

# Adrenal tumors, explained from the guidelines

Most adrenal tumors are found by chance on a scan done for another reason, and most of them are benign. This page explains how the National Comprehensive Cancer Network (NCCN) approaches an adrenal mass: the imaging and hormone tests that sort it out, the tumors that make too much hormone, the rare adrenal cancer, and follow-up. It is educational and does not replace a conversation with your own care team.

## How it is usually found

By chance, on a CT or MRI done for another reason (an incidentaloma)

## The two key questions

Does it make extra hormones, and does it look benign or worrying on imaging?

## Reassuring imaging sign

A density under +10 Hounsfield units on a non-contrast CT suggests a benign, fat-rich adenoma

## Before any biopsy

Pheochromocytoma must be ruled out first with blood or urine metanephrine testing

## Adrenal cancer

Adrenocortical carcinoma is rare (0.7 to 2 per million); open surgery is recommended when it is suspected

## Typical follow-up

Depends on the tumor type, from endocrine follow-up to scans every 12 weeks to 12 months for at least 5 years

## Adrenal tumors at a glance

The adrenal glands are two small glands that sit on top of the kidneys and make hormones that control blood pressure, salt balance, blood sugar and the body's response to stress. An adrenal tumor is a growth in one of these glands. Most are found by chance on a CT or MRI done for some other reason, such as belly pain or a kidney check. Doctors call these chance findings adrenal incidentalomas. According to NCCN, most adrenal tumors that do not make hormones are benign (not cancer) and can be left untreated.

Two questions guide almost every decision. First, does the tumor make too much of a hormone? A tumor that does is called functional. Second, does it look benign or worrying on imaging? NCCN recommends that every person with an adrenal tumor have hormone (biochemical) testing and appropriate imaging. The answers usually sort the tumor into one of a few groups: a non-functioning benign adenoma, a tumor that makes too much aldosterone, a tumor that makes too much cortisol, a

pheochromocytoma, an adrenocortical carcinoma (adrenal cancer), or a spread of cancer from another organ.

Adrenal cancer is rare. NCCN cites an incidence of adrenocortical carcinoma of 0.7 to 2 cases per million people. Pheochromocytomas and paragangliomas occur in 0.05% to 0.1% of people with high blood pressure, with an estimated 500 to 1,600 cases each year in the United States.

This page draws on the NCCN Guidelines for Neuroendocrine and Adrenal Tumors (version 2.2024). The American Urological Association (AUA) and the European Association of Urology (EAU) do not have a dedicated adrenal tumor guideline among the sources used here. For the detailed hormone work-up of incidentalomas, aldosterone excess and Cushing syndrome, NCCN refers to guidelines from endocrine societies, so this page describes that part in general terms. Your endocrinologist will explain the exact testing steps.

#### WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024

All patients with adrenal gland tumors need hormone testing and appropriate imaging. Testing for aldosterone excess, cortisol excess, pheochromocytoma and suspected adrenal cancer should be done with every adrenal mass. (NCCN; recommendations are category 2A unless stated otherwise.)

## How adrenal tumors start

Each adrenal gland sits above a kidney, close to large blood vessels such as the inferior vena cava (the body's largest vein) and near the liver, spleen, pancreas and diaphragm. This location matters for surgery, because a large cancer may grow into these neighbors.

Each gland has two parts that work almost like two different organs. The outer layer, the cortex, makes steroid hormones: cortisol, which helps control blood sugar, blood pressure and the stress response; aldosterone, which controls salt, potassium and blood pressure; and small amounts of androgens (male-type sex hormones). Tumors of the cortex include adenomas, which are common and benign, and adrenocortical carcinoma, which is rare. Either kind can make too much of one or more of these hormones.

The inner part, the medulla, makes adrenaline (epinephrine) and noradrenaline (norepinephrine), together called catecholamines. A pheochromocytoma is a tumor of the hormone-making chromaffin cells. NCCN notes that 80% to 90% of these tumors arise in the adrenal medulla. Similar tumors that grow outside the adrenal gland, along nerve chains in the abdomen, chest or neck, are called paragangliomas.

Finally, the adrenal gland is a place where cancer from elsewhere in the body can spread. When a person has a history of cancer in another organ, NCCN notes that a new adrenal mass raises the question of a metastasis, which is handled differently from a tumor that starts in the adrenal gland.

## Risk factors and inherited conditions

Most adrenal tumors appear without a known cause. Most adrenocortical carcinomas are sporadic, meaning they are not inherited. Adrenocortical carcinoma has two age peaks, one in early childhood and one in the fourth to fifth decades of life (roughly ages 40 to 59), and NCCN reports that women make up 55% to 60% of cases.

Some adrenocortical carcinomas are linked to inherited syndromes, including Li-Fraumeni syndrome (TP53 gene), Lynch syndrome, Beckwith-Wiedemann syndrome, multiple endocrine neoplasia type 1 (MEN1) and familial adenomatous polyposis. NCCN cites one study in which 5.8% of adults with adrenocortical carcinoma had Li-Fraumeni syndrome and another in which about 3% had Lynch syndrome. For this reason, NCCN recommends genetic counseling and testing for everyone with adrenocortical carcinoma.

