrosis	1	Vascular invasion		
Diffuse architecture (> 33% of the area)	1	Invasion of the handbag	1			
Confluent necrosis	1					

HPF — high-power fields

ence of over 90% oncocytic cells, the Lin-Weiss-Bisceglia system is applied for evaluation (see Tab. 7).

The primary tool for evaluating adrenal cortex tumours suspected of ACC is the Weiss system, which assesses 9 microscopic parameters in haematoxylin and eosin stained specimens (refer to Tab. 6). The modified Weiss system is based on 5 selected parameters [40]. The reticulin algorithm combines a parameter obtained from histochemical staining of reticulin fibres with 3 parameters from the Weiss system (mitoses, necrosis, and vascular invasion).

Assessment of the Ki-67 proliferation index is recommended for all ACC material (postoperative or biopsy) and is one of the most important prognostic factors in histopathological examination. However, it should be noted that the Ki-67 index determined in biopsy material may not be representative of the entire tumour. The use of the proliferation index for prognostic purposes is advised, in conjunction with other microscopic criteria such as the mitotic index and necrosis, as part of the Helsinki score. If the Ki-67 index is unavailable, the mitotic index can be used for prognostic purposes. A mitotic index exceeding 20 mitoses per 50 high power fields (HPF) defines a low differentiation grade (high grade) in ACC.

Table 7. *Criteria according to Lin-Weiss-Bisceglia for oxyphilic tumours of the adrenal cortex [41]*

Main criteria	Additional
> 5 mitoses/50 HPF	Size: >10 cm and or > 200 g
Atypical mitoses	Necrosis
Vascular invasion (with muscular wall)	Invasion of the handbag
	Sinusoidal invasion

Malignant lesion — presence of 1 major criterion; borderline (of uncertain malignant potential) — presence of 1–4 additional criteria; mild — absence of both main and additional criteria; HPF — high-power field

Recommendations

5.1. The diagnosis of ACC should be confirmed by immunohistochemistry, SF1 antibody or panel: melan-A, inhibin-α, and calretinin.
SoR: I QoE: 1

5.2. The basic system for assessing the degree of malignancy in suspected ACC is the Weiss system or the modified Weiss system.
SoR: I QoE: 1

5.3. The pathology report of an adrenal cortical tumour suspected to be a primary carcinoma should include the following:
— type of operating procedure;
— assessment of the integrity of the preparation;
— the location of the tumour;
— tumour dimensions;

Table 8. *Stages according to and European Network for the Study of Adrenal Tumors (ENSAT)*

Degree of progression	Definition	
I	T1, N0, M0	T1: tumour ≤ 5 cm
II	T2, N0, M0	T2: tumour > 5 cm
III	T1–T2, N1, M0	N1: lymph node with metastatic cancer
	T3–T4, N0–N1, M0	T3: infiltration into surrounding tissues
		M0: no distant metastases
IV	T1–T4, N0–N1, M1	T4: infiltration of surrounding organs or thrombus in the vena cava or renal vein
		M1: presence of distant metastases

— tumour weight;
— the histological type of the tumour;
— assessment according to the Weiss system with the exact number of mitoses in oncocytic tumours
— assessment according to the Lin-Weiss-Bisceglia system;
— Ki-67 index;
— assessment of surgical margins;
— tumour stage with status of lymph nodes removed, if any, according to European Network for the Study of Adrenal Tumours (ENSAT) (Tab. 8) and American Joint Committee on Cancer (AJCC) (Tab. 9).

6. Surgical treatment

Before the surgical treatment of adrenal tumours exhibiting hormonal hypersecretion, appropriate patient preparation is required according to guidelines for the surgical treatment of hormonally active adrenal tumours. In patients preoperatively diagnosed with hypercortisolism, irrespective of its severity, perioperative steroid coverage and postoperative hydrocortisone substitution should be given. In cases of severe hypercortisolism, consideration should be given to incorporating a steroidogenesis inhibitor in the preoperative period, alongside intensive internal medicine management of complications arising from excessive cortisol levels.

