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

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About the Adrenal Glands

What Are Adrenal Glands?

Everyone has 2 adrenal glands. They are small, about the size of a walnut, and shaped like a pyramid. They sit in position on top of each kidney. They are sometimes called ‘supra-renal glands’ which is Latin for ‘above the kidney’.

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 the way you think and feel. The adrenal glands are organs that make and secrete hormones. The hormones produced by these small powerhouses affect the way every tissue, organ and gland in your body works.

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

The adrenal glands play an important role in how your body responds to stress. The adrenal medulla makes a chemical called epinephrine that is also called adrenaline. It also makes norepinephrine (noradrenaline), which is very similar to epinephrine. Epinephrine and norepinephrine are responsible for the regulation of blood pressure, blood flow and your body’s acute response to stress. Both of these hormones can be secreted by pheochromocytomas and paragangliomas.

The adrenal cortex makes a variety of hormones including:

- Mineralcorticoids (such as aldosterone) that help regulate blood pressure and the fluid and salt balance in the body,

- Glucocorticoids (such as cortisol) are released by the adrenal cortex to help the body to cope with long term stress. Glucocorticoids help regulate the amount of sugar and fat stores in the body and act as anti-inflammatory agents, and

- Hormones related to sex hormones. While proper sexual development and function is regulated by ‘real’ sex hormones secreted by the gonads (testis & ovaries), there is no definite function assigned to sex hormones secreted by the adrenal cortex.

    However, the adrenal cortex is not involved in the formation of pheochromocytoma.
**What are paraganglia?**

Paraganglia are specialized organs at multiple locations in the human body. They are closely associated with the autonomous nervous system, that regulates all non-voluntary body functions (e.g. digestion, urination, blood pressure regulation, sweating etc.). Paraganglia can be found in the head and neck region, the thorax and the abdomen. The adrenal medulla is a specialized paraganglion.

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

Normal cells grow, divide, and die in a controlled way that is regulated in the body. Cancer is a disease that causes cells to divide and grow in an abnormal, out of control way where the balance of cell growth and death is disturbed. Medical research has led to a better understanding of these abnormalities and continues to be a focus in the understanding of how to treat cancer.

Cells that continue to grow and divide without control become a mass or tumor. This mass will eventually affect how an organ works. The original site of the abnormal cell growth is called the cancer’s “primary site”. In pheochromocytoma, the primary site is the adrenal gland, specifically the adrenal medulla. Paragangliomas arise in different parts of the body from cells associated with the autonomous nervous system.

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 benign adrenal tumors never spread or invade other organs. Pheochroocytomas and paragangliomas can be benign (90%) or malignant (10%)
**Tumors of the Adrenal Medulla and Paraganglia**

As described above the adrenal medulla secretes epinephrine (adrenaline) and norepinephrine (noradrenaline). The two main types of primary tumors of the adrenal medulla are *pheochromocytomas*, occurring in children and adults, and *neuroblastomas*, which are almost exclusively diagnosed in children during the very first years of life. This handbook will not focus on neuroblastomas. The adrenal medulla is a specialized part of the autonomic nervous system (ANS), specifically the sympathetic nervous system. There are smaller conglomerates of cells, which are also part of the ANS, scattered throughout the human body. These small organs are called *paraganglia*. They are mainly located near the vertebral column, but also in areas of the head and neck and close to internal organs, such as the bladder, and large blood vessels, such as the aorta. They are very much related to the adrenal medulla. Most of them produce norepinephrine, a close relative of epinephrine. Tumors that arise from these cells are called *paragangioma*, or sometimes *extra-adrenal pheochromocytoma*. The role of the paraganglia, including the adrenal medulla is to coordinate, what is known as the ‘flight-and-fight’ response. Release of epinephrine and norepinephrine (together called catecholamines) will increase the body’s and mind’s ability to cope with short term stress, by e.g. increasing heart rate, increasing blood flow to the muscles etc..

