All About Adrenal Cancer

What are the adrenal glands?

The adrenal glands' function is to produce hormones. Hormones are chemicals produced by the body and secreted into the blood, which carries them to various organs and tissues in the body, and there they exert their functions. The adrenal glands produce hormones such as adrenaline, aldosterone and cortisol. You have two adrenal glands, each located just above each kidney. The adrenal glands are surrounded by a layer of connective tissue and a layer of fat. Each adrenal gland has two parts, the outer portion, which is the adrenal cortex and the inner portion, which is the medulla.

The medulla produces the chemicals epinephrine (also called adrenaline) and norepinephrine. Both of these chemicals are involved in regulation of the nervous system. Epinephrine controls the short-term stress response (fight-or-flight response). While norepinephrine also plays a role in short-term stress response, it functions in regulating mood and attention, as well.

The adrenal cortex is largely responsible for producing steroid hormones in the body. There are several types of steroid hormones that are produced by the adrenal glands. Mineralocorticoids(such as aldosterone) are steroid hormones that help regulate the sodium (salt) levels in the body by controlling the absorption and excretion of salt and water in the kidneys. This in turn helps to regulate blood pressure. Glucocorticoids (such as cortisol) are steroid hormones that play a critical role in the regulation of sugar within the body. These hormones also help to regulate the fat stores within the body, act as a strong anti-inflammatory force, and play an important role in fetal development, particularly in lung maturation. The adrenal cortex also produces several sex steroid hormones, including androgens(critical for male sexual development) and precursors to estrogen(critical for female sexual development).

What is adrenal cancer?

Normally, cells in the body will grow and divide to replace old or damaged cells in the body. This growth is highly regulated, and once enough cells are produced to replace the old ones, normal cells stop dividing. Tumors occur when there is an error in this regulation and cells continue to grow in an uncontrolled way. Tumors can either be benign or malignant. Although benign tumors may grow in an uncontrolled fashion sometimes, they do not spread beyond the part of the body where they started (metastasize) and do not invade into surrounding tissues. Malignant tumors, however, will grow in such a way that they invade and damage other tissues around them. They also may spread to other parts of the body, usually through the blood stream or through the lymphatic system where the lymph nodes are located. Over time, the cells within a malignant tumor become more abnormal and appear less like normal cells. This change in the appearance of cancer cells is called the tumor grade, and cancer cells are described as being well-differentiated, moderately-differentiated, poorly-differentiated, or undifferentiated. Well-differentiated cells are quite normal appearing and resemble the normal cells from which they originated. Undifferentiated cells are cells that have become so abnormal that often we cannot tell what types of cells they started from.

The most common tumor of the adrenal gland is actually a benign tumor called an adrenal adenoma. In most patients, these benign tumors never cause a patient to have any symptoms and do not need to be treated. They are usually found when a patient has a CT scan of the body for an unrelated reason, and are thus sometimes called "incidentalomas" because they are found accidentally. An adrenal adenoma will cause symptoms if it is producing an excess of hormones like aldosterone, which can cause high blood pressure.

Cancers that arise directly from the adrenal cortex are called adrenal cortical carcinoma (also called adrenocortical cancer or adrenal cancer). Like an adenoma, they are commonly found through imaging such as a CT for an unrelated issue. However, they can be found after a workup for symptoms that they are causing. Symptoms of overproduction of hormones include: weight gain, fluid retention, early puberty in children, or excess facial hair growth in women. A large adrenal tumor can cause symptoms such as pain or a feeling of fullness since the tumor may press against other organs due to its size. These cancers can either be functioning (meaning they secrete excess steroid hormones) or non-functioning (meaning they do not secrete steroids). Functioning adrenal cortical cancers are more common than non-functioning cancers.

The most common malignant tumors found in the adrenal gland are tumors that come from cancer cells that have metastasized (or spread) from other parts of the body to the adrenal gland through the blood stream. Several different types of cancer may spread to the adrenal glands, most commonly melanomas, lung cancers, and breast cancers. The adrenal glands are the fourth most common site in the body for cancer cells to metastasize to, after the lungs, liver, and bone.

Cancers can also arise within the adrenal medulla, the most common of which are pheochromocytomas. In children, neuroblastoma tumors can develop within the adrenal medulla. Pheochromocytomas and neuroblastomas are discussed in separate articles and will not be discussed further in this review. Other types of adrenal cancers can occur, such as lymphoma; however, these cases are rare.

What causes adrenal cancer and am I at risk?

Adrenal cancer is very rare and the actual number of those diagnosed in the United States is not known. It is estimated that the number is between 200-500. About one in every 10 people who have an imaging test of the adrenal gland are found to have adrenal tumors; however, a vast majority of these are adenomas (benign tumors), which are fairly common in the middle aged and elderly population. Adrenal cancer is more common in women than men.