Pheochromocytomas and paragangliomas are even more often inherited. They occur in people with MEN2A, MEN2B, neurofibromatosis type 1 and von Hippel-Lindau (VHL) syndrome, and with changes in the SDH family of genes and several others. NCCN notes that SDHB gene changes carry a 40% to 60% risk of metastatic disease. People younger than 45, or those with tumors in more than one place, on both sides or that come back, are more likely to have an inherited cause, but many people with a hereditary syndrome have a single tumor and no family history.

A genetic result matters for the whole family. NCCN recommends that people who carry a known gene change linked to these tumors have lifelong hormone and clinical checks, beginning around ages 6 to 8, with the type and timing based on the specific gene. MRI may be preferred in these people to limit radiation.

### WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024

Genetic counseling and testing for inherited syndromes is recommended for every person with adrenocortical carcinoma and every person with pheochromocytoma or paraganglioma (NCCN category 2A).

## Symptoms and how it is usually found

Most adrenal masses cause no symptoms at all. They show up on a scan done for an unrelated reason, which is why the word incidentaloma exists. Even a mass that causes no symptoms is still tested for hormones, because hormone excess can be mild and still affect health over time.

When a tumor makes too much hormone, the symptoms depend on which hormone. Too much cortisol causes Cushing syndrome. Too much aldosterone causes high blood pressure, sometimes with low potassium in blood tests. A pheochromocytoma releases catecholamines, which can cause high blood pressure, a fast or irregular heartbeat, sweating, high blood sugar and fainting. Too much androgen can cause extra hair growth and, in women, masculine features (virilization).

Adrenocortical carcinoma often makes hormones: NCCN reports that about 60% of patients have signs of steroid hormone excess. Cancers that do not make hormones tend to cause symptoms from their

size, such as belly or back pain, feeling full early when eating, and weight loss.

- Cortisol excess (Cushing syndrome): weight gain around the trunk, weakness in the upper arms and thighs, high blood pressure, high blood sugar, depression or mood changes, purple stretch marks, fat pads behind the neck or above the collarbones, extra hair growth.
- Aldosterone excess (primary aldosteronism): high blood pressure, sometimes low potassium.
- Pheochromocytoma: high blood pressure, fast heartbeat, sweating, fainting, high blood sugar.
- Androgen excess: extra hair growth, masculine features in women.
- Large non-functioning tumors: belly or back pain, early fullness, weight loss.

## **How an adrenal mass is evaluated**

NCCN describes two parallel evaluations for every adrenal mass: a morphologic evaluation (what the mass looks like on imaging) and a functional evaluation (which hormones it makes). Together they answer most questions without the need for surgery or a biopsy.

The imaging test is usually an adrenal protocol CT. It starts with a scan without contrast dye that measures the density of the mass in Hounsfield units (HU). Benign adenomas usually contain fat, which makes them low in density. If the mass measures under +10 HU, it is probably benign and NCCN says no further imaging is needed; the NCCN algorithm also notes that pheochromocytoma screening is not needed in that case. If the mass measures more than +10 HU, a contrast CT with washout is done: the scan is repeated after contrast and again about 15 minutes later. An absolute washout above 60% suggests a benign tumor, while washout below 60% means the tumor is possibly malignant. MRI with and without contrast is the other option; it can show fat content and shows growth into the vena cava more clearly than CT. Depending on the results, more imaging may be suggested.

Imaging features that raise concern for cancer include a size of 4 cm or more (some centers use 6 cm), an uneven (inhomogeneous) appearance, irregular edges, growth into nearby tissue, enlarged nearby lymph nodes and spots in the liver. When cancer is suspected, NCCN recommends an FDG-PET/CT, a chest CT and CT or MRI of the abdomen and pelvis.

Hormone testing looks for the four main problems listed in the table below. Some medicines interfere with the pheochromocytoma tests, including acetaminophen, labetalol, sotalol, tricyclic antidepressants and monoamine oxidase inhibitors, so your team will review your medicine list first. NCCN notes that urine or blood catecholamines are no longer routinely used to look for pheochromocytoma, because 15% to 20% of people with the tumor have normal urine catecholamine levels; the metanephrine tests are preferred. Because most adrenocortical carcinomas make several hormones, a tumor that makes more than one hormone is more suspicious for cancer.

NCCN recommends an endocrinology evaluation when cortisol excess is found, and refers to Endocrine Society guidance for the detailed testing of cortisol and aldosterone problems. Your endocrinologist will explain how to prepare for each test.

| Condition                                             | What it can cause                                                        | Screening test                                                                                                                                                 |
|-------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Primary aldosteronism (aldosterone excess)            | High blood pressure, low potassium                                       | Blood aldosterone and renin; a suppressed renin with aldosterone above 10 ng/dL is a positive screen, then confirmation with salt loading                      |
| Hypercortisolemia (cortisol excess, Cushing syndrome) | Weight gain, weakness, high blood pressure and blood sugar, mood changes | One of: 1 mg overnight dexamethasone suppression test, 2 to 3 late-night saliva cortisol tests, or 24-hour urine free cortisol; then morning ACTH if confirmed |
| Pheochromocytoma                                      | High blood pressure, fast heartbeat, sweating, fainting                  | Plasma free or 24-hour urine fractionated metanephrines and normetanephrines; levels 3 times above the upper limit of normal are diagnostic                    |
| Suspected adrenocortical carcinoma                    | Cortisol or aldosterone excess, androgen excess                          | Cortisol and aldosterone screening plus adrenal androgens (DHEAS, androstenedione, testosterone, 17-hydroxyprogesterone)                                       |

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

Adrenal masses should be evaluated with an adrenal protocol non-contrast CT (with contrast and washout if above +10 HU) or MRI with and without contrast, together with hormone testing for aldosterone excess, cortisol excess, pheochromocytoma and androgen excess (NCCN category 2A).