Most pheochromocytomas and paragangliomas are confined to the organ, where they developed, but occasionally they spread to other organs and are then considered *malignant pheochromocytoma* or *malignant paragangioma*. It can be difficult to determine (even if the tumor is removed and analysed by a pathologist), whether a tumors has the ability to spread or not. Therefore thorough follow-up is needed.

**How common are pheochromocytomas and paragangliomas and who is at risk?**

Pheochromocytomas and paragangliomas are very rare – they occur in roughly 3-6 patients per million per year, roughly a couple of thousand patients in the US per year.
To date there are no known risk factors that may cause pheochromocytomas or paragangliomas.

**Are pheochromocytomas hereditary?**

When pheochromocytomas occur just by chance, they are called *sporadic pheochromocytomas*. There are also several hereditary syndromes that predispose to the development of pheochromocytomas and paragangliomas. Most of these hereditary tumors will affect patients younger than 50 years of age. It is estimated that roughly half of all pheochromocytomas and paragangliomas arise in patients with a hereditary predisposition. Medical and surgical managements of these tumors are just the same as for sporadic pheochromocytomas. It can be still very important to know, whether an individual patient has one of these predisposing conditions for two main reasons:

1. The same condition may predispose to the development of pheochromocytomas or paragangliomas somewhere else in the body (e.g. the other adrenal gland) or tumors of other organs. In these cases physicians will suggest an individual screening and surveillance to increase the chances to diagnose these tumors at an early treatable stage.

2. It may be important to identify other members of the patient’s family, who may be at risk to have the same hereditary genetic predisposition. These family members can then be screened early for any tumor growth (e.g. blood tests, imaging).

Patients, who may have tumors suggestive of hereditary conditions, should be referred to a Cancer Genetics Clinic and should receive Genetic Counseling. Geneticists and genetic counselors will help to identify possible causes of hereditary conditions and will also guide patients through screening and surveillance processes.
Which hereditary syndromes can cause pheochromocytomas or paragangliomas?

Every patient with a diagnosis of pheochromocytoma or paraganglioma should seek evaluation in a Cancer Genetics Clinic, even in the absence of any family history of these tumors. Please ask your treating doctor for a referral. Patients with certain hereditary syndromes have a higher chance to develop pheochromocytomas or paragangliomas or other tumors. When a patient has one of these syndromes, it does not necessarily mean that they will ever have a pheochromocytoma, but they should undergo regular screening, simply because they have a higher chance than the rest of the population.

The program of all functions of all cells in the human body is coded in the genome. The genome-code consists of several smaller units, so called genes, which chemically are made of DNA, which is localized 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 of them have a special function in preventing the occurrence of unregulated growth, from which tumors may arise. They are called tumor suppressor genes. Patients 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 (e.g. induced by background radiation, which is normal on earth). In case these mechanisms ever fail, there is usually one healthy gene left, because we have two genes, one form each parent. The exception is, when one of the genes is already not working properly (as in inherited syndromes), loss of the second one can lead to loss of the tumor-preventive function.

All of the hereditary syndromes, described below, are very rare, but in some cases there are enough very active patients and patient families, who have formed support groups. A lot of these support groups are organized on a national and global level.
Contact with a support group is very helpful to learn more about these syndromes and to share experiences. They are also very important patient advocacy groups.

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

**Multiple Endocrine Neoplasia Type 2 (MEN2)** – high calcium levels due to tumors of the parathyroid glands, pheochromocytoma, medullary thyroid cancer

**Von Hippel Lindau Disease (VHL)** – kidney cancer, blood vessel tumors of the nervous system and the retina (eye), pheochromocytomas, pancreas tumors

**Neurofibromatosis Type 1 (NF1)** – several skin tumors arising from peripheral nerves, areas of skin pigmentation (café-au-lait spots), pheochromocytoma

**Hereditary Paraganglioma Syndrome (HPGL, mutations in SDHA, SDHB, SDHC, SDHD, SDHAF2)** – paragangliomas, pheochromocytomas, possibly other tumors