In ACC or in tumours suspected of this diagnosis, open surgery with transperitoneal access is the recognised standard of care for patients at ENSAT stage I–III, i.e. tumours confined to the adrenal gland (stage I–II) or infiltrating adjacent tissues and/or organs (stage III) [1].

Surgical treatment should only be performed by surgeons experienced not only in adrenal tumour surgery, but also in surgical oncology. The rationale for this approach includes the rarity of the disease, poor prognosis, especially in cases of initially non-radical resection, the possible need for multi-organ and vascular surgery, and the necessity for early incorporation of adjuvant treatment post-surgery.

Table 9. *Staging according to the American Joint Committee on Cancer (AJCC) (8th ed.)*

T — primary tumour	
Tx	Primary tumour cannot be assessed
T0	No primary tumour is found
T1	Tumour ≤ 5 cm in largest dimension; no infiltration beyond the adrenal gland
T2	Tumour > 5 cm in greatest dimension; no infiltration beyond the adrenal gland
T3	Tumour regardless of its size with local infiltration (surrounding tissues), without infiltration of adjacent organs
T4	Tumours infiltrating adjacent organs (kidneys, diaphragm, large vessels such as the renal vein or vena cava, pancreas and liver) regardless of size
N — regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	Absence of regional lymph node metastases
N1	Metastases in regional lymph nodes
M — distant metastases	
M0	Absence of distant metastases
M1	Distant metastases
Degree of progression	
Grade I	T1 N0 M0
Grade II	T2 N0 M0
Grade III	T1, T2 N1 M0
	T3, T4 N0, N1 M0
Grade IV	Any T Any N M1

The extent of resection (R0 — radical resection, R1 — microscopically non-radical resection or R2 — macroscopically non-radical resection) is one of the most important prognostic factors in ACC. An R0 resection is fundamental for achieving long-term survival; thus, to achieve macroscopic and microscopic margins in locally advanced ACC, partial or total removal of infiltrated organs such as the liver, spleen, colon, pancreas, stomach, or the wall of the inferior vena cava may be necessary

[1]. Total "en bloc" resection of the tumour mass with removal of the entire adrenal gland and surrounding adipose tissue is essential to avoid damaging the tumour capsule and worse prognosis. However, routine kidney resection is not recommended in the absence of tumour infiltration.

Laparoscopic or robotic surgery is an acceptable method of surgical treatment in low-grade ACC (without features of infiltration of surrounding tissues and organs) if performed by surgeons experienced in surgery using these techniques [1].

There is no unanimity regarding the size of a tumour suspected to be ACC at which minimally invasive surgery can be considered. Some recommendations consider this to be a limit of < 6 cm [1, 2], while the National Comprehensive Cancer Network (NCCN) recommends considering laparoscopic surgery in tumours up to 4 cm in diameter [1].

The indications and extent of locoregional lymphadenectomy are also debated. Some authors believe that removal of the locoregional lymph nodes allows better disease staging and so improves survival [4]. Although most researchers agree on the necessity of removing clinically or radiologically suspected lymph nodes, i.e. therapeutic lymphadenectomy [1, 2, 4, 42], the need for prophylactic (elective) lymphadenectomy is much more controversial. Some clinicians advocate it only for large tumours and locally advanced disease [43, 44]. There is no clear evidence that prophylactic lymphadenectomy improves survival. Reports indicate that resection of at least 5 lymph nodes is associated with a reduced risk of recurrence and improved prognosis [44]. Similarly, a multicentre study demonstrated the benefit of prophylactic lymphadenectomy on overall survival (OS) [45]. However, there are significant difficulties in determining the optimal extent of prophylactic lymphadenectomy in ACC. Reibetanz et al. demonstrated greater variability in the locations of lymph node metastases within the retroperitoneal space than previously documented [46]. Further research is essential to elucidate the role and scope of prophylactic lymphadenectomy. Nevertheless, conducting this procedure enhances the accuracy of clinical staging and facilitates the tailored selection of adjuvant therapies based on these findings [42].

