Tumors of the Adrenal Medulla and Paraganglia (Pheochromocytoma & Paraganglioma)

A Guide for Patients and Families

Multidisciplinary
Endocrine Oncology Clinic

ROGEL CANCER CENTER

MICHIGAN MEDICINE

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Important Phone Numbers

Cancer Center Clinic Contact

New Patient Coordinator 734-232-0040
Clinic Call Center 734-647-8906
M-Line (doctor to doctor). 800-962-3555

Appointments

CT Appointments 734-936-4500
Endocrine Oncology Scheduling 734-647-8906
General Surgery Scheduling 734-936-5783
Nuclear Medicine Department. 734-936-4500
Preoperative Center at Domino Farms. 734-936-3604

Resources

Cancer Center Nutrition Clinic. 877-907-0859
Complementary Therapy Programs. 877-907-0859
Patient & Family Support Services. 877-907-0859
Patient & Visitor Lodging/Accommodations Program 800-544-8684
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Operating Rooms

Main OR Family Waiting Room. 734-936-4000
East Ann Arbor Surgical Center 734-232-3000
Surgery Cancellation 734-936-8800

Introduction

The doctors and healthcare staff at the University of Michigan Rogel Cancer Center Endocrine Oncology Program created this book to explain tumors of the adrenal medulla and paraganglia (pheochromocytoma and paraganglioma) and the treatment options available to you.

This is not a comprehensive guide to treatment options — they are changing every day. Rather, we hope this guide helps you move forward with a firm understanding of pheochromocytoma and paraganglioma, how it is treated, and what the experience may include. With this information in hand, you will be prepared to make thoughtful decisions along with your medical team.

You will find blank pages at the back of the book to use for writing down questions, appointments, or other notes.

Overview

About the Adrenal Glands

What are adrenal glands?

Everyone has 2 adrenal glands. These pyramid-shaped glands, each about the size of a walnut, are located on top of each kidney. They are sometimes called "supra-renal" glands which is Latin for "above the kidney".

Each adrenal gland is made up of 2 parts: an inner area called the **medulla,** and an outer area called the **cortex**.

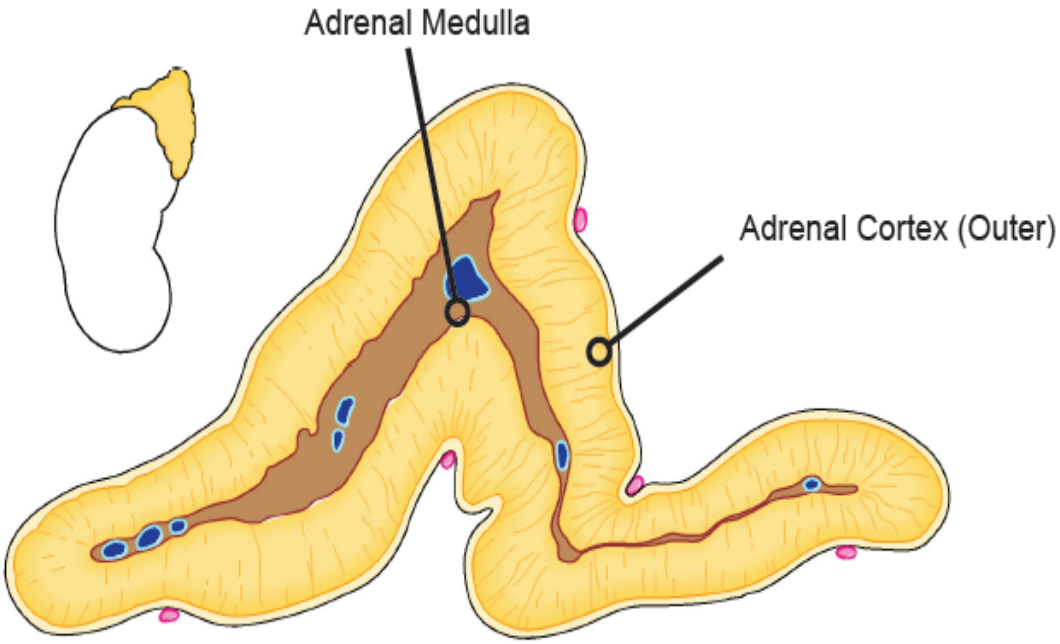

Figure 1: Anatomy of the Adrenal Gland

What do the adrenal glands do?

The adrenal glands may be small, but they play an important role in how you think and feel. These small powerhouse organs produce and secrete hormones that affect the way every tissue, organ and gland in your body works.

The adrenal medulla plays an essential role in how your body responds to stress. It makes a chemical called **epinephrine**, also called adrenaline, as well as a similar chemical called **norepinephrine** or noradrenaline.

The adrenal cortex makes a variety of hormones, including:

- **Mineralocorticoids** (such as aldosterone) that help regulate blood pressure and the fluid and salt levels in the body.
- **Glucocorticoids** (such as cortisol) are released by the adrenal cortex to help the body cope with long term stress. They also help regulate the amount of sugar and fat stored in the body and act as anti-inflammatory agents.
- **Hormones related to sex.** While proper sexual development and function is regulated by "real" sex hormones secreted by the gonads (testis and ovaries), there is no definite function assigned to sex hormones secreted by the adrenal cortex.

The adrenal cortex is not involved in the formation of pheochromocytoma tumors.

What are paraganglia?