## When a biopsy is used, and why it is often avoided

Many cancers are confirmed with a needle biopsy before treatment. Adrenal tumors are different. In most cases the imaging pattern and hormone results are enough to decide on a plan, and the NCCN pathways for functional tumors and for suspected adrenocortical carcinoma move from imaging and hormone tests straight to treatment planning, without a biopsy step.

NCCN discusses biopsy mainly in one situation: a person with a current or past cancer elsewhere, in whom the adrenal mass might be a metastasis. Even then, NCCN stresses that it is very important to rule out pheochromocytoma before any biopsy. NCCN explains that stress on a pheochromocytoma, such as surgery, can cause a sudden release of large amounts of catecholamines and dangerously high blood pressure, which is why this tumor must be excluded before a needle is placed.

According to NCCN, an image-guided needle biopsy may be considered only when the suspicion for pheochromocytoma is low, the blood or urine metanephrines are normal, and the result will change management. Biopsies can miss the diagnosis (a false-negative result), so in selected cases going straight to surgery may be the better choice.

#### WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024

Pheochromocytoma should be ruled out before a diagnostic biopsy of an adrenal mass. Image-guided needle biopsy may be considered if suspicion for pheochromocytoma is low, metanephrines are normal and the result will affect management; false negatives are possible (NCCN category 2A).

## Staging and grading of adrenocortical carcinoma

Staging describes how far a cancer has grown and spread. It applies to adrenocortical carcinoma; benign adenomas are not staged. NCCN uses the American Joint Committee on Cancer (AJCC) 8th edition system, which looks at the size of the tumor (5 cm is the dividing line), whether it grows outside the adrenal gland or into nearby organs or large veins, whether lymph nodes are involved, and whether the cancer has spread to distant organs.

The diagnosis of adrenocortical carcinoma is usually confirmed by a pathologist after the tumor is removed. Pathologists use scoring systems (such as the Weiss and modified Weiss systems) that look at features like invasion of blood vessels or the tumor capsule, dead tumor tissue (necrosis) and how fast cells are dividing. The grade is based on the number of dividing cells: low grade is 20 or fewer mitoses per 10 square millimeters, and high grade is more than 20. The Ki-67 index, another measure of cell growth, is also reported.

Pheochromocytomas and paragangliomas are handled differently. NCCN states that all of them should be considered to carry a lifelong risk of spreading, and pathologists no longer label them benign or malignant. Several scoring systems have been proposed to predict spread, but none is currently endorsed for routine use.

AJCC 8th edition stages for adrenocortical carcinoma, as reproduced in NCCN

| Stage     | What it means in plain words                                                                                                                                                        |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Stage I   | Tumor 5 cm or smaller, confined to the adrenal gland, no lymph node or distant spread (T1 N0 M0)                                                                                    |
| Stage II  | Tumor larger than 5 cm, confined to the adrenal gland, no lymph node or distant spread (T2 N0 M0)                                                                                   |
| Stage III | Cancer in nearby lymph nodes, or tumor of any size growing into surrounding tissue or into nearby organs or large veins such as the renal vein or vena cava, without distant spread |
| Stage IV  | Cancer has spread to distant parts of the body (M1), regardless of size or lymph nodes                                                                                              |

## How treatment decisions are made

The type of tumor decides the path. A small, benign-looking mass that makes no hormones is usually watched or simply left alone. A tumor that makes too much hormone is usually removed, after the hormone effects have been controlled with medicine. A tumor that looks like cancer is removed with an

operation designed for cancer. A metastasis is treated according to the guideline for the original cancer.

Adrenal care is a team effort. An endocrinologist confirms the hormone diagnosis and prepares the body for surgery; NCCN recommends an endocrinology evaluation for cortisol excess. Adrenal surgery is performed by surgeons with adrenal experience, who may be urologic oncologists, endocrine surgeons or other surgical oncologists depending on the center. A medical oncologist leads drug treatment for adrenocortical carcinoma or advanced pheochromocytoma. Radiologists, pathologists, radiation oncologists and genetic counselors complete the team, and NCCN suggests evaluation by a comprehensive multidisciplinary team for people with inherited syndromes.

For surgery, NCCN prefers a minimally invasive adrenalectomy (laparoscopic or robotic, through small incisions) for benign tumors that make aldosterone or cortisol and for pheochromocytoma when safe and feasible. When cancer is suspected, NCCN recommends an open adrenalectomy, because removing the tumor whole, without breaking its capsule, matters greatly for adrenocortical carcinoma.

Many decisions involve trade-offs: watching versus removing a borderline mass, open versus minimally invasive surgery, or whether to take mitotane after surgery. These are shared decisions. Your team should explain the options, the uncertainty in the evidence and how each choice fits your health and priorities. NCCN also states that the best management of any patient with cancer is in a clinical trial.