**What are the symptoms of pheochromocytomas?**

Pheochromocytomas and paragangliomas are either discovered by chance, e.g. by imaging work-up for other health issues, or because they cause symptoms due to hormone secretion. Paragangliomas can also be diagnosed as a swelling of a certain body site, for example when they arise in the head or neck area, or because they may cause symptoms due to compression of a blood vessel or nerve.
Most, but not all of these tumors secrete catecholamines (epinephrine and/or norepinephrine). These can be measured in the blood or urine and facilitate the diagnosis. The classical five symptoms are:

1. Hypertension (high blood pressure)
2. Headache
3. Pallor
4. Orthostatic Hypotension (a drop in blood pressure, when e.g. getting up from a chair, causing dizziness or near fainting)
5. Sweating
6. Tachycardia, palpitation (racing heart)

Classically these symptoms occur in an 'attack-like fashion', which last a few minutes to several hours. These attacks are very often interpreted as anxiety attacks, which of course are much more common than catecholamine-secreting tumors. Not all of these symptoms are necessarily present in every patient and they can also occur in a sustained, non-attack-like fashion. For example some patients just have hypertension, which is also a very common health concern and usually treated without thorough investigation for a pheochromocytoma.
How are pheochromocytomas and paragangliomas diagnosed?

As mentioned above, some tumors may be diagnosed just by compressing on other body structures, such as blood vessels or nerves. If a patient has symptoms suggestive of a pheochromocytoma or paraganglioma blood or urine tests can help making the diagnosis. There are several specialized imaging methods only used for these tumors:

- **Blood and urine tests:** As most of these tumors secrete catecholamine, diagnostic procedures aim to measure these either in the urine or in the blood. Because the body alters the original catecholamine (epinephrine and norepinephrine) quickly, physicians will rather look for altered catecholamine degradation products, called metanephrine and normetanephrine, which can be measured in blood or 24-hour urine collections. Another product that can be measured in the urine is vanillylmandelic acid (VMA) or homovanillic acid (HVA).

- **Computed Tomography (CT):** The CT scan can show small tumors as well as important blood vessels that the tumor might be growing into or around. A CT scan can 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. You will lie still on a table while it is being done. Usually, you will need an IV placed for a dye injection just before the scan. 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 the area and can be helpful in making a decision, whether a certain tumor is a pheochromocytoma or a paragangioma or rather a different tumor.

- **Ultrasound of the abdomen or neck:** An ultrasound can identify a tumor or mass by using sound waves to make a picture of the inside of the abdomen. This is the fastest and cheapest test used; however it is the least accurate. It can be difficult to tell the
difference between an adenoma and cancer with an ultrasound. An ultrasound may be used to guide a biopsy procedure. However this should not be done with tumors which are possibly a pheochromocytoma, because this procedure can lead to a release of catecholamine causing high blood pressures.

- **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 taking up the sugar. Cancer cells take up sugar 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 adrenal tumors and identifying metastasis.

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

- **Octreotide scan:** This scan uses a different radioactive substance. In this case it is a radioactive hormone that binds (amongst other sites in the body) to pheochromocytomas and paragangliomas. Therefore it will visualize these tumors.

**How are pheochromocytomas and paragangliomas staged?**

There is no unified staging system. Tumors are usually referred to as:

* Localized benign pheochromocytoma

* Regional pheochromocytoma

* Metastatic pheochromocytoma
Localized Benign Pheochromocytoma

Most pheochromocytomas are of this category, they are confined to the area of origin and have not spread locally and do not have distant metastasis.

Regional Pheochromocytoma

This category refers to a local spread to adjacent organs, tissues or lymph nodes.

Metastatic Pheochromocytoma

Metastatic Pheochromocytoma shows spread to distant organs (e.g. liver, lung, bone)

Treatment of pheochromocytoma and paraganglioma

What are the treatment options?

The primary treatment option for benign pheochromocytomas and paragangliomas is surgical removal, which usually leads to cure of the patient. This approach is also taken for regional pheochromocytomas. Because irritation of the tumor can lead to release of catecholamines and blood pressure crisis with very high blood pressure values, patients need to be treated before surgery with medications blocking the effect of catecholamines. Classes of medications used are α-blockers and β-blockers. These medications are used in fairly high doses, usually until the patient starts to develop side-effects from these medications, such as low blood pressure and edema.