Paraganglia are specialized organs found at multiple locations in the body. The adrenal medulla is one example. Paraganglia are mainly located near the vertebral column, but are also found in the head and neck region, the thorax (chest), the abdomen, close to internal organs such as the bladder, and close to large blood vessels, such as the aorta. They are closely associated with the Autonomous Nervous System (ANS), which controls all non-voluntary body functions (including digestion, urination, blood pressure, sweating and more).

The role of both the adrenal medulla and paraganglia is to coordinate what is known as the "fight-or-flight" response. Release of epinephrine and norepinephrine (together called catecholamines) increases the ability of the mind and body to cope with short term stress by increasing heart rate, blood pressure, and blood flow to muscles. (As you will read later, both of these hormones can be produced by certain tumors of the adrenal glands.)

What is cancer and how does it affect the adrenal glands and paraganglia?

Normal cells grow, divide, and die in a controlled way regulated by the body. Cancer is a disease that causes cells to divide and grow in an abnormal, out-of-control way, disturbing the balance of cell growth and death. In time, cells that grow and divide abnormally will become a mass or tumor which will eventually affect how an organ works.

Abnormal or uncontrolled cells can also grow and invade nearby organs and structures. This spreading is called **metastasis**. Tumors that invade and spread are called **malignant** or cancerous, while tumors that never spread or invade other organs are called **benign**. Tumors of the adrenal medulla and paraganglia can be benign 90 out of 100 (90%) or malignant 10 out of 100 (10%).

Medical research has led to a better understanding of abnormal cell activity, which is a primary focus in the treatment of cancer.

Tumors of the adrenal medulla and paraganglia

The original site of abnormal cell growth is called the cancer's **"primary site."**

- In tumors known as **pheochromocytoma**, the primary site is the adrenal gland, specifically the adrenal medulla.
- In tumors known as **paragangliomas** the primary site is in the paraganglia (sometimes called extra-adrenal pheochromocytoma).

The two main types of primary tumors of the adrenal medulla are pheochromocytomas, which occur in children and adults, and neuroblastomas, which are almost exclusively diagnosed in children during the very first years of life. This handbook will focus only on pheochromocytomas and paragangliomas.

Most pheochromocytomas and paragangliomas are confined to the organ where they originate. Occasionally they spread to other organs and are then

considered malignant pheochromocytoma or malignant paraganglioma. Even if a tumor is removed and analyzed by a pathologist, it can be difficult to determine whether or not it has the ability to spread. Therefore, thorough follow-up is needed.

How common are these tumors and who is at risk?

Pheochromocytomas and paragangliomas are very rare, occurring in roughly 3 to 6 people per million, per year — roughly a couple of thousand people in the United States annually. To date, no known risk factors for pheochromocytomas or paragangliomas have been identified.

Are these tumors hereditary?

About 70 out of 100 (70%) of pheochromocytomas occur by chance; these are called sporadic pheochromocytomas. About 30 out of 100 (30%) of pheochromocytomas and an even larger portion of paragangliomas result from a hereditary condition (one passed on from parents). Therefore, every person with a diagnosed pheochromocytoma or paraganglioma should meet with a genetic counselor to discuss genetic testing.

Several hereditary syndromes predispose individuals to the development of these tumors, most affecting people younger than 50 years of age. While the medical and surgical management of these tumors is the same regardless of whether or not they are hereditary, genetic testing is still very important for two main reasons:

1. People with these hereditary syndromes may be more likely to develop pheochromocytomas or paragangliomas somewhere else in the body (such as in the other adrenal gland) or to develop tumors in other organs. In these cases, doctors will suggest an individual screening and surveillance to increase the chances of diagnosing these tumors at an early, more treatable stage.

2. It is important to identify other members of the person's family who may be at risk due to the same hereditary genetic predisposition. Screening, such as blood tests and imaging, can be done early with these family members to identify any tumor growth.

Every person with a diagnosis of pheochromocytoma or paraganglioma should seek evaluation in a cancer genetics clinic to receive counseling, even in the absence of any family history of these tumors. Geneticists and genetic counselors will help to identify possible causes of hereditary conditions and will also guide you through screening and surveillance processes. Please ask your treating doctor for a referral.

How do hereditary syndromes develop?

The code that directs every function of every cell in the human body is contained in the **genome**. The genome code is made up of units called **genes**. Genes are made of the chemical **deoxyribonucleic acid (DNA)**, located in the nucleus of every cell. Humans have two "versions" of each gene, one inherited from the mother and one from the father.

While genes serve very diverse functions in the human body, some have the special function of preventing unregulated growth, from which tumors may form. They are tumor suppressor genes. People with a predisposition to tumors are often born with a defect in one of these genes. This usually does not matter, because the healthy gene takes over the function.

Although the genome is very stable over a lifetime, changes can occur simply by chance. The whole genome has to be copied with every cell division and it needs to be constantly monitored by the cell for changes. In case these mechanisms ever fail, there is usually one healthy gene left, because we have two of each gene (one from each parent). The exception is when one of the genes is already not working properly, as is the case in inherited syndromes. When an inherited

syndrome is present, the loss of the second gene can lead to loss of the tumor-preventive function.

Which hereditary syndromes can cause pheochromocytomas or paragangliomas?

People with certain hereditary syndromes have a higher chance of developing pheochromocytomas, paragangliomas or other tumors. They will not necessarily develop a pheochromocytoma, but because they face a higher risk than the rest of the population, they should undergo regular screening.