Even more challenging in ACC is the decision to reoperate in cases of recurrence. The authors of the European Society of Medical Oncology (ESMO) recommendation believe that it is only to be considered if there is a realistic chance of R0 resection and the time to recurrence is longer than 12 months [2]. Similarly, according to these authors, palliative cytoreductive surgery should only be considered in strictly selected cases in hormonally active tumours to reduce hypercortisolaemia [2].

If the initial surgery was non-radical (R2 resection), decisions regarding a potential reoperation should be made individually by a multidisciplinary team at a centre dedicated to the comprehensive management of ACC patients. This includes determining the necessity for multivascular resection, such as vascular surgery, especially in cases where the tumour has infiltrated large vessels. This approach ensures that less experienced centres do not prematurely classify lesions as unresectable [4].

It is also believed that palliative resections in patients with stage IV disease may positively influence disease control. However, the significance of tumour removal or locoregional resection in the disseminated stage remains unclear and necessitates additional research to assess their impact on enhancing survival [42].

Recommendations

6.1. The surgical treatment of adrenocortical carcinoma should be carried out in a reference centre by a multispecialised experienced surgical team.
SoR: I QoE: 1

6.2. Open radical adrenalectomy (block resection with removal of peri-adrenal fat) is the recommended surgical procedure for lesions with a high risk of malignancy or confirmed adrenocortical carcinomas.
SoR: 1 QoE: III

6.3. In the case of locally advanced, potentially resectable ACC, the aim of the surgery should be R0 resection, i.e. consideration should be given to extend the operation to include resection of adjacent organs (liver, pancreas, spleen, kidney, diaphragm, bowel — either in its entirety or within the limits of normal, non-infiltrated tissue) and to perform vascular surgery with removal of the tumour stump.
SoR: 1 QoE: III

6.4. If clinically and/or radiologically suspicious lymph nodes (perinephric, renal hilar region or retroperitoneal space) are found, their removal is recommended.
SoR: 1 QoE: III

6.5. Prophylactic lymphadenectomy is not recommended.
SoR: 2A QoE: III

6.6. Laparoscopic or robotic adrenalectomy is an acceptable procedure if preoperative examinations show no signs of infiltration of the surrounding tissues,

the risk of damage to the organ capsule is minimal, and the operating surgeon has extensive experience with minimally invasive techniques.
SoR: 2A QoE: III

6.7. In the case of locoregional recurrence of ACC, the decision of reoperation should be made on an individual basis by the multidisciplinary treatment team, as in the case of patients with non-radical (R2) operaction or referred for surgery at M1 stage.
SoR: 2A QoE: III

7. Systemic and locoregional treatment

Systemic treatment for adrenal cortex cancer includes the following: (1) suppression of hormonally active tumours; (2) adjuvant therapy; and (3) palliative treatment of advanced, non-resectable disease. Given the rarity of the disease and the limited evidence from prospective studies, patients should be treated within clinical trials whenever possible. This approach ensures access to the latest treatments and contributes to the broader understanding and development of effective therapies for this condition.

7.1. General principles of mitotan treatment

Mitotane is a derivative of dichlorodiphenyltrichloroethane (DDT) that selectively damages mitochondria in corticosteroid-producing cells and inhibits enzymes involved in steroidogenesis, including CYP11A1 (cholesterol side-chain cleavage enzyme) and CYP11B1 (11β-hydroxylase) [47, 48].

The target plasma concentration of mitotane should be maintained between 14 and 20 ng/mL, which is generally achieved within 3 to 5 months. The drug accumulates in adipose tissue, is primarily metabolised in the liver, and is contraindicated in severe liver and kidney damage. Mitotane exhibits neurotoxic, hepatotoxic, and myelotoxic effects, prolongs bleeding time, causes adrenal insufficiency, may lead to dysfunction of the thyrotropic and gonadotropic axes, and disrupts lipid metabolism parameters [49, 50]. Common adverse effects include nausea, taste disturbances, anorexia, numbness, tingling, dizziness, drowsiness, and fatigue. Mitotane has not been studied in pregnant women and is contraindicated during breastfeeding. It is a potent inducer of the CYP3A4 enzyme, leading to numerous drug interactions [51, 52]. Due to its induction of CYP3A4, mitotane may reduce the effectiveness of contraceptives containing oestradiol derivatives.