Paragangliomas of the neck are often very close to large nerves and vessels and 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 often preserves the function of close by structures, such as nerves or blood vessels. Any surgery of paraganglioma needs to be done by a very experienced surgeon and only after agreement of a multidisciplinary tumor board that supports surgery as a therapy.

Metastasized pheochromocytomas and paragangliomas are initially treated with hormone or chemotherapy, such as octreotide therapy or cytotoxic chemotherapy (see below).

**How does the patient decide on treatment?**

Treatment of pheochromocytomas and paragangliomas involves the expertise of several medical specialities. Therefore a patient will be best served at an institution specialized in the treatment of these tumors. These institutions have a specialized Endocrine Tumor Board that involves discussion of every patient amongst specialist of several medical professionals, including endocrinologists, oncologists, endocrine surgeons, nuclear medicine doctors, radiologists and pathologists as well as a health care team of nurses and study coordinators.

Especially the diagnosis of a metastasized pheochromocytoma or paraganglioma can be overwhelming. For this reason it is very helpful to involve family members or friends in the discussion about this disease and ask them to join you for doctor visits. In the discussion between you and the physician treatment options will be discussed and a decision for the treatment plan best suitable for you will be decided. It is often very helpful to make a list of your questions and concerns to discuss them at your visit.

**Treatment of Symptoms**

It is important to treat symptoms of pheochromocytomas and paragangliomas before surgery. The standard treatment is α-blocker therapy (e.g. phenoxybenzamine or doxazosin). Usually this treatment is able to control symptoms. For treatment before
surgery very high doses are used and doses are often increased until patients develop low blood pressure and edema. This strategy lowers the risk of anesthesia and surgery of these tumors. Both procedures can lead to excessive catecholamine release, leading to high blood pressure, that may threaten other organ functions (e.g. kidney failure, retinal bleeds) or cause strokes. Only after sufficient initiation of treatment with α-blockers, additional therapy with β-blockers is started.

**Surgery**

The primary treatment for pheochromocytomas and paragangliomas is surgical removal. Surgical resection is not performed until the patient has had adequate preoperative treatment with an alpha blocker and possible beta blocker as the stress of surgery or manipulation of the tumor can cause excessive catecholamine release, which put the patient at risk for heart attacks and stroke during surgery. It is very important to work with your doctors on finding the right levels of blood pressure medications before surgery.

There are a variety of approaches that a surgeon can use to remove these tumors. The type of surgical approach will be decided by your surgeon based on multiple factors:

- **Type of tumor.** Pheochromocytomas will typically be removed along with the involved adrenal gland. However in patients that have a high risk for development of a pheochromocytoma in the other adrenal gland (e.g. patients with von Hippel Lindau disease) should preferably have adrenal preserving surgery. Paragangliomas can be located in multiple areas of the body and the approach will depend on its location.

- **Location of the tumor.** Obviously paragangliomas of the head and neck area will undergo very different surgery than abdominal pheochromocytoma or paraganglioma. Indeed for paragangliomas of the head and neck area other therapies, such as 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. Patients who have had previous abdominal surgery will have scar tissue. This can make removal difficult, but does not eliminate the laparoscopic approach to surgery.

- Presence of metastatic disease. Tumor deposits in areas separate from the primary tumor may alter the surgical approach depending on the location. In many cases, it may even preclude surgical resection.

**How is my tumor 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 of these methods results in the complete removal of the adrenal gland and the entire tumor. Occasionally, a surgeon may start the adrenalectomy with a smaller, laparoscopic approach, but may have to convert to an open approach. This happens in about 5% of cases. The surgeon will do this 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 or back. Your surgeon will make 3-4 small incisions. A camera is used to assist the surgeon in visualizing 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. An anterior approach utilizes an incision on the anterior abdominal
wall and provides the surgeon with the most complete view of the anatomy; however, recovery can be longer. A posterior approach utilizes 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. A retroperitoneal or flank approach uses an incision on the patient's side. It is less invasive than the anterior approach; however, if both glands need to be removed, the patient 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 still often be used to remove these tumors.