Here is a list of hereditary syndromes that are regularly seen with pheochromocytomas, along with some of their characteristics:

- **Multiple Endocrine Neoplasia Type 2 (MEN2)** — high calcium levels due to tumors of the parathyroid glands, pheochromocytoma or medullary thyroid cancer.
- **Von Hippel-Lindau Disease (VHL)** — kidney cancer, blood vessel tumors of the nervous system and the retina (eye), pheochromocytomas or pancreas tumors.
- **Neurofibromatosis Type 1 (NF1)** — skin tumors arising from peripheral nerves, areas of skin pigmentation (cafe-au-lait spots) or pheochromocytoma.
- **Hereditary Paraganglioma Syndrome (HPGL)** — mutations in the genes SDHA, SDHB, SDHC, SDHD or SDHAF2, paragangliomas, pheochromocytomas or possibly other tumors.

All of these hereditary syndromes are very rare. But in some cases, enough affected people and their families have gathered to form national and even international support groups. Contact with a support group is very helpful to learn more about these syndromes, to share experiences and to advocate.

What are the symptoms of pheochromocytomas and paragangliomas?

There are six primary symptoms of pheochromocytomas and paragangliomas:

1. Hypertension (high blood pressure)
2. Headache
3. Pallor (paleness)
4. Orthostatic hypotension (for example, when getting up from a chair causes a drop in blood pressure, dizziness or near fainting)
5. Sweating
6. Tachycardia or palpitation (racing heart)

Usually these symptoms occur in an "attack-like fashion" that lasts from a few minutes to several hours. These attacks are very often interpreted as anxiety attacks, which of course are much more common than pheochromocytomas and paragangliomas.

Not all of these symptoms are necessarily present in every person and they can also occur in a sustained, "non-attack-like fashion." For example, some people have only hypertension, a very common health concern usually treated without thorough investigation for a pheochromocytoma.

How are pheochromocytomas and paragangliomas diagnosed?

Pheochromocytomas and paragangliomas are either discovered by chance, such as when imaging is performed related to other health issues, or because the hormones they secrete cause symptoms. Paragangliomas can also be diagnosed when there is swelling of a certain body site such as the head or neck area, or because they may cause symptoms by pushing against a blood vessel or nerve.

There are several specialized tests used to diagnose these tumors:

- **Blood and urine tests:** Most of these tumors secrete the hormones epinephrine and/or norepinephrine (called catecholamines), which can be measured in the urine or in the blood. Because the body alters the original catecholamine quickly, doctors will look for altered catecholamine products, called metanephrine and normetanephrine. These can be measured in blood or 24-hour urine collections. Other markers that can be measured in the urine are vanillylmandelic acid (VMA) or homovanillic acid (HVA).

- **Computed Tomography (CT):** CT scans can use a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body. It can show small tumors as well as important blood vessels that the tumor might be growing into or around. It can also look at surrounding organs for spread (metastasis) of the cancer into lymph nodes or other organs in the abdomen or chest.

  A CT scan takes longer than a regular x-ray, and requires you to lie still on a table. Usually, you will need an IV placed for a dye injection just before the scan. This helps tissues and organs to show up more clearly. You may also be asked to drink a contrast solution before the exam. This helps outline the intestine so it is not mistaken for tumors.

- **Magnetic Resonance Imaging (MRI):** The MRI scan uses magnets to make a picture of the inside of the body. MRIs produce very sharp, precise pictures of an area and can be helpful in determining whether a certain tumor is a pheochromocytoma, a paraganglioma, or a different tumor type.

- **Ultrasound of the abdomen or neck:** An ultrasound uses sound waves to make a picture of the inside of the abdomen. This is the fastest and cheapest test available; however, it is also the least accurate. It can be difficult to tell the difference between adenoma benign tumors and cancer using ultrasound.

  An ultrasound may be used to guide a biopsy procedure (removing a sample of cells for analysis by a pathologist). However, this is not recommended for tumors which are suspected to be pheochromocytomas, since it can lead to a release of catecholamine that can elevate blood pressure.

- **Positron emission tomography (PET):** A PET scan involves the injection of radioactive sugar or other substances into a vein followed by a body scan that looks for areas that absorb the radioactive substance.

  Cancer cells take up these much faster than normal tissue, so cancerous areas can be located with this test. Research studies have shown the usefulness of PET scanning in identifying both primary adrenal tumors and metastases.

- **MIBG-scintigraphy:** MIBG-scintigraphy uses a radioactive substance that is taken up by catecholamine-producing cells to find and image pheochromocytomas and paragangliomas.

- **DOTATATE scan:** This scan uses a radioactive hormone that binds to pheochromocytomas and paragangliomas (as well as other sites in the body) to visualize tumors.

How are pheochromocytomas and paragangliomas staged?

Staging refers to a determination of how far a tumor has grown or progressed. While there is no unified staging system for this category of tumors, they are usually referred to as:

- **Localized benign pheochromocytoma**

  Most pheochromocytomas are of this category, meaning that they are confined to their area of origin and have not spread or metastasized locally or to distant areas.

- **Regional pheochromocytoma**

  This category refers to a tumor that has spread locally to adjacent organs, tissues or lymph nodes.

- **Metastatic pheochromocytoma**

  Metastatic pheochromocytoma are those that have spread to distant organs, most commonly the liver, lungs or bones.

Treatment of Pheochromocytoma and Paraganglioma

What are the treatment options for these tumors?

The primary treatment option for benign pheochromocytomas and paragangliomas is surgical removal, which usually leads to a cure. This approach is also taken for regional pheochromocytomas.