Recommendations

7.1.1. It is necessary to monitor mitotane levels during and after discontinuation/termination of therapy.
SoR: 2A QoE: II

7.1.2. Initiation of therapy and dosing may be with a prolonged or rapid regimen (Tab. 10); mitotane concentrations should be aimed for within the so-called therapeutic window, i.e. 14 –20 mg/L, provided there is acceptable toxicity and treatment tolerance.
SoR: 2A QoE: II

7.1.3. In the event of severe adverse reactions [Common Terminology Criteria for Adverse Events (CTCAE) 3 or 4], treatment should be temporarily discontinued.
SoR: 1 QoE: I

7.1.4. Due to the hepatotoxicity of mitotane, transaminase levels should be monitored initially every 3–4 weeks, then every 2–3 months. An increase in transaminase activity > 5× the upper limit of normal is an indication to discontinue treatment. Once transaminase levels have normalised, re-initiation of mitotane at a reduced dose may be considered.
SoR: 2A QoE: II

7.1.5. Due to the development of adrenal insufficiency, patients treated with mitotane require hydrocortisone substitution treatment. In view of mitotane's effect on hydrocortisone metabolism, doses should be 2–3 times higher than in classical substitution treatment, usually 50–70 mg/d. In cases of uncompensated hyponatraemia, hyperkalaemia, and high renin levels during hydrocortisone substitution, fludrocortisone should be included at a dose of 0.05–0.2 mg/d.
SoR: 1 QoE: II

Table 10. *Mitotane dosage regimens*

Initial dose	1.5 g (3 × 1 tabl)/d	1 g (2 × 1 tabl)/d
Day 2	3 g (3 × 2 tabl)/d	As above
Day 3	4.5 g (3 × 3 tabl)/d	As above
Day 4 and beyond	6 g (3 × 4 tabl)/d	1.5 g (3 × 1 tabl)/d and further increase by 0.5 g (1 tabl) every 3 days to a dose of 3–4 g (6–8 tabl)/d

7.1.6. Assessment of thyroid-stimulating hormone (TSH) and free thyroxine (fT4) concentrations during mitotane treatment should be performed every 3 months. A decrease in fT4 concentrations is an indication to start levothyroxine (LT4) replacement therapy.
SoR: 1 QoE: I

7.1.7. Assessment of luteinising hormone (LH) and testosterone concentrations in men on mitotane treatment should be performed every 3 months. In case of decreased testosterone levels and clinical signs of hypogonadism, initiation of testosterone replacement therapy should be considered. Dose selection should take into account the inhibition of 5α-reductase by mitotane.
SoR: 1 QoE: I

7.1.8. Due to the inhibition of cholesterol conversion to pregnanolone as a result of mitotane treatment, cholesterol and triglyceride levels should be monitored. If pharmacotherapy is indicated, statins not metabolised by CYP3A4 (pravastatin, rosuvastatin) are preferred.
SoR: 1 QoE: I

7.1.9. It is necessary to assess the interaction of mitotane with other drugs.
SoR: 1 QoE: I

7.1.10. It is necessary to inform the patient of childbearing age of the possible teratogenic effects of mitotane on the foetus. Recommended use of non-hormonal contraception [optimally double barrier or intrauterine device (IUD)] or sexual abstinence during the treatment period until an undetectable mitotane concentration is confirmed.
SoR: 1 QoE: I

7.2. Treatment of hormonally active tumours

One factor impacting the clinical course of ACC is its endocrine function, present in 60% of cases [53]. Hypercortisolaemia is most commonly observed, while a smaller proportion of ACCs exhibit mixed endocrine functions, producing both cortisol and androgens, or solely androgens. Production of aldosterone or oestradiol is even less common [4]. Mitotane significantly inhibits steroidogenesis, blocking the transcription of several enzymes involved in cortisol production. However, its effects may be delayed up to several months and may be insufficient in cases of severe hypercortisolaemia [4].