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

Adrenalectomy for benign-appearing functional tumors and pheochromocytoma is done by a minimally invasive approach when safe and feasible; open adrenalectomy is recommended for suspected malignancy (NCCN category 2A).

## **Small non-functioning masses and surveillance**

If the hormone tests are normal and the imaging looks benign, the mass is usually a non-functioning adenoma. NCCN describes tumors smaller than 4 cm that are even in appearance, have smooth edges and look fat-rich on CT or MRI as benign, and states that most non-functioning tumors are benign and can be left untreated. Masses that show the typical features of a myelolipoma, a tumor made largely of fat, are also considered benign.

How often, and for how long, such a mass should be re-imaged or re-tested is not set out in the NCCN guideline. NCCN refers instead to the adrenal incidentaloma guidelines of the American Association of Clinical Endocrinology and American Association of Endocrine Surgeons (AACE/AAES) and the European Society of Endocrinology (ESE). Under the NCCN imaging pathway, a mass under +10 HU on non-contrast CT does not need further imaging. Your team will tell you whether any repeat scan or hormone test is planned for you.

If a mass that looked benign grows and removal is recommended, NCCN prefers a minimally invasive adrenalectomy. If cancer becomes a concern and the disease is localized or regionally advanced, an open adrenalectomy is recommended.

Hearing the word tumor is frightening. It may help to know that for most people with a small, fat-rich, non-functioning adrenal mass, the guideline expects no treatment at all.

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

Most non-functioning adrenal tumors are benign and can be left untreated. If resection is needed because of growth, minimally invasive adrenalectomy is preferred; NCCN refers to AACE/AES and ESE incidentaloma guidelines for ongoing management.

## **Aldosterone-producing tumors (primary aldosteronism)**

Primary aldosteronism means the adrenal glands make too much aldosterone, which holds on to salt, loses potassium and raises blood pressure. Screening looks for a high aldosterone level with a low renin level. NCCN notes that the aldosterone-to-renin ratio is usually greater than 30 in this condition, and that confirmation with a salt-loading test is often recommended when results are borderline.

There are two common causes, and they are treated differently: a single adenoma on one side, which can be removed, or overgrowth (hyperplasia) of both glands, which is treated with medicine. CT cannot always tell these apart. For people who would consider surgery, NCCN says adrenal vein sampling can be considered. In this test, a thin tube is passed through a vein to take blood from each adrenal vein; cortisol is measured in the samples to confirm the tube is in the right place. Some NCCN member centers recommend sampling in all cases, while it may be reasonable to skip it in people younger than 40 when imaging shows only one affected gland.

When one gland is the source, NCCN recommends adrenalectomy, with a minimally invasive approach preferred. When both glands are involved, or the person is not a surgical candidate, high blood pressure and low potassium are treated with spironolactone or eplerenone, medicines that block aldosterone.

Aldosterone-producing tumors are rarely cancer. NCCN notes that cancer should be suspected if the tumor is uneven, low in fat, does not wash out on contrast CT, is larger than 4 cm or makes more than one hormone.

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

For benign primary aldosteronism in a surgical candidate, consider adrenal vein sampling; one-sided disease is treated with adrenalectomy (minimally invasive preferred), and two-sided disease or non-surgical candidates with spironolactone or eplerenone (NCCN category 2A).

## **Cortisol-producing tumors and Cushing syndrome**

When symptoms or a mass suggest cortisol excess, NCCN lists three screening tests: an overnight 1 mg dexamethasone suppression test, 2 to 3 late-night saliva cortisol measurements, or a 24-hour urine free cortisol. If cortisol excess is confirmed, a morning blood ACTH level shows whether the cause is the adrenal gland itself (ACTH-independent, with a low ACTH) or a signal coming from the

pituitary or another tumor (ACTH-dependent). An adrenal tumor that makes cortisol is ACTH-independent.

NCCN recommends an endocrinology evaluation, and medicine to control cortisol excess may be used until definitive treatment can be arranged.

For a tumor smaller than 4 cm that looks benign, NCCN recommends adrenalectomy, with a minimally invasive approach preferred. For a tumor 4 cm or larger, or one that is uneven, has irregular edges, invades nearby tissue or has other worrying features, NCCN adds an FDG-PET/CT, a chest CT and adrenal protocol imaging, and recommends an open adrenalectomy when cancer is suspected and the disease can be removed. That operation may require removing part of a nearby organ to get the whole tumor out.

A cortisol-making tumor switches off the other adrenal gland for a while. For this reason, NCCN recommends stress-dose steroids (such as hydrocortisone or methylprednisolone) around the time of surgery, and steroid replacement is usually needed afterward until the remaining gland recovers.

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

Cortisol-producing tumor under 4 cm and benign-appearing: adrenalectomy, minimally invasive preferred. 4 cm or larger or suspicious: FDG-PET/CT and chest CT, then open adrenalectomy for suspected malignancy. Perioperative stress-dose steroids are needed (NCCN category 2A).