Irritation of the tumor can lead to release of catecholamines and **blood pressure crises** (very high blood pressure values) so people need to be treated before surgery with medications to block the effect of catecholamines. Classes of medications used are alpha-blockers and beta-blockers.

Paragangliomas of the neck are often very close to large nerves and vessels; therefore, surgery is often not the best choice. As these tumors are rarely cancerous and grow very slowly, they can often be simply observed and followed.

Another option is radiation therapy, which can help to preserve the function of nearby structures such as nerves or blood vessels. Any surgery of paraganglioma needs to be done by a very experienced surgeon and only after a multidisciplinary tumor board agrees that surgery is the best option.

Metastasized pheochromocytomas and paragangliomas are initially treated with hormone therapy (see below).

How do I decide on treatment?

Treatment of pheochromocytomas and paragangliomas involves the expertise of several medical specialties. Therefore, you are best served at an institution specializing in the multidisciplinary treatment of these tumors. These institutions have a specialized Endocrine Tumor Board that gathers specialists

to discuss every patient. Participating specialists include endocrinologists, oncologists, endocrine surgeons, nuclear medicine doctors, radiologists and pathologists, as well as a healthcare team of nurses and study coordinators.

A diagnosis of a metastasized pheochromocytoma or paraganglioma can be especially overwhelming. In those cases it is very helpful to ask family members or friends to join you for doctor visits to discuss the disease and the treatment options. It is also very helpful to bring a list of questions and concerns to discuss during your visit.

How are symptoms treated?

Doctors treat symptoms of pheochromocytomas and paragangliomas before surgery. The standard treatment is alpha-blocker therapy (such as phenoxybenzamine or doxazosin) which is usually able to control symptoms. Very high doses are used and often increased up to a point where a patient develops low blood pressure and edema (swelling).

This strategy has been shown to lower the risk of both anesthesia and surgery, either of which can lead to excessive catecholamine release. The release of too much catecholamine can lead to high blood pressure that may threaten other organ functions (such as kidney failure or retinal bleeding) or cause stroke. Only after starting treatment with alpha-blockers will additional therapy with beta-blockers be started.

Surgery

The primary treatment for pheochromocytomas and paragangliomas is surgical removal (or resection). As detailed above, surgery is not performed until the person has had treatment with an alpha blocker and possible beta blocker. It is very important to work with your doctors on finding the right levels of blood pressure medications before surgery.

How might my tumor be removed?

The surgical procedure for removing one or both adrenal glands is called an **adrenalectomy**. This procedure is used to remove pheochromocytomas and can be done different ways. Each method results in the complete removal of the adrenal gland and the entire tumor. In about 5 out of 100 (5%) of cases, a surgeon starts with a smaller, laparoscopic approach, later converting to an open approach if it becomes clear that it is necessary to safely remove the tumor.

- **Laparoscopic adrenalectomy**

  This surgery is done using instruments that are inserted through tiny "keyhole" incisions. The surgical approach may be through your flank (your side between the ribs and hip) or back.

  The surgeon starts by making three to four small incisions. The surgeon uses a camera to see the operative field. Any tumor suspicious of or known to be cancerous will not be removed with this procedure.

- **Open adrenalectomy**

  There are three different approaches the surgeon may choose when performing an open adrenalectomy: **anterior, posterior, or retroperitoneal/flank**.

  1. An **anterior** approach uses an incision on the front abdominal wall and provides the surgeon with the most complete view of the anatomy; however, recovery can take longer.

  2. A **posterior** approach uses an incision in the back just beneath the rib cage. This approach has more limited access to other organs, but is less invasive and recovery is usually quicker.

3. A **retroperitoneal or flank** approach uses an incision on the person's side. It is less invasive than the anterior approach; however, if both glands need to be removed, the person needs to be repositioned in the operating room to complete the other side.

The surgical approach for paragangliomas is completely dependent on its location. A laparoscopic approach can often be used to remove these tumors.

How will my surgeon determine which approach to use?

Your surgeon will consider a number of factors before deciding on an approach:

- **Type of tumor**:

  Pheochromocytomas are typically removed along with the involved adrenal gland. However, in people with a high risk for development of a pheochromocytoma in the other adrenal gland (such as those with von Hippel-Lindau disease) adrenal preserving surgery may be preferable.

  Paragangliomas can be located in multiple areas of the body and the approach will depend on its location.

- **Location of the tumor:**

  Paragangliomas of the head and neck area require a very different approach than abdominal pheochromocytoma or paraganglioma. For these paragangliomas, radiation therapy may be the better choice.

- **Size of the tumor:**

  Large masses are more difficult to remove laparoscopically.

- **Surgeon experience**:

  A surgeon's experience with the laparoscopic technique is an important factor in whether this approach is considered.

- **Previous abdominal surgery:**

  People who have had previous abdominal surgery will have scar tissue. This can make tumor removal difficult, but does not rule out the laparoscopic approach to surgery.

- **Presence of metastatic disease:**

  Depending on their location, tumors that have spread to areas beyond the primary tumor site may alter the surgical approach. In many cases, this may even rule out surgical removal.

What can I expect after surgery?

Your recovery after surgery will depend on the type of surgery you had and your activity level before surgery. You can expect about 2 to 4 weeks of recovery after a laparoscopic approach and about 3 to 6 weeks with an open approach.