Recommendations

7.2.1. Mitotane is the steroidogenesis inhibitor of first choice for cortisol-producing ACC, provided there is acceptable treatment tolerance and no contraindications.
SoR: 1 QoE: I

7.2.2. Indications for the use of steroidogenesis inhibitors other than mitotane in cortisol-secreting ACC may arise:
— severe hypercortisolaemia, also in combination therapy with mitotane;
— if rapid control of excess cortisol is required, e.g. preparation for surgery;
— in case of intolerance and/or unacceptable toxic effects of mitotane;
— when the justification for the use of mitotane for oncological indications ceases.
SoR: 1 QoE: III

7.2.3. These drugs should be used according to the principles generally accepted for the treatment of endogenous Cushing's syndrome under the supervision of an endocrinologist.
SoR: 1 QoE: III

7.2.4. Patients treated with steroidogenesis inhibitors should be educated about the symptoms of adrenal insufficiency and, if necessary, provided with substitutive therapy using hydrocortisone.
SoR: 1 QoE: III

7.2.5. Therapy of hormonally active ACCs producing aldosterone, androgens in women, or oestrogens in men should be carried out according to the principles generally accepted in hormonally active tumours under the supervision of an endocrinologist.
SoR: 1 QoE: I

7.3. Complementary treatment of ACC

Most patients with ACC experience locoregional recurrence and/or distant metastases during postoperative follow-up [4], highlighting the necessity for adjuvant therapy. Mitotane is the only recognised drug used for this purpose, although the mechanism of its cytotoxic action is not fully understood. A retrospective study evaluating adjuvant treatment outcomes in 177 patients found that mitotane treatment significantly prolonged progression-free survival, but its impact on overall survival was inconclusive [54, 55]. The recently published ADJUVO trial, a prospective, randomised study that assigned low/intermediate-risk patients with Ki-67 < 10% to mitotane treatment, did not show an impact on progression-free survival or OS [56]. The optimal duration of mitotane therapy has not been precisely determined, but it is generally agreed that it should last at least 2 years. Data on adjuvant chemotherapy are limited, and such treatment should primarily be conducted within clinical trials and considered only in high-risk patients.

In every patient considered for adjuvant therapy with mitotane, the indications for adjuvant external beam radiotherapy should be assessed. While this treatment reduces the risk of locoregional recurrence, it does not improve OS. Patients with R1 postoperative status benefit most from adjuvant radiation treatment [57, 58].

Recommendations

73.1. Patients should be referred for adjuvant treatment based on risk groups (Tab. 11).
SoR: 1 QoE: I

7.3.2. Adjuvant treatment with mitotane is recommended for high-risk patients (see Fig. 2). Optimally, treatment should begin within 3 months after surgical treatment and should be conducted based on the general principles described in point 7.1. For intermediate-risk patients, the decision should on an individual basis.
SoR: 1 QoE: I

7.3.3. It is recommended that mitotane treatment should last no less than 2 years and no more than 5 years.
SoR: 1 QoE: III

7.3.4. Complementary radiotherapy should be given for R1 surgery, Rx (tumour capsule rupture), and locoregional recurrence. Radiotherapy should be implemented as soon as possible after surgery (no later than 3 months after treatment) to avoid overlapping side effects of radiotherapy and mitotane treatment.
SoR: 1 QoE: III

7.3.5. Adjuvant chemotherapy may be considered in very high-risk patients with a proliferation index > 30%.
SoR: 1 QoE: I

7.4. Palliative treatment

The prognosis for patients with advanced-stage ACC is poor, with 5-year survival rates below 15% [59]. The goal of palliative treatment for patients in advanced/metastatic stages is to control tumour growth, manage symptoms related to hypersecretion, and prolong survival. Factors influencing survival in advanced-stage disease include the number of organs involved, tumour differentiation, patient age, hormonal activity, and radical resection of the primary lesion (GRAS parameters) [60, 61].