## **Pheochromocytoma and paraganglioma**

A pheochromocytoma makes catecholamines, the fight-or-flight hormones, which can cause high blood pressure, heart rhythm problems and high blood sugar. NCCN notes that about 10% to 15% of pheochromocytomas and paragangliomas spread (and up to 40% in some reports), that paragangliomas spread more often than adrenal pheochromocytomas (about 40% versus 10%), and that tumors linked to inherited syndromes tend to be more aggressive.

The evaluation NCCN recommends includes blood or 24-hour urine metanephrines, adrenal protocol CT or MRI, and genetic counseling and testing for everyone. If spread or several tumors are suspected, other scans may be used, such as somatostatin receptor PET (SSTR-PET), FDG-PET/CT, chest CT or an MIBG scan. NCCN also advises that if MEN2 is suspected, pheochromocytoma be checked for before any procedure.

Preparation before surgery is essential. NCCN states that alpha blockade is necessary for all hormone-secreting pheochromocytomas and paragangliomas, even without symptoms. Alpha blockers (doxazosin, terazosin, prazosin or phenoxybenzamine) are given for 7 to 14 days before surgery, together with generous fluids and a high-salt diet, until blood pressure is stable. A calcium channel blocker may be added if more blood pressure control is needed, and metyrosine can be added as well. A beta blocker may be added for a fast heart rate, but only after alpha blockade has started; NCCN does not recommend combined alpha-beta blockers. Medicines that can trigger a hormone crisis are avoided.

Removal of the tumor is the main treatment, with a minimally invasive approach preferred when safe and feasible. After the tumor is out, blood pressure and blood sugar can drop, so the team watches closely and treats with intravenous fluids and dextrose. NCCN suggests a medical alert ID for people with hormone-secreting tumors.

When the tumor cannot be removed or has spread, NCCN lists observation for slow-growing tumors without symptoms, or, for secreting tumors, continued alpha blockade plus a clinical trial, radiation with or without surgery to reduce tumor bulk, or drug treatment. Drug options include high-specific-activity iobenguane I-131 (for tumors that show up on an MIBG scan), sunitinib, chemotherapy (CVD or temozolomide), lutetium Lu 177 dotatate (for tumors positive on SSTR imaging, where data are limited) and octreotide or lanreotide. Outcomes vary widely, and NCCN notes that many people survive long term after treatment of metastatic disease.

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

Before surgery for any hormone-secreting pheochromocytoma or paraganglioma, alpha blockade with volume repletion and a high-salt diet for 7 to 14 days, or until stable, is recommended; resection is minimally invasive when safe and feasible (NCCN category 2A).

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

Plasma free or 24-hour urine fractionated metanephrines, adrenal protocol imaging, and genetic counseling and testing are recommended for every patient with pheochromocytoma or paraganglioma (NCCN category 2A).

## **Adrenocortical carcinoma that can be removed**

NCCN says adrenocortical carcinoma should be strongly suspected when a tumor is larger than 4 cm, has irregular edges or an uneven inside, or makes several hormones; enlarged lymph nodes or spots in the liver may also be seen. The work-up includes FDG-PET/CT, chest CT, CT or MRI of the abdomen and pelvis, and hormone tests including adrenal androgens. NCCN also recommends genetic counseling and testing, and suggests considering tumor testing for microsatellite instability (MSI), mismatch repair (MMR) and tumor mutational burden (TMB), which can open the door to certain treatments.

Surgery is the main treatment for cancer that has not spread. NCCN recommends an open adrenalectomy with removal of visibly involved lymph nodes, and the operation may require removing part of the liver, kidney, pancreas, spleen or diaphragm to take out the whole tumor. The goals are clear (negative) margins and an unbroken tumor capsule. NCCN explains that minimally invasive removal of a likely cancer carries a higher risk of local recurrence and spread inside the abdomen. NCCN also notes that if the tumor is small enough for laparoscopy, a surgeon may start minimally invasively and plan to convert to open surgery if invasion is found; the choice depends on tumor size, how strongly cancer is suspected and local surgical expertise.

After surgery, some people have a high risk of the cancer coming back: positive margins, a Ki-67 above 10%, a ruptured capsule, a large tumor or a high grade. For them, NCCN lists a clinical trial,

radiation to the tumor bed, or adjuvant mitotane. No randomized trials of adjuvant treatment have been published. A meta-analysis of five retrospective studies (1,249 patients) found longer recurrence-free and overall survival with mitotane, but NCCN rates it category 3, meaning the panel disagrees, and several NCCN centers do not advise it. A randomized trial called ADIUVO is studying mitotane in lower-risk patients.

Mitotane is a pill that destroys adrenal cortex tissue. Blood levels are monitored, and some centers aim for 14 to 20 mcg/mL if tolerated; reaching a steady level can take several months. Because mitotane shuts down the adrenal glands, lifelong hydrocortisone, sometimes with fludrocortisone, is usually required. NCCN notes that mitotane may help hormone symptoms more than it controls the tumor.

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

Localized adrenocortical carcinoma: resect the tumor and evident lymph nodes, with open adrenalectomy recommended; achieve negative margins and avoid breaching the capsule (NCCN category 2A).

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

If the risk of local recurrence is high, options are a clinical trial, radiation to the tumor bed, or adjuvant mitotane. Adjuvant mitotane is category 3, reflecting major disagreement within the NCCN panel.