The final pathology results will be available for review by you and your care team approximately 1 week after surgery. You will have no dietary restrictions; however, your appetite may take a little while to recover. Additionally, you will want to avoid heavy lifting for about 4 to 6 weeks after surgery. You will follow up with your surgeon a few weeks after surgery.

Cytotoxic Chemotherapy

What is chemotherapy?

Chemotherapy is the treatment of cancer with drugs that can destroy cancer cells. These drugs often are called anticancer drugs.

How does chemotherapy work?

Normal cells grow and die in an orderly way. When cancer occurs, the abnormal tumor cells keep dividing and forming more cells without control. Anticancer

drugs destroy cancer cells by stopping them from growing or multiplying. Healthy cells can also be harmed, especially those that divide quickly. Harm to healthy cells is what causes side effects. However, healthy cells usually repair themselves after chemotherapy.

Other types of drugs may be used to treat your cancer. These may include certain drugs that can block or increase the effect of your body's response to the cancer or affect hormone production by the tumor.

When is chemotherapy given to treat pheochromocytomas?

Chemotherapy is the treatment of choice for pheochromocytoma and paraganglioma that cannot be cured by surgery alone, usually in cases of metastasis (cancer that has spread to other organs). Chemotherapy drugs can have an effect by stopping the growth of cancer cells or their ability to multiply.

The goals of chemotherapy treatment are to:

- Control the cancer
- Keep it from spreading by slowing its growth
- Improve or reduce symptoms

The most common chemotherapy used to treat pheochromocytoma and paraganglioma is the CVD protocol, using cyclophosphamide, vincristine and dacarbazine. These medications are given on day one and day two of repeated 21-day cycles. These cycles are repeated multiple times. Another chemotherapy often used is the combination of temozolomide and capecitabine.

Targeted therapy

There are several drugs that are used to specifically target pheochromocytomas. One such drug is octreotide. Octreotide mimics the action of a human hormone called somatostatin, known to slow the growth of pheochromocytomas. Like

a key in a lock, somatostatin binds to a specific receptor on the surface of pheochromocytoma cells, blocking tumor growth. While the drug will not cure pheochromocytoma, it can slow disease progression and also provide some symptom relief. Octreotide is given as weekly or monthly injections and side effects are usually mild.

Several other substances are currently being tested in clinical trials. Most of these are classified as either receptor-antagonists or kinase-inhibitors. They block the action of several molecules in the cell that drives tumor growth.

Use of these drugs is new and very limited, but doctors are gaining more experience with them through clinical studies.

Radioligand therapy

This therapy is offered at specialized nuclear medicine treatment centers. It uses substances like those described in the imaging section (see pages 14–15).

When used for imaging, substances called **radioligands** are used to provide the least amount of radioactivity necessary to visualize a tumor while minimizing the risk of radiation to healthy tissues.

Higher amounts of radioactivity and sometimes different kinds of radiation are used when radioligands are used for treatment. Just as is the case with imaging, radioligands will be taken up by the pheochromocytoma cell, at which point the radiation will kill the tumor cells. This procedure has also been shown to significantly slow tumor growth.

Currently, a number of new radioligand substances are under development.

Clinical trials

Your doctor may suggest that you consider participating in a clinical trial (a research study or protocol) for the treatment of pheochromocytoma. Clinical

trials are one very important reason that the University of Michigan Rogel Cancer Center is able to offer our patients access to the latest cancer treatment options.

Clinical trials are used to test new treatments. The goal is to find ways to improve the effectiveness of therapy or decrease side effects. While a trial or study is active (or in-progress), it is not yet known whether it offers any potential improvement. The trial must be closed and the data analyzed before the treatment being studied is made widely available to people.

There may be some risks associated with a clinical trial. Your doctor will discuss both the potential risks and benefits in detail with you and obtain your written permission before starting you on a research protocol.

Oversight committees at Michigan Medicine conduct an extensive review of all clinical trials. These committees include an **"Institutional Review Board"** or **IRB** composed of cancer doctors, doctors in other specialties, and lay people. The IRB reviews all protocols before they are available to patients and again at different times during the research to be sure that the protocol remains appropriate and safe for patients.

All patients on a protocol receive the best care possible, and their reactions to the treatment are watched very closely. If the treatment does not seem to be helping, a doctor can take a patient out of a study. Also, the patient may choose to leave the study at any time. If a patient leaves a study for any reason, they receive standard care and treatment.

There are three phases of clinical trials in which a treatment is studied before it is eligible for approval by the Food & Drug Administration (FDA). These are:

Phase I:

The objectives of these trials are to find the best way to give a new treatment and to determine how much of it can be given safely. Phase 1 begins after the treatment has been well tested in animal and laboratory studies, but before the side effects in people are completely known. The main purpose of a Phase 1 study is to test the safety of the drug, although doctors are always hoping to help people in the process.

Phase II:

These studies are designed to see if the drug or treatment works. The cancer team closely evaluates the effect of the new treatment on the cancer itself.

Phase III:

These studies compare the new drug or treatment to the most widely accepted or standard treatment currently used. This is done with large numbers of people placed into one of two groups:

- One group receives the standard treatment.
- The other group receives the new treatment being studied.

Clinical trials are voluntary. Your pheochromocytoma or paraganglioma cancer will be treated whether you decide to join a clinical trial or not.

What is the prognosis for pheochromocytoma?

The prognosis for pheochromocytoma is dependent on the stage of the tumor and on its functionality — meaning whether or not it secretes catecholamines.