Generally, the first-line treatment for patients with advanced/metastatic disease is mitotane as monotherapy or combined with chemotherapy according to the EDP (etoposide, cisplatin, doxorubicin) regimen. Mitotane monotherapy may be considered for patients with a low tumour burden and/or slow disease progression, with an expected response rate (RR) of 20–25% [62, 63]. There is no clear evidence defining the optimal duration of mitotane use with chemotherapy, but considering the pharmacokinetics of the drug, it should not be discontinued at the first sign of progression [64]. Surgery and locoregional therapies should be used to complement systemic therapy in selected patient populations.

Table 11. *Adrenocortical cancer (ACC) risk groups*

ACC low/intermediate risk	ACC high risk*
ENSAT I–II	ENSAT III
Ki-67 < 10%	Ki-67 > 10%
Operation R0	Surgery R1, Rx, rupture of tumour capsule

*Ki-67 > 30% very high-risk group. ENSAT — European Network for the Study of Adrenal Tumours; Ki-67 — proliferation index

In patients with rapid disease progression, mitotane monotherapy may not provide sufficiently quick symptom control as therapeutic drug concentrations are achieved over a relatively long period. Based on data from the First International Randomised Trial in Locally Advanced and Metastatic ACC Treatment (FIRM-ACT) study, the first-line treatment for this group of patients is combined therapy with mitotane and chemotherapy. The FIRM-ACT trial, which compared the EDP-M regimen (etoposide, doxorubicin, cisplatin, and mitotane; n = 151 patients) with the streptozotocin plus mitotane regimen (STZ-M; n = 153), demonstrated higher efficacy of EDP-M [23% RR, median progression free survival (mPFS) 5 months] *vs*. STZ-M (9% RR, mPFS 2.1 months). There was a trend towards improved OS in the EDP-M group (14.8 months *vs*. 12 months in STZ-M), although statistical significance was not achieved, probably due to the crossover design of the study and the use of mitotane in both arms [65]. Due to the high toxicity of the EDP-M regimen, for patients not suitable for the full EDP-M schedule, EP-M (etoposide, cisplatin, and mitotane) or P-M (cisplatin and mitotane) may be considered [66, 67].

In patients with oligometastatic disease, slow progression, palliative radiotherapy may be considered. In a retrospective study evaluating 132 ACC foci undergoing irradiation, the median time to progression of the treated lesion was 7.6 months and was dependent on the radiotherapy dose used [68].

Streptozocin with mitotane may be used in second-line chemotherapy based on the FIRM-ACT trial, with a median time to progression of 2 months [65]. Treatment with STZ is currently unavailable in Poland (05.2024) but efforts are being made to have the drug registered in Poland.