## **Adrenocortical carcinoma that has spread or cannot be removed**

When adrenocortical carcinoma has spread or cannot be fully removed, NCCN lists several approaches, often combined. Surgery to remove the primary tumor and metastases may be considered if more than 90% of the disease can be removed, especially when the tumor makes hormones. If the disease is bulky or less than 90% removable, surgery can be reconsidered after a good response to drug treatment. For slow-growing disease without symptoms, observation with scans and hormone markers about every 12 weeks is an option, with drug treatment started if the cancer grows.

Local treatments such as stereotactic body radiation therapy (SBRT), thermal ablation (heat or cold applied through a needle) and liver-directed therapy may be used for selected sites.

NCCN recommends that drug treatment be given preferably in a clinical trial. Preferred regimens are chemotherapy with carboplatin or cisplatin plus etoposide, with or without doxorubicin, with or without mitotane. Other recommended options are mitotane alone and the immunotherapy drug pembrolizumab, with or without mitotane. In the international FIRM-ACT trial, the four-drug combination of etoposide, doxorubicin, cisplatin and mitotane improved response rates and the time before the cancer grew compared with streptozocin plus mitotane, but overall survival was not significantly different (14.8 versus 12.0 months). Mitotane alone produces partial responses in at most 10% to 30% of people, and small studies of pembrolizumab reported responses in about 14% to 23%.

These numbers are sobering, and they reflect how rare this cancer is and how few large trials exist. The side effects of chemotherapy combined with mitotane are weighed carefully, and mitotane alone

may still be appropriate for some people. This is a setting where a clinical trial and a team with experience in adrenal cancer are especially valuable.

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

Unresectable or metastatic adrenocortical carcinoma: consider resection if more than 90% is removable, local therapy, or systemic therapy preferably in a clinical trial. Preferred: carboplatin or cisplatin plus etoposide, with or without doxorubicin and mitotane. Other recommended: mitotane alone, or pembrolizumab with or without mitotane (NCCN category 2A).

## **When cancer from another organ spreads to the adrenal gland**

In someone who has or has had cancer elsewhere, a new adrenal mass may be a metastasis. NCCN asks for the same two steps first: imaging and hormone testing, with pheochromocytoma ruled out before any biopsy.

If suspicion for pheochromocytoma is low, metanephrines are normal and the answer would change treatment, an image-guided needle biopsy may be considered. If the biopsy shows a metastasis, treatment follows the NCCN guideline for the original cancer, which may involve drug treatment, radiation or surgery depending on the cancer type and how much disease there is. If the biopsy instead shows adrenal cortex tissue, the evaluation continues as for any other adrenal tumor. Because biopsies can miss a cancer, going directly to surgery may be considered in selected cases.

**WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024**

If an adrenal mass proves to be a metastasis from another site, treatment follows the NCCN guideline for that cancer (NCCN category 2A).

## **Side effects and how they are managed**

Adrenalectomy is an abdominal operation, with the usual risks of bleeding, infection and injury to nearby organs. The NCCN guideline does not list complication rates, so ask your surgeon about their approach and what to expect. An open operation for adrenocortical carcinoma is larger and may include removing part of a neighboring organ.

The most specific side effects are hormonal. After removal of a cortisol-making tumor, the other adrenal gland has been switched off, so steroids are given around surgery and usually continued for a time; your endocrinologist will taper them as the gland recovers. After removal of a pheochromocytoma, blood pressure and blood sugar can fall, which is why the team monitors closely and uses intravenous fluids and dextrose. Your team will also review your blood pressure medicines after surgery for an aldosterone- or catecholamine-making tumor, since the need for them may change.

Mitotane causes adrenal insufficiency (the body cannot make enough of its own steroid hormones), so hydrocortisone, sometimes with fludrocortisone, is prescribed and may be needed for life. Higher mitotane levels can be hard to tolerate, which is why blood levels are checked. People on long-term

steroid replacement are usually taught by their endocrinology team how to adjust doses during illness and when to seek urgent care.

Chemotherapy for adrenal cancer and treatments for advanced pheochromocytoma have their own side effects. For high-specific-activity iobenguane I-131, NCCN reports nausea, low blood counts and fatigue as the most common. Your oncology team will explain the specific risks of any drug before you start and how they will be monitored.

- Cortisol-making tumor: temporary low cortisol after surgery; steroid replacement until the other gland recovers.
- Pheochromocytoma: low blood pressure and low blood sugar right after surgery; close monitoring.
- Mitotane: adrenal insufficiency needing hydrocortisone with or without fludrocortisone, often lifelong; blood level checks.
- Open surgery for cancer: larger incision and possible removal of part of a nearby organ.

## **Follow-up after treatment**

Follow-up depends on the type of tumor. For benign tumors, follow-up is mostly about hormones and blood pressure and is led by endocrinology. For adrenocortical carcinoma and pheochromocytoma, NCCN gives scan and blood test schedules, summarized in the table below.

For removed adrenocortical carcinoma, NCCN suggests visits every 12 weeks to 12 months for up to 5 years, then as clinically indicated, because recurrences after 5 years are thought to be very rare. For pheochromocytoma and paraganglioma, follow-up continues for up to 10 years, and longer for people with inherited syndromes or a young age at diagnosis. NCCN notes that tumors can spread many years after the first diagnosis, which is why people diagnosed in childhood, adolescence or young adulthood need careful, lifelong surveillance.