Catecholamine–producing tumors can lead to crisis situations when very high blood pressure damages organs such as the heart, brain or eye. Blood pressure crises can also lead to heart attacks or strokes.

Therefore, the right medical treatment of blood pressure in pheochromocytoma patients is very important. Usually alpha-blockers are used as a first-line treatment to dampen the effect of catecholamines. When a pheochromocytoma is successfully and entirely removed, these symptoms subside.

The prognosis for people with tumors which can be completely removed by surgery is excellent. Moreover, recent progress in screening family members of people with hereditary pheochromocytoma early in life has reduced their risk of organ damage and death caused by secretion of catecholamines.

For people with regional or metastatic pheochromocytoma, the greatest threat is the involvement of other organs by either local tumor growth or distant metastases. It is difficult to give an individual prognosis for these people because the individual growth of pheochromocytomas varies greatly from person to person. These people appear to fall into one of two different groups: those with fast growing tumors and those with slow growing tumors.

Overall, the five-year survival rate for people with malignant pheochromocytoma is in the range of 20 out of 100 (20%) to 60 out of 100 (60%). This wide range is due to the differences in tumor behavior discussed earlier, as well as the fact that pheochromocytoma is a rare disease, so only a very limited number of people have been studied.

Following treatment, your cancer doctor will work closely with your primary care doctor to address any late effects (issues that arise after cancer and cancer treatment) you may experience.

Overcoming Barriers

If you have cancer, you may notice every ache, pain, or sign of illness. Even little aches may make you worry. The information in this section is designed to help you become an informed partner in your care. It is only a guide, self-help can never take the place of professional health care.

Ask your medical team any questions you may have and do not hesitate to tell them about any side effects you may be experiencing. They want and need to know.

Not all people will experience the symptoms or side effects listed in this section. We include them to help you understand what may be happening to you. Your multidisciplinary care team understands that these are obstacles to health and quality of life, and we will work with you to reduce or eliminate these problems.

Managing Pain

Why does pain occur?

People who are diagnosed with pheochromocytoma can have pain specifically when the cancer has spread to other organs. Pain is described differently by each person, but many describe it as a feeling of cramping or aching that can radiate (spread) to one's flank or shoulders. There are many causes of pain including the tumor itself, which may press on other organs, nerves and vessels.

What can be done to treat my pain?

Pain can be treated, but there are often barriers that hinder effective treatment. These barriers include a lack of understanding of how to take the pain medications, fear of addiction and a concern that taking medicine at the time of

initial pain may make pain uncontrollable later. These are all issues that should be addressed with your medical team. Do not let these barriers prevent you from keeping any pain you may have under control.

Good pain control can lead to increased physical activity and well-being in people with pheochromocytoma. People who have chronic pain may need to take medications regularly to obtain the best pain control. Understanding how to take these medications will help you get better control of your pain.

There are many different medications used to treat pain. Narcotics (opioids) are the most common. Other types of medications used to treat pain include anti-depressants, anti-convulsants (anti-seizure medications), anti-inflammatory and steroid medications.

Narcotic medications come in several forms: tablets, liquids, skin patches and intravenous pumps. These medicines are available in either immediate release or sustained release (also called long–acting) preparations. Long-acting and immediate release pain medications may be used together.

Sustained release or long acting pain medications

Long-acting (sustained release) pain medications work best when taken on a regular schedule that does not change (usually morning and evening), whether or not you have pain.

Examples of these types of medications include:

- Fentanyl (Duragesic® patch)
- Morphine (Oramorph®, MS Contin®)
- Oxycodone (Oxycontin®)

Immediate release medications “Breakthrough pain medications”

Pain experienced while you are taking a regularly-scheduled long-acting pain medication is called "breakthrough pain". Breakthrough pain may require extra medication to control and to prevent it from becoming severe.

Because this pain can vary from day to day, breakthrough pain medications are usually taken on an "as needed" basis. These immediate release medications, which usually work within 15 to 20 minutes, can be taken at any time, even if it is the same time as the sustained release or long-acting pain medications.

Examples of breakthrough pain medications include:

- Oxycodone
- Hydrocodone (Vicodin®)
- Hydromorphone (Dilaudid®)
- Morphine immediate release (MSIR)
- Morphine oral solution (Roxanol®)
- Fentanyl lozenge (Actiq®)

Suggestions for people on sustained release/long-acting pain medications AND immediate release pain medications:

- Continue the sustained release medication on a regular basis, whether or not you are having pain at that time. **Do not** change this schedule without talking to your doctor.
- Use your "breakthrough" pain medication as needed. Do not wait until pain becomes severe or it will become difficult to get good control.

- Keep a record of the breakthrough medications taken over a 24 hour period. This information is helpful when you talk to your doctor about your pain control.

> **Remember:** If breakthrough pain medication is needed 4 – 6 times a day on a regular basis **OR** if pain keeps you up consistently at night, notify your doctor. They may consider increasing your sustained release pain medication.

What are other ways to reduce pain?

In addition to medications, you can use a number of other treatment strategies to relieve pain. On their own, these tools might not be enough to eliminate moderate to severe pain, but they are often helpful when used in combination with medication.

Some of these strategies commonly referred to as "complementary therapies" include:

- Relaxation/guided imagery
- Hypnosis
- Biofeedback
- Creative therapies such as music and art
- Prayer or meditation
- Massage
- Acupressure and acupuncture
- Application of heat or cold
- Therapeutic exercise

Information about the complementary therapy programs offered at the Rogel Cancer Center can be obtained at https://www.rogelcancercenter.org/support or by calling (877) 907-0859.