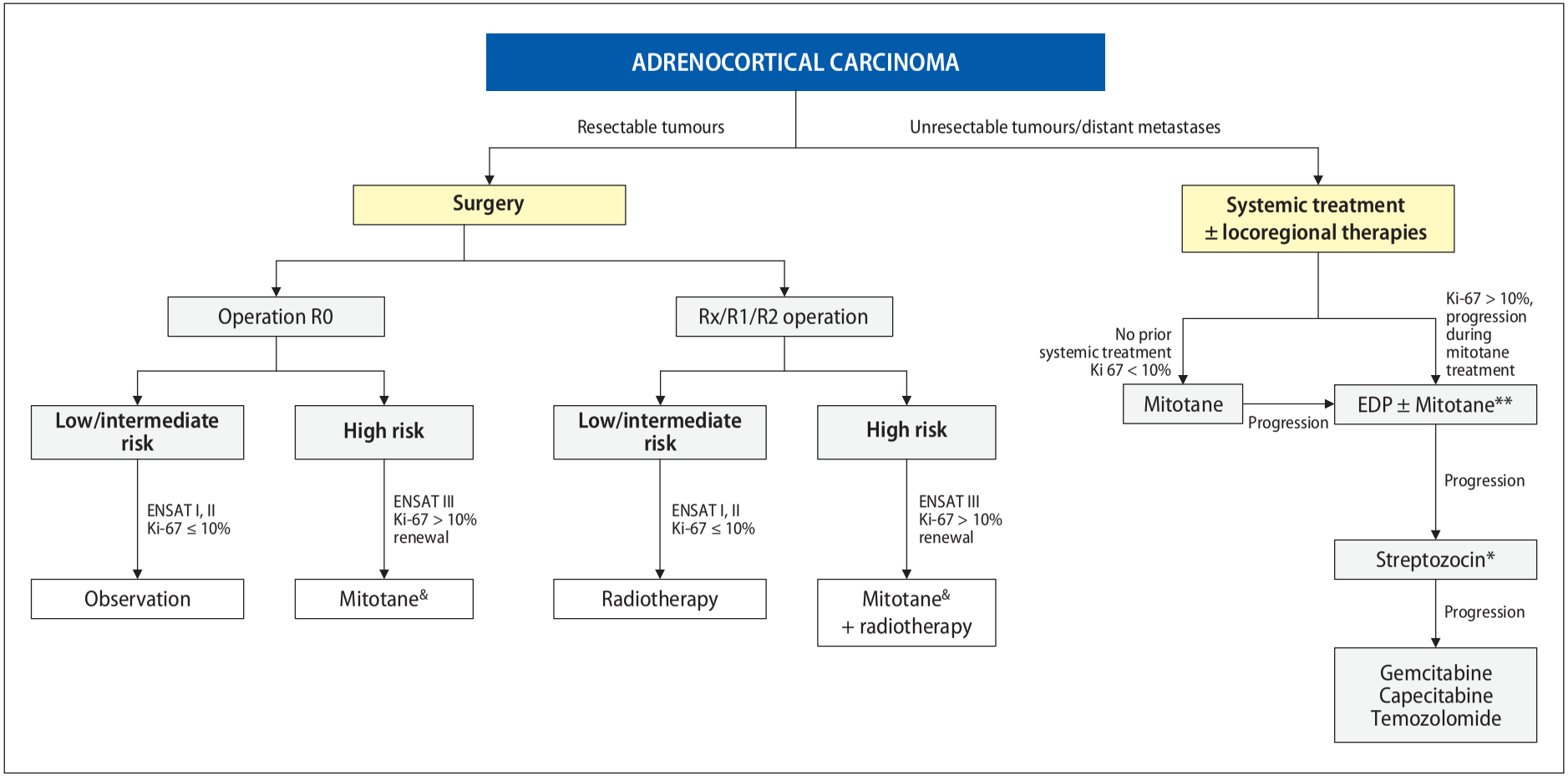

Figure 2. *Systemic treatment for adrenocortical carcinoma (ACC). &Ki 67 > 30% to consider chemotherapy with EP (etoposide, doxorubicine) regimen (especially in young patients in good general condition) 6 cycles; *Currently not available in Poland; **Continue mitotane in hormonally active tumours and in case of first progression on mitotane; EDP (etoposide, doxorubicine, cisplatine); ENSAT — European Network for the Study of Adrenal Tumours*

Subsequent lines of treatment can be gemcitabine plus capecitabine, with or without mitotane, with an mPFS of approximately 2 months and a response rate < 10% [69, 70]. Temozolomide can be considered as another line of treatment based on a small retrospective study of 38 patients, with a response rate of approximately 20%, and median PFS and OS of 3.5 and 7.2 months, respectively [71]. Further lines of treatment available only through salvage access to drugs include cabozantinib and immunotherapy. The efficacy of cabozantinib, a next-generation tyrosine kinase inhibitor (TKI), was reported in a phase II trial presented at ESMO 2022, involving 18 patients who achieved a 78% disease control rate (DCR), and median PFS and OS of 7.2 and 23.9 months, respectively [72]. In a retrospective study from 2018 [73], disease control was achieved in 50% of patients, and the median OS was 58 weeks. In patients with a high tumour mutational burden (TMB l) or in cases of established microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) DNA damage repair mechanisms, immunotherapy with pembrolizumab may be considered [65].