**What can I expect after surgery?**

Your recovery after surgery will depend on the type of surgery you had and your previous activity level prior to surgery. Patients can expect about 2-4 weeks of recovery after a laparoscopic approach and about 3-6 weeks with an open approach. The final pathology results will return about a 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 heaving lifting for about 4-6 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, which can not be cured by surgery alone. This stage of pheochromocytoma and paraganglioma is usually metastatic (spread to other organs). Chemotherapy drugs can have an effect on the cancer 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 the cancer’s growth and improve or reduce the symptoms of the disease.

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 1 and 2 of repeated 21 day cycles. 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, that is known to slow the growth of pheochromocytomas. The hormone is called somatostatin and it binds to a specific receptor – like a key in a lock – on the cell surface of pheochromocytoma cells and blocks tumor growth. This drug will not cure pheochromocytoma, but it can slow down disease progression and also lead to some symptom relief. Octreotide is given as weekly to monthly injections and side-effects are usually mild.

Several other substances are in clinical trials. Most of these are of the classes of receptor-antagonists or kinase-inhibitors. They block the action of several molecules in the cell, that are driving forces for tumor growth. There is only little experience with these substances so far, but physicians are getting more and more experience with these drugs though treatment studies.

**Radioligand Therapy**

This therapy is offered at specialized nuclear medicine treatment centers. Several substances, just like the ones described in the imaging section, like octreotide or MIBG, are used in these treatment procedures. While radioactive substances, used in imaging procedures have as little radioactivity as necessary to visualize a tumor and to minimize the risk of radiation to healthy tissues, the radioactive substances used for treatment have a higher dose of radioactivity and sometimes different kind of radiation. They will be (like with imaging) specifically taken up by the pheochromocytoma cell, and then the radiation will kill the tumor cells. This procedure has also been shown to significantly slow tumor growth. New 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 Comprehensive Cancer Center is able to offer our patients access to the latest cancer treatments.

Clinical trials are used to test new treatments. The goal of these trials is to find ways to improve therapy or decrease side effects. While a trial or study is active or in-progress, we will not know whether any potential improvement has been found. The trial must be closed and the data analyzed before the treatment being studied is made widely available to patients.

There may be some risks associated with research. 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 the University of Michigan Medical Center 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, standard care and treatment will be given.

There are 3 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 1: The purpose of these trials is to find the best way to give a new treatment and to determine how much of it can be given safely. Phase I begins after the treatment has been well tested in animals and lab studies, but the side effects in patients are not 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 patients.

Phase 2: 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 3 clinical trials: These studies compare the new drug or treatment to the most accepted or standard treatment currently used. This is done with large numbers of patients who are placed into one of 2 groups. One group receives the standard treatment; the other group receives the new treatment under study.

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

What is the prognosis for pheochromocytoma?

The prognosis of pheochromocytoma is dependent on the extent of tumor and on the functionality, meaning whether it secretes catecholamines or not.

Catecholamine-producing tumors can lead to crisis situations with very high blood pressure, which can damage other organs, such as the heart, brain or eye. Blood pressure crises can lead to heart attacks or strokes. Therefore the right medical treatment of blood pressure in pheochromocytoma patients is very important. Usually α-blockers, that can dampen the effect of catecholamines are used as a first line
treatment. When a pheochromocytoma is successfully and entirely removed, these symptoms subside.

Prognosis for patients with tumors, which can be completely removed by surgery, is excellent. Moreover, recent progresses in screening family members of patients with hereditary pheochromocytoma early in life have reduced the risk of organ damage and death caused by secretion of catecholamines.