> **Note:** Many pain medications cause constipation. If you are taking pain medications on a regular basis, you will need to review the section on "Preventing Constipation".

Maintaining Weight and Appetite

Why does weight loss and loss of appetite happen?

Weight loss can be a problem for people with malignant pheochromocytoma. You may see your appetite decrease or feel bloated after eating. It may be hard to eat normally because foods taste different to you. You may have times when you feel nauseated, or have constipation or diarrhea.

Cancer can also cause changes in your body that affect your metabolism and contribute to appetite and weight loss.

What can be done?

The overall goal during treatment is to keep your weight stable. Your care team will monitor your weight throughout your treatment.

Talk to your medical team about your symptoms. There are medications available to reduce or treat the pain, nausea, constipation or digestion problems you may be experiencing. Your doctor can order these for you.

Nutrition specialists are also available at the Rogel Cancer Center to offer suggestions and guidance, and to prepare a dietary plan during your treatment.

The Nutrition Clinic is open Monday through Friday from 8:00am to 4:30pm. Appointments can be made in advance at your clinic checkout area or you can call (734) 647-8902 or (877) 907-0859.

Listed below are some steps you can take to improve your diet and prevent weight loss:

- Eat five to six small meals or snacks throughout the day.
- Choose foods that are high in protein and calories.
- Try new foods regularly as taste can change from day to day.
- Limit fluids at meals and drink liquids in-between to avoid fullness at meals.
- Increase protein and calories by using supplements such as Carnation Instant Breakfast®. There are several flavors from which to choose and you can add ice cream, whole milk, yogurt and fruit to increase calories.
- Take anti-nausea medications as prescribed by your doctor during your chemotherapy treatments.
- Appetite stimulating medications such as megestrol acetate (Megace®) or dronabinol (Marinol®) may be recommended by your doctor.

If you need additional nutrition information you may contact the Rogel Cancer Education Program:

- Telephone: (734) 647-8626
- E-mail: CCC-PERC@med.umich.edu

You may also visit the Rogel Cancer Center Nutrition Services website:

- https://www.rogelcancercenter.org/support/symptoms-and-side-effects/cancer-nutrition-services

> **Most important to remember:**
> Weight loss should be addressed. We will work with you to help prevent and treat this problem.

Preventing Constipation

Why does constipation happen?

Constipation is common during cancer treatment. It is a decrease in the number of bowel movements combined with hard stool, excessive straining, bloating, increased gas or abdominal cramping.

People with cancer are at risk for constipation because of any of the following:

- Pain medications.
- Chemotherapy and anti-nausea medications.
- Decrease in physical activity.
- Change in eating and drinking habits.
- Dehydration.
- Lack of fiber in your diet.
- Changing hormone levels in your body.

What can be done?

There are a number of strategies to help prevent constipation:

- Increase fiber in your diet with high fiber foods such as fresh, raw fruits and vegetables, whole grains, prunes, nuts and dates.
- Increase fluids in your diet (drink at least 2 quarts of non-caffeinated fluid daily).
- Avoid cheese products.
- Get regular exercise every day, keep up your activity as much as possible.
- Go to the bathroom whenever you have an urge to go.

For people taking narcotic pain medications, we recommend a combination of stool softener and laxative on a regular basis. Here are some suggestions:

- **To keep regular daily bowel movements:** take 2 – 6 Senokot-S® laxative (docusate sodium) tablets daily in divided doses. This dosage can be decreased or increased according to results and tolerance. Generic versions of Senokot-S® can be substituted. Ask your pharmacist for information about these often less expensive generic versions.
- If you haven't had a bowel movement in **24 hours (1 day)**: take 2 tablespoons of Milk of Magnesia® (MOM) at bedtime with a full glass of water.
- If you haven't had a bowel movement in **48 hours (2 days)**: take 3 Senokot-S® tablets twice a day (total of 6 tablets per day) plus 2 tablespoons of MOM at bedtime.
- If you haven't had a bowel movement in **72 hours (3 days)**, add **one** of the following:

- Take 8 oz. (1/2 bottle) of Magnesium Citrate and repeat in 6 hours.
- If no bowel movement occurs by that time, take 2–3 Dulcolax® tablets.

Maintaining Emotional Well-being

How do I cope with my feelings?

If you have been diagnosed with cancer, it is normal for you and your family to experience a wide range of emotions.

There are many **misconceptions** about cancer and how people cope with it, including:

- All people with cancer are depressed.
- Depression in people with cancer is normal.
- Treatment does not help the depression.
- Everyone with cancer faces suffering and a painful death.

Do not accept these mistaken beliefs. Any individual or family member facing a diagnosis of cancer may face one or more significant life issues, including:

- Fear of death.
- Interruption of life plans.
- Changes in body image and self-esteem.
- Changes in social role and lifestyle.
- Money and legal concerns.

Each person diagnosed with cancer reacts to these issues differently. Many people experience feelings of anxiety, depression, sadness, stress, and have difficulty sleeping or eating. It is important to know when and where to seek help for these concerns.

For many people, these feelings and symptoms lessen as they adjust to the diagnosis. However, people who continue to struggle over a significant period of time and who lose interest in activities that are usually pleasurable may be depressed.

Even mild symptoms of depression can be distressing and should be addressed. People with mild to moderate symptoms of depression, and even people without obvious symptoms of depression, may benefit from counseling.