There are risk factors associated with adrenal cancer. However, having one or more of these risk factors does not mean you will get adrenal cancer. You could have none of these risk factors and develop adrenal cancer. A number of genetic related syndromes are risk factors for adrenal cancer including: Li Fraumeni syndrome, Beckwith-Wiedmann syndrome, multiple endocrine neoplasia, hereditary nonpolyposis colorectal cancer, and familial adenomatous polyposis. These syndromes are caused be genetically inherited or acquired after birth gene defects, which can not be changed. High-fat diet, smoking, sedentary lifestyle, and exposure to cancer-causing substances can all increase your risk for cancer in general but not specifically adrenal cancer.

How can I prevent adrenal cancer?

There are no preventable risk factors associated with adrenal cancer so there is no way to prevent adrenal cancer. However, genetic testing and counseling may be suggested if you are known to have any of the previously mentioned syndromes.

What screening tests are available?

Adrenal cancers are rare and because of this there are no recommendations for routine testing and screening.

What are the signs of adrenal cancer?

Both adrenal adenomas and adrenal cancers can produce excess steroid hormones, producing symptoms, which lead to further workup and the identification of the tumor. Symptoms vary depending on the steroid that is produced.

- Aldosterone, which is a type of steroid hormone, can cause Conn's syndrome(also known as primary hyperaldosteronism). Conn's syndrome most commonly occurs with pituitary adenomas, but it can also occur in the setting of adrenal hyperplasia(an overgrowth of normal adrenal cortical tissue) and adrenal cortical cancers. Signs of Conn's syndrome include elevated blood pressure, decreased levels of potassium in the blood, and decreased levels of a chemical produced by the kidneys called renin in the blood. In most cases of Conn's syndrome, elevations in blood pressure are mild to moderate. Other symptoms include weakness, muscle cramps, increased thirst, and increased frequency of urination.
- Cortisol is a separate steroid hormone produced within the adrenal cortex. If a tumor produces excess cortisol, Cushing's syndrome(also known as hypercortisolism) can develop. This syndrome is seen not only with adrenal tumors, but can also be the result of excessive levels of adrenal cortical stimulating hormone(also known as ACTH, a hormone that is responsible for stimulating the adrenal glands to produce cortisol) produced by the pituitary gland or another tumor in the body. Cushing's syndrome may also develop in patients who are taking steroids as medication for other disorders. The symptoms of Cushing's syndrome can vary greatly from patient to patient and involve a number of different parts of the body. Symptoms include weight gain and water retention resulting in a round face and collection of fat on the back of the shoulders and neck (so-called "buffalo hump"). Red or purple stretch marks, known as striae can appear on the skin. Excessive hair growth (hirsutism)can also be seen. Excessive cortisol levels can interfere with the body's immune system, predisposing a patient to unusual infections. Patients with Cushing's syndrome are at high risk for development of diabetes. Patients may also have mental changes, including mood swings, irritability, and in the worst case, psychotic episodes. In children, excessive cortisol can lead to premature sexual development and maturation (also called precocious puberty).
- Sexual hormones can also be overproduced by an adrenal tumor. If excess testosterone is produced, virilizationcan occur in either men or women. Virilization causes increased masculine characteristics, resulting in deepened voice, loss of hair, and increase in the size of the clitoris in women. Feminization may occur in men with excess estrogen production, and may cause sexual impotence and/ or breast growth (gynecomastia).

As an adrenal tumor grows it can cause symptoms. Patients with large adrenal tumors may experience feelings of abdominal fullness or localized pain. Patients may feel as though they are quickly full when eating and may experience weight loss. In some cases of large adrenal tumors, patients may actually feel a mass in their abdomen.

How is adrenal cancer diagnosed?

Functioning adrenal cortical cancers and adenomas are frequently diagnosed because of the symptoms caused by the over production of hormones caused by the cancer. A full work-up will be completed to determine the cause of this overproduction and if it is related to an adrenal tumor.

Patients with Cushing's syndrome need to be evaluated to see if the syndrome is caused by a problem in the adrenal glands, the pituitary gland, or another tumor somewhere else in the body. The first step is measuring the amount of cortisol in the urine (called a 24-hour urinary free cortisol test). This test is sometimes performed while giving the patient an extra dose of steroids to see how the body responds. After this is done, most patients undergo a dexamethasone suppression testwhere patients are given a high dose of the steroid dexamethasone. In normal patients, and in patients with Cushing's syndrome due to a problem in the pituitary gland, a high dose of dexamethasone will cause the levels of cortisol in the blood and urine to decrease. In patients with adrenal tumors or another tumor in the body that produces ACTH, cortisol levels remain high even after a patient

receives a high dose of dexamethasone.