Schedules are tighter in the first years and if symptoms appear, and looser when things are stable. Your team will set a schedule for you.

Typical follow-up schedules from the NCCN guideline

| Situation                                                     | How often                                                                                                                                                   | What is usually checked                                                                                         |
|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Small non-functioning benign-appearing mass                   | Not set by NCCN; follows endocrine society incidentaloma guidance                                                                                           | Repeat imaging or hormone tests only if your team recommends them                                               |
| Adrenocortical carcinoma, after complete removal              | Every 12 weeks to 12 months for up to 5 years, then as clinically indicated                                                                                 | Consider chest CT and abdominal CT or MRI with contrast; hormone markers if the tumor was functional            |
| Adrenocortical carcinoma, unresectable or metastatic          | Every 12 weeks to 12 months (every 12 weeks if observing indolent disease)                                                                                  | Chest CT and abdomen/pelvis CT or MRI with contrast, or FDG-PET/CT; hormone markers                             |
| Pheochromocytoma or paraganglioma, after removal              | First check 12 weeks to 12 months after surgery; then every 6 to 12 months in years 1 to 3; yearly in years 4 to 10; after 10 years as clinically indicated | History, exam, blood pressure, plasma or urine metanephrines; consider chest CT and abdomen/pelvis CT or MRI    |
| Pheochromocytoma or paraganglioma, unresectable or metastatic | Every 12 weeks to 12 months                                                                                                                                 | History, exam, blood pressure, metanephrines; imaging such as CT, MRI, MIBG, FDG-PET or SSTR-PET as appropriate |
| Known gene change linked to pheochromocytoma                  | Lifelong, starting around ages 6 to 8                                                                                                                       | Hormone and clinical checks tailored to the gene; MRI may be preferred to limit radiation                       |
| Metastasis to the adrenal from another cancer                 | Per the guideline for the original cancer                                                                                                                   | Set by the original cancer's team                                                                               |

#### WHAT THE GUIDELINES SAY · NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) V2.2024

After resection of pheochromocytoma or paraganglioma: history, exam, blood pressure and metanephrines every 6 to 12 months in years 1 to 3 and yearly up to 10 years. After resection of adrenocortical carcinoma: follow-up every 12 weeks to 12 months for up to 5 years (NCCN category 2A).

## Living with and after an adrenal tumor

For many people, removing a hormone-making tumor changes daily life. Blood pressure may improve and medicines may be reduced, and changes from cortisol excess may ease over time. The pace differs from person to person, and your endocrinologist will track it with you.

Living with steroid replacement, whether temporary after Cushing surgery or lifelong with mitotane, means taking pills on schedule and knowing what to do when you are sick. A medical alert ID, which

NCCN suggests for hormone-secreting pheochromocytoma and paraganglioma, can help emergency staff understand your condition quickly.

A genetic result can raise questions for children, siblings and parents. Genetic counselors can explain who else might benefit from testing and what lifelong checks look like for carriers.

Uncertainty is hard, especially with a rare cancer like adrenocortical carcinoma, where evidence is limited. Anxiety, low mood and fatigue are common and treatable. Ask your team about counseling, support groups and survivorship care; NCCN points people with pheochromocytoma to its survivorship guidance.

## **Clinical trials and second opinions**

NCCN states that the best management of any patient with cancer is in a clinical trial, and encourages participation. This is especially relevant for adrenocortical carcinoma and advanced pheochromocytoma, where few large trials exist and many questions, such as who benefits from mitotane after surgery, remain open.

Because adrenal tumors are uncommon, a second opinion can be valuable, particularly a review of the imaging and, after surgery, of the pathology, since the diagnosis of adrenocortical carcinoma rests on detailed scoring. Asking for a second opinion is a normal part of care and will not offend your team.

You can search for trials at [ClinicalTrials.gov](https://clinicaltrials.gov) or ask your oncologist whether a trial fits your situation.

## **When to contact your care team**

Contact your care team promptly if you notice new or worsening symptoms, especially during preparation for surgery, after surgery or while on steroid replacement. Call emergency services for chest pain, fainting, severe shortness of breath or a sudden, severe rise in blood pressure.

- Episodes of pounding heartbeat, sweating, fainting or very high blood pressure readings, especially with a known or suspected pheochromocytoma.
- Dizziness or lightheadedness on standing while taking alpha blockers before surgery.
- After surgery: fever, worsening belly pain, wound redness or drainage, or very low blood pressure readings.
- While on hydrocortisone or after cortisol-tumor surgery: vomiting, being unable to keep pills down, severe weakness or feeling faint.
- New belly or back pain, early fullness or unexplained weight loss after treatment of adrenal cancer.
- Return of earlier symptoms such as rising blood pressure, low potassium, weight gain or muscle weakness.

## **Questions patients often ask**

### **My scan found an adrenal mass by accident. Is it cancer?**

Usually not. NCCN states that most adrenal tumors that do not make hormones are benign and can be left untreated. Your team will check hormones and look closely at the imaging to be sure.

### **Why do I need hormone tests if I feel fine?**

Hormone excess can be mild and still affect blood pressure and blood sugar over time, and a pheochromocytoma must be ruled out before any procedure. NCCN recommends hormone testing for every adrenal mass.