When symptoms are intense and long-lasting, or when they keep coming back, more intensive treatment is needed. These are often signs of what is called "major depression."

Major depression is not simply sadness or a blue mood. Major depression has been found to affect about 25 out of 100 (25%) of people with cancer and has common symptoms that can be diagnosed and treated. The symptoms of major depression include:

- Having a depressed mood for most of the day and on most days.
- Loss of pleasure and interest in activities that you usually enjoy.
- Changes in eating and sleeping habits.
- Nervousness or sluggishness.
- Tiredness.
- Feelings of worthlessness or guilt.
- Poor concentration.
- Thoughts of suicide or thinking constantly about death.

One or more of these symptoms may be noticed at the time a person is diagnosed with cancer, indicating that they may have been struggling with depression even before their cancer diagnosis. If you are experiencing these symptoms at any time, or if you have a history of depression, talk to your healthcare team.

Depression can affect caregivers too. Just as people with cancer need to be evaluated for depression throughout their treatment, so too do caregivers. Caregivers have been found to experience a good deal more anxiety and depression than people who are not caring for people with cancer.

If the person with cancer and their family members are able to express feelings openly and solve problems effectively, everyone will have less depression. Good communication within the family reduces anxiety.

Where can I seek help and support?

It is important to remember that depression can and should be treated. The Rogel Cancer Center's Multidisciplinary Adrenal Cancer Team believes that helping patients cope with their cancer diagnosis is an essential part of providing care.

A social worker is an essential member of the team who provides evaluation, counseling, and referral to additional resources such as support groups, the PsychOncology Clinic and community resources. Remember, our team is here to help address any emotional needs you or your family may have. Do not hesitate to contact us at (877) 907-0859.

Seeking peer support from others with cancer and cancer survivors can also be beneficial in helping you deal with feelings of isolation and loneliness. But people with rare cancers like pheochromocytoma may find it difficult to locate others with rare cancers.

Fortunately there are resources available on the internet, from national organizations, as well as the American Cancer Society. You may try an online support group or a telephone group hosted by one of these organizations.

You can also participate in lectures and discussions and receive information about cancer-related issues on-line or over the telephone. Many of these resources are listed on the following pages.

Connect with others during your cancer treatment; research has found this is helpful in reducing anxiety and depression as well as improving knowledge and overall quality of life.

Resources

It is important to us that every patient receives the right support at the right time. However, resources specific to pheochromocytoma are uncommon in the general community. Pheochromocytomas and paragangliomas affect 2,000 Americans throughout the entire country annually.

Therefore, you will find pheochromocytoma and paraganglioma resources most commonly on the internet and in large academic healthcare centers that have specialized endocrine cancer clinics.

University of Michigan Rogel Cancer Center web resources

- **The Rogel Cancer Center Multidisciplinary Endocrine Oncology Clinic at the University of Michigan**
  This site has information about the Multidisciplinary Adrenal Cancer Clinic at the University of Michigan as well as links to additional resources that may be of interest to people with adrenal cancer and their caregivers.
  https://www.rogelcancercenter.org/endocrine-cancer

- **The Rogel Cancer Center Complementary Therapies Program**
  Patients and their families are encouraged to take advantage of complementary therapy services at the Rogel Cancer Center including art therapy, music therapy, guided imagery, spiritual care, and families facing cancer.
  https://www.rogelcancercenter.org/support/managing-emotions/complementary-therapies

- **The Rogel Cancer Center Patient Education Program**
  Patients and their families can access information guides to learn about cancer types, treatment options, and coping with cancer. These guides provide links and references to reliable and current information. A customized search can also be requested.

  https://www.rogelcancercenter.org/support/learning-about-cancer

Web resources

- **Pheochromocytoma and Paraganglioma Treatment (PDQ®) – Patient Version:** An Overview of pheochromocytoma and paraganglioma from the National Cancer Institute.

  https://www.cancer.gov/types/pheochromocytoma/patient/pheochromocytoma-treatment-pdq

- **Pheochromocytomas: Adrenal Gland Tumors:** A section of the **EndocrineWeb.com** site that reviews the anatomy of the adrenal glands and links to information on pheochromocytomas.

  https://www.endocrineweb.com/conditions/pheochromocytoma/pheochromocytoma-tumor-central-adrenal

- **Pheochromocytoma (The Basics) (UpToDate):** Overview of pheochromocytoma. You can also choose from a variety of topics on Pheochromocytoma. UpToDate is an online medical information resource where people can learn about medical conditions.

  https://www.uptodate.com/contents/pheochromocytoma-the-basics?search=pheochromocytoma%20patient%20information&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

- **American Cancer Society video. ACS Research Grantee — Dr. Hammer's Story:** Dr. Gary Hammer, the director of the Rogel Cancer Center Endocrine Oncology Program at the University of Michigan, shares how his lab was first funded by the ACS and the importance of investing in young researchers.

  https://www.youtube.com/watch?v=YdK4nP9py8A

- **Von Hippel-Lindau disease — VHL Alliance:**
  The VHL Alliance (VHLA) is dedicated to research, education, and support to improve awareness, diagnosis, treatment, and quality of life for those affected by VHL.

  https://www.vhl.org/patients/

- **Hereditary Pheochromocytoma & Paraganglioma — the PheoParaTroopers:** Formed to empower and support pheochromocytoma and paraganglioma patients globally through knowledge, education, advocacy, and camaraderie while sponsoring key initiatives in data collection, treatment, collaboration, and patient wellness.

  https://pheopara.org/

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