Recommendations

7.4.1. First-line treatment for patients with advanced unresectable disease is mitotane in monotherapy or mitotane with chemotherapy according to the EDP regimen.
SoR: 1 QoE: II

7.4.2. The standard palliative treatment is chemotherapy according to the EDP-M regimen.
SoR: 1 QoE: II

7.4.3. Mitotane in monotherapy may be considered in patients with a low cancer burden and/or a slower disease course.
SoR: 1 QoE: II

7.4.4. For patients not eligible for the full EDP-M regimen, a two-drug EP regimen or platinum derivative monotherapy may be considered.
SoR: 1 QoE: II

7.4.5. In case of progression during EDP treatment, subsequent lines of treatment include:
— streptozocin, gemcitabine with capecitabine or temozolomide;
— cabozantinib can be considered as another line of treatment, but tyrosine kinase inhibitor (TKI) therapy should not be combined with mitotane.
SoR: 2B QoE: IV

7.4.6. In patients with high TMB, immunotherapy with pembrolizumab may be considered in cases of established high-grade microsatellite instability or mismatch-type DNA damage repair mechanisms.
SoR: 1 QoE: I

8. Monitoring

Given the lack of research on surveillance strategies for patients with adrenocortical cancer, in this guideline we rely on existing recommendations [2–4].

The most common pattern of recurrence or progression of adrenocortical carcinoma involves local recurrences or metastases to lymph nodes, liver, and lungs. Metastases to bones or brain are very rare [3, 4, 74]. Computed tomography and/or magnetic resonance imaging should be evaluated at regular intervals during treatment and monitoring of the patient. In the absence of research, the recommended intervals between imaging studies based on the experiences of the centres dealing with adrenocortical carcinoma patients. Most disease recurrences occur within 5 years of diagnosis; hence, more intensive surveillance should take place during this time. At the same time, there are no data supporting discontinuation of further observation after this period; hence, the recommendation to continue monitoring beyond 5 years from diagnosis. After 5 years, the approach to observation must be determined individually because there is no evidence that long-term observation is beneficial. In most centres, patients remain under further observation, also due to patient expectations. Recurrence after 10 years from surgery are incidental. Imaging in advanced ACC primarily depends on the treatment used and the overall prognosis of the patient. Typically, exams are performed at intervals of 2–3 months. For patients treated only with mitotane, intervals between imaging may be even longer (e.g. 2–5 months) based on treatment tolerance and cancer progression. For patients undergoing locoregional therapies, decisions about imaging studies should be made in consultation with the therapy team. In symptomatically treated patients, systematic imaging is not recommended.

Hormonal assessment, together with clinical evaluation, allows early detection of recurrence as well as an opportunity for early implementation of steroidogenesis inhibitors in patients with recurrent hypercortisolaemia. Biochemical assessment should focus on hormones or hormone metabolites found at the diagnosis of primary ACC, but even in patients with hormonally inactive ACC, hormonal control may be indicated, due to the possible hormonal activity of metastases [16]. Biochemical tests include cortisol, testosterone (in women), DHEAS, androstenedione, 17β-oestradiol (in men),

aldosterone, 11-deoxycortisol, and 17OHPG [3, 4]. For baseline assessment of steroid profile analysis in urine or plasma, this method can also be helpful in monitoring patients.

Recommendations

8.1. Regular follow-up of patients with abdominal, pelvic, and thoracic imaging is recommended.
SoR: 1 QoEV

8.2. Patients after total tumour resection are advised to have regular imaging follow-up: every 3 months during the first 2 years; then every 3–6 months for 3 years; after 5 years an evaluation every 12 months is suggested, but decisions should be made on an individual basis. After 10 years of follow-up, the indications for further monitoring by imaging and the type of imaging are decided on an individual basis.
SoR: 1 QoE: V

8.3. In advanced ACC, the extent and frequency of monitoring studies depends on prognostic factors, expected treatment efficacy and toxicity, as well as available alternative therapeutic options.
SoR: 1 QoE: V

8.4. Regular monitoring of adrenal hormone testing is recommended in all patients as well as:
— TSH, fT4 every 3–4 months. Levothyroxine (LT-4) substitution is indicated in patients with symptoms of hypothyroidism;
— testosterone, LH, and sex hormone binding globulin (SHBG) in men for symptoms of hypogonadism.
SoR: 1 QoE: V

Conflict of interest
Authors declare no conflict of interest.

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