For patients with regional or metastatic pheochromocytoma a threat is the involvement of other organs by local tumor growth or distant metastasis, which can e.g. lead to the instability of areas of bone metastasis. It is difficult to give an individual prognosis for patients at these stages, because the individual growth of pheochromocytomas is very variable from patient to patient. It seems that here are two different main groups, one with fast growing tumors and another one with very slow growing tumors. The overall 5 year survival rate for patients with malignant pheochromocytoma is in the range of 20-60%. This wide range is probably caused by the mentioned differences in tumor behavior as well as the fact that pheochromocytoma is a rare disease and only a very limited number of patients have been studied.

Your cancer doctor will work closely with your primary care physician to address any late effects you may experience from the cancer itself or from the cancer treatment. Late effects are those that are seen after cancer treatment.

**Meeting Obstacles**

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, but 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. Also don't hesitate to tell them about any side effects you may have. They want and need to know.
Not all patients will experience the symptoms or side effects listed in this section. We include them to help you understand what may be happening to you. We know these are obstacles to your health and quality of life. Your multidisciplinary team will work with you in reducing or eliminating these problems.

What can be done to treat my pain?

Why does this happen?

Patients who are diagnosed with pheochromocytoma can have pain, specifically in cases, where the tumor has spread to other organs. Pain is described differently by each patient, but many describe it as a cramping, aching, and radiating (spreading) to your flank or shoulders. There are many causes of pain including the cancer itself, which may cause pressure on other organs, nerves and vessels.

What can be done?

Pain can be treated, but there are often barriers that prevent proper treatment. Some of these barriers are a lack of understanding in how to take the pain medications, fear of addiction and a concern that pain may be uncontrollable later if medicines are used at the time of initial pain. 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 patients with pheochromocytoma. Patients who have chronic pain may need to take medications regularly to obtain the best control of pain. An understanding of how to take these medications will help you get better control of your pain.
There are many different medications used to treat pain. Narcotics are the most common. Other types of medications used to treat pain include antidepressants, anticonvulsants (anti seizure medications), anti-inflammatory and steroid medications.

Narcotic medications come in several forms: tablets, liquids, skin patches and intravenously via a pump. These medicines are available as a sustained release or long acting preparation, and as an immediate release pain medication. The long acting and immediate release pain medications are often used together. 34

Sustained release or long acting pain medications

Long Acting Pain Medications (sustained release) work best when taken on a regular schedule that does not change.

These should be taken at a regular, scheduled time, usually morning and evening, whether you have pain or not. They are taken on a schedule and work best when that schedule is not changed.

Examples of these types of medications include;

• Fentanyl (Duragesic® patch )

• Morphine (Oramorph®, MSContin® )

• Oxycodone (Oxycontin®)

Immediate release medications “Breakthrough pain medications”

The immediate release medications should be taken when you are having pain while taking a long acting pain medication. This is called “breakthrough pain” as it occurs while you are taking regularly scheduled medication, but may need some extra medication for control and to prevent it from becoming severe. These medications work within 15-20 minutes and are usually taken on an ‘as needed’ basis because pain can vary from day to day. These medications 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:

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

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

- Continue the sustained release medication on a regular basis whether you are having pain or not 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.

Rule of thumb:

If breakthrough pain medication is needed 4-6 times a day regularly OR if pain keeps you up consistently at night THEN Notify your doctor who may consider increasing your sustained release pain medication.
Other Ways to Reduce Pain

In addition to medications, a number of other treatment strategies can be employed to relieve pain. Although on their own, these tools might not be enough to eliminate moderate to severe pain, 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, meditation,

• Massage

• Acupressure and acupuncture,

• Application of heat or cold, and

• Therapeutic exercise.

Information about these programs can be found at the Patient Education Resource Center on Level B1 of the Cancer Center.

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”
What can I do to maintain my weight and increase my appetite?

Why does this happen?

Weight loss can be a problem for patients 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 will contribute to weight loss. These are some common reasons that you may not feel hungry and lose weight.

What can be done?

The overall goal during treatment is to keep your weight stable. We will monitor your weight throughout your treatment.

Talk to your medical team about your symptoms

There are medications available to reduce or treat pain, nausea, constipation or digestion problems you may be experiencing. Your doctor can order these for you.