### **Why won't my doctor biopsy the mass?**

In most cases imaging and hormone tests are enough to decide, and a needle placed into an unrecognized pheochromocytoma could be dangerous. NCCN reserves biopsy mainly for possible spread from another cancer, and only after pheochromocytoma has been ruled out.

### **What does a Hounsfield unit number on my report mean?**

It measures density on a CT scan without contrast. A number under +10 suggests a fat-rich, benign adenoma. Higher numbers lead to a contrast washout study or MRI.

### **Will the surgery be done through small incisions?**

For benign hormone-making tumors and for pheochromocytoma, NCCN prefers a minimally invasive approach when safe. When cancer is suspected, NCCN recommends open surgery to remove the tumor whole and lower the risk of spread.

### **Why do I need to take pills for 1 to 2 weeks before pheochromocytoma surgery?**

Handling the tumor can release large amounts of adrenaline-type hormones and cause dangerous blood pressure spikes. Alpha blockers, extra fluids and salt for 7 to 14 days make surgery much safer.

### **Will I need steroid pills after surgery?**

If your tumor made cortisol, yes, usually for a while, because the other gland needs time to wake up. If you take mitotane, replacement is usually needed for life. Your endocrinologist will guide the dose.

### **Is adrenocortical carcinoma curable?**

When it is found while still confined and is removed completely with clear margins, surgery offers the best chance of cure. Some people need added treatment, and when the cancer has spread, treatment aims to control it; trials are encouraged.

### **Should my family be tested?**

NCCN recommends genetic counseling and testing for everyone with adrenocortical carcinoma, pheochromocytoma or paraganglioma. If a gene change is found, relatives may be offered testing and,

if positive, lifelong checks.

### **How long will I be followed?**

It depends on the tumor. After adrenal cancer surgery, NCCN suggests follow-up for up to 5 years and then as needed. After pheochromocytoma surgery, follow-up continues up to 10 years, and lifelong for people with inherited syndromes.

## **Glossary**

### **Adrenal glands**

Two small hormone-making glands that sit on top of the kidneys.

### **Adrenal cortex**

The outer layer of the adrenal gland, which makes cortisol, aldosterone and androgens.

### **Adrenal medulla**

The inner part of the adrenal gland, which makes adrenaline and noradrenaline.

### **Incidentaloma**

An adrenal mass found by chance on a scan done for another reason.

### **Adenoma**

A benign (non-cancerous) tumor of the adrenal cortex; the most common adrenal mass.

### **Functional tumor**

A tumor that makes too much of a hormone.

### **Hounsfield units (HU)**

A measure of tissue density on CT. Fat-rich benign adenomas usually measure under +10 HU without contrast.

### **Contrast washout**

How quickly contrast dye leaves a mass on CT. Washout above 60% at 15 minutes suggests a benign tumor.

### **Adrenalectomy**

An operation to remove an adrenal gland, done through small incisions (minimally invasive) or a larger open incision.

### **Primary aldosteronism**

Too much aldosterone from the adrenal glands, causing high blood pressure and sometimes low potassium.

### **Adrenal vein sampling**

A test that takes blood from each adrenal vein through a thin tube to see which side makes too much aldosterone.

### **Cushing syndrome**

The effects of too much cortisol, such as weight gain around the trunk, weakness, high blood pressure and high blood sugar.

### **ACTH**

A pituitary hormone that tells the adrenal glands to make cortisol. It is low when an adrenal tumor makes cortisol on its own.

### **Pheochromocytoma**

A tumor of the adrenal medulla that makes catecholamines (adrenaline-type hormones).

### **Paraganglioma**

A tumor like a pheochromocytoma that grows outside the adrenal gland along nerve chains.

### **Metanephrines**

Breakdown products of adrenaline and noradrenaline measured in blood or urine to test for pheochromocytoma.

### **Alpha blockade**

Medicines such as doxazosin or phenoxybenzamine given before pheochromocytoma surgery to control blood pressure.

### **Adrenocortical carcinoma**

A rare cancer that starts in the adrenal cortex.

### **Mitotane**

An oral drug that destroys adrenal cortex tissue, used for adrenocortical carcinoma.

### **Adrenal insufficiency**

When the body cannot make enough of its own steroid hormones, treated with hydrocortisone and sometimes fludrocortisone.

### **Stress-dose steroids**

Extra steroid medicine given around surgery when the body may not make enough cortisol on its own.

### **Ki-67**

A lab measure of how many tumor cells are dividing; higher values suggest faster growth.

### **FDG-PET/CT**

A scan that uses a sugar-based tracer to show active tumor anywhere in the body.

### **Metastasis**

Cancer that has spread from where it started to another part of the body.

## **Sources**

These are the professional guidelines this page is written from. They are copyrighted by their societies and are linked here rather than copied. Where a society publishes a free patient version, that link is included too.

- **National Comprehensive Cancer Network (NCCN) v2.2024:** NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors

<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1448>

<https://www.nccn.org/patientresources/patient-resources/guidelines-for-patients>

This guide is general education written from published clinical guidelines. It is not medical advice, does not describe any individual's care, and does not replace the judgment of your own care team. Guidelines change; the versions used are listed above.