Patients with excess levels of aldosterone should have the blood levels of the chemical renin tested. In cases of hyperaldosteronism due to a tumor in the adrenal gland, renin levels will be low. Patients who have elevated aldosterone levels due to a problem with the blood vessels of the kidney (a condition called renal artery stenosis), will have high blood levels of renin.

In addition to tests for increased steroid production, imaging is an important part of the diagnosis of adrenal tumors. Computed Tomography(also referred to as CT or CAT) scans are commonly used. CT scans use x-rays to form a three-dimensional picture of the inside of the body. If the adrenal tumor is larger than 6 centimeters (cm) on CT scan, it is much more likely to be an adrenal cancer than an adrenal adenoma. In most cases, CT scans can also differentiate between a normal adrenal gland and adrenal hyperplasia (enlarged adrenal gland).

Ultrasound and MRI are less commonly used but still can be useful in diagnosing adrenal cancer. Ultrasounds use sound waves to form a picture of the inside of the body. At times, it can be difficult to tell if an adrenal tumor is an adenoma or a cancer. For tumors that are larger than 3 cm, ultrasound is a good method of telling the difference between the two. MRI (Magnetic Resonance Imaging) can be useful to determine if a growth is cancer. MRI uses magnets to produce a very sharp picture of the inside of the body. Certain types of changes on MRI are more commonly seen in adrenal cancers than adenomas and can be used to tell the two apart.

Many cancers are diagnosed using biopsy. A biopsy is a procedure in which a portion of a tumor is removed and then visualized under a microscope. However, this is not the case with adrenal cancer. Adrenal adenomas and cancers look very similar when visualized under a microscope. It has also been found that the biopsy procedure to diagnose adrenal cancer is likely to spread tumor cells and may cause metastasis of the cancer. Therefore, it is best to use imaging techniques and workup of hormonal issues rather then biopsy to diagnose adrenal cancer.

How is adrenal cancer staged?

In addition to diagnosing adrenal cortical cancers, radiology tests performed also help to determine the stage of the tumor. Adrenal cancer is most commonly staged using the TNM staging system, which is created by the American Joint Committee on Cancer. The "T stage" represents the extent of the primary tumor itself. The "N stage" represents the degree of involvement of the lymph nodes. The "M stage" represents whether or not there is spread of the cancer to distant parts of the body. The T, N, and M are combined to assign a stage, from I (one) denoting more limited disease, to IV (four) denoting more advanced disease.

American Joint Committee on Cancer (AJCC)
TNM Staging System for Adrenal Tumors, 7th Edition, 2010

The TNM breakdown is quite technical, but is provided here for your reference.

Primary Tumor (T)

TX	Primary tumor cannot be assessed

T0	No evidence of primary tumor
T1	Tumor 5cm or less in greatest dimension, no extra-adrenal invasion
T2	Tumor greater than 5cm, no extra-adrenal invasion
T3	Tumor of any size with local invasion, but not invading adjacent organs
T4	Tumor of any side with invasion of adjacent organs

(Adjacent organs include kidney, diaphragm, great vessels, pancreas, spleen, and liver.)

Regional Lymph Nodes (N)

NX	Nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 T2 T3	N1 N1 N0	M0 M0 M0
Stage IV	T3 T4 T4 Any T	N1 N0 N1 Any N	M0 M0 M0 M1

How is adrenal cancer treated?

Most adrenal adenomas are detected on a CT scan or MRI scan that is performed for an unrelated reason. It is only necessary

to treat adrenal adenomas if they are causing symptoms. Otherwise, they can be followed with scheduled scans. In the event that an adenoma does need to be treated, surgical removal is the most frequent treatment used. In many cases, this can be performed using a *laparoscopic* procedure. A laparoscope is a small fiberoptic camera that can be inserted into the abdomen through small incisions. Other small instruments can also be inserted through these incisions. The adrenal adenoma can be resected while inside the body, without making a large incision in the abdomen, and removed through the small holes through which the camera and other instruments are inserted. Occasionally, because of the size or location of the adenoma, a laparoscopic procedure cannot be performed, and a larger incision will need to be made in the abdomen in order to remove the tumor.

In the majority of cases of hyperaldosteronism, symptoms resolve with surgical removal of the adenoma; however, 30% of patients will have repeat episodes of high blood pressure even after the adenoma is removed. If the adrenal adenoma produces cortisol, the patient should take steroids by mouth before and for some time after the surgery until the body is able to produce these steroids on its own again.

Surgery

Currently, the only known way to cure adrenal cortical cancers is complete surgical removal of the tumor known as an adrenalectomy. Unfortunately, this is only possible for some patients with this disease. At least half of patients with adrenal cortical cancers have metastases or cancer invading into other organs, so that complete removal of the tumor is not possible. The best results with surgical resection have been with an *en bloc* resection, meaning that the entire tumor is removed in one piece. This also may include removing the entire kidney on the same side as the adrenal cancer. Because of this, it is unusual for adrenal cancers to be removed using a laparoscopic procedure, although as techniques of laparoscopic resection improve, more patients are being treated with this method. Occasionally, adrenal cancers will grow into the large blood vessel that carries blood back from the lower body to the heart (the *vena cava*). Even in these cases, complete removal of the cancer can sometimes be performed, but will require input from a general surgeon, an urologist, and a vascular surgeon.

Even in cases where the tumor cannot be removed in its entirety, surgical removal of as much tumor as possible can improve symptoms, particularly if they are due to excessive steroid secretion. Some providers may decide that a patient should be treated with chemotherapy or radiation prior to or after treatment with surgery depending upon the size of the tumor, if there is metastasis, and how successful the surgery was in removing all of the cancer.

Chemotherapy

Chemotherapy refers to a group of medications that are given to treat cancer. These medications travel throughout the body to kill cancer cells. This is one of the big advantages of chemotherapy. If cancer cells have broken off from the tumor and are somewhere else inside the body, chemotherapy has the chance of killing them.

The most common chemotherapy used in treatment of adrenal cortical cancers is mitotane. Mitotane acts to block the hormones produced by the cancer and can also kill adrenal cancer cells. Mitotane or other chemotherapy is almost always used when surgery is not possible, or if surgery is done, but some cancer cells remain in the body. In many cases, mitotane is also used for patients after surgery, even if all visible cancer has been removed. Mitotane is one part of the two most commonly used regimens to treat adrenal cancer. The first includes mitotane, etoposide, doxorubicin, and cisplatin. The second regimen is mitotane and streptozotocin. In addition to treating the cancer, mitotane can also suppress the function of your normal adrenal gland, so you may need to take hormone replacement tablets to prevent adrenal insufficiency. Your lab work will be monitored to determine if and which hormones are being affected and what supplements you will need to take.

Exactly which chemotherapeutic agents are given varies according to your provider's preference, your own health and the side effects associated with the medications.

Radiation Therapy

Radiation therapy is not part of the routine management of adrenal cancers, particularly in cases where the cancer is completely removed by surgery. Radiation may be used in cases where surgical removal of the cancer is incomplete or in cases where the cancer comes back after surgery. It may also be used as a palliative treatment. Palliative meaning that the intention of the treatment is not to cure the cancer, but to manage a symptom such as pain.

Other Medication Treatments

Patients who are treated for adrenal cortical cancers may have symptoms that are due to levels of hormones that are either too high or too low. Providers may recommend other medications, such as ketoconazole or metyrapone, to treat these symptoms.

Clinical Trials

There are clinical research trials for most types of cancer, and every stage of the disease. Clinical trials are designed to determine the value of specific treatments. Trials are often designed to treat a certain stage of cancer, either as the first form of treatment offered, or as an option for treatment after other treatments have failed to work. They can be used to evaluate medications or treatments to prevent cancer, detect it earlier, or help manage side effects. Clinical trials are extremely important in furthering our knowledge of disease. It is through clinical trials that we know what we do today, and many exciting new therapies are currently being tested. Talk to your provider about participating in clinical trials in your area. You can also explore currently open clinical trials using the OncoLink Clinical Trials Matching Service.

Follow-Up Care and Survivorship

Because adrenal cancer is so rare, the plan for follow-up treatment may vary from provider to provider. You will be followed closely for recurrence of the disease and to monitor any side effects of the treatment you received. Your provider will determine what testing you need depending upon your treatment and any new symptoms you may be experiencing. If part of your treatment plan includes taking mitotane, you will frequently have blood drawn to check the level of mitotane in your blood. You may have CT scans to monitor you for recurrence or to check if a tumor is growing. If you are taking medications to suppress hormone production by the cancer you will have intermittent tests of your blood and urine to check hormone levels.

Fear of recurrence, financial impact of cancer treatment, employment issues and coping strategies are common emotional and practical issues experienced by adrenal cancer survivors. Your healthcare team can identify resources for support and management of these practical and emotional challenges faced during and after cancer.

Cancer survivorship is a relatively new focus of oncology care. With some 15 million cancer survivors in the US alone, there is a need to help patients transition from active treatment to survivorship. What happens next, how do you get back to normal, what should you know and do to live healthy going forward? A survivorship care plan can be a first step in educating yourself about navigating life after cancer and helping you communicate knowledgeably with your healthcare providers. Create a survivorship care plan today on OncoLink.

Resources for More Information

[Adrenal Cancer Support]
This website offers information and support for those affected by adrenal cancer.

[American Cancer Society]

[Cancer Compass]
Connect online with others affected by adrenal cancer. This site provides information and resources on a variety of cancers including adrenal cancer.