Also, nutrition specialists are available at the cancer center to offer suggestions and guidance, and will prepare a dietary plan during your treatment. The nutrition clinic is open Monday through Friday from 8am to 3pm.

Appointments can be made in advance at your clinic checkout area or you can call (734) 647-8902.
There are some steps you can take to improve your diet and prevent weight loss. These include:

• 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 to choose from 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.

There are many nutrition resources available to patients and families at the Cancer Center. The Patient Education Resource Center (PERC) has many recipe books and other information resources for patients with cancer. They also have a nutrition information guide available that lists websites, books, pamphlets and other resources for cancer patients seeking nutrition information.

The most important thing to remember is that weight loss should be addressed; and we will work with you to help prevent and treat this problem.

What can be done to prevent constipation?
**Why does this happen?**

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

Cancer patients are at risk for constipation because they are often treated with pain medications, receive chemotherapy and antinausea medications, have decreased their physical activity and have had a change in their eating and drinking habits…. all of these can cause constipation. Other causes of constipation include dehydration, a lack of fiber in your diet, and the changing hormone levels in your body.

**What can be done?**

There are a number of preventative things to do. These include:

- Increasing the fiber in your diet with foods high in fiber 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 if possible…keep up your activity as much as you are able.

- Go to the bathroom whenever you have an urge to go.

For patients taking narcotic pain medications, we recommend a combination of stool softener and laxative on a regular basis. Here are some suggestions:
• Take Senokot-S®, two to six tablets daily in divided doses to keep regular bowel movements every day. This can be decreased or increased according to results and your tolerance. Generic versions of Senokot-S® can be substituted. Ask your pharmacist for information about generic versions. They are often cheaper.

• If no bowel movement in any 24 hour period (1 day), take two tablespoons of Milk of Magnesia® (MOM) at bedtime with a full glass of water.

• If no bowel movement in any 48 hour period (2 days), take three Senokot-S® tablets twice a day (total of 6 tablets per day) plus two tablespoons of MOM at night before bedtime.

• If no bowel movement in any 72 hour period (3 days), add one of the following:
  1. Magnesium Citrate 8 oz (1/2 bottle) now then repeat in 6 hours. 2. If no bowel movement, then 2-3 Dulcolax® tablets.

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. Important issues in the life of any person with cancer may include the following:

• Fear of death.

• Interruption of life plans.

• Changes in body image and self-esteem.

• Changes in social role and lifestyle.

• Money and legal concerns.
Everyone who is diagnosed with cancer will react to these issues in different ways. Many patients 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 feelings. These symptoms and fears usually lessen as a person adjusts to the diagnosis.

There are many misconceptions about cancer and how people cope with it, such as the following:

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

**Seeking Support**

Being diagnosed with cancer is a scary and isolating experience for most people. It is even more difficult when are diagnosed with a rare cancer. This makes it difficult to speak to others who know what you are going through. It makes the isolation even more profound, and you may feel even more alone.

For this reason, you may want to reach out in different ways than patients do with common cancers. You may find it difficult to locate resources in your community, but there are many resources available to patients through the internet, national
organizations, and 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 online or via the telephone and can receive information about cancer related issues.

These resources are listed in the last section of this booklet. We suggest you connect with others during your cancer treatment. Research has found this to be helpful in reducing anxiety and depression, improving your knowledge, and your overall quality of life.

A person who cannot adjust to the diagnosis after a period of time, and who loses interest in usual activities, may be depressed. Mild symptoms of depression can be distressing and may be helped with counseling. Even patients without obvious symptoms of depression may benefit from counseling; however, when symptoms are intense and long-lasting, or when they keep coming back, more intensive treatment is important. 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% of cancer patients and has common symptoms that can be diagnosed and treated. Symptoms of depression that are noticed when a patient is diagnosed with cancer may be a sign that the patient had a depression problem before the diagnosis of cancer. Anyone experiencing these symptoms, or who has a history of depression should talk to their healthcare team.

It is important to remember that depression can, and should be treated. The symptoms of major depression include the following:

- 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.

Depression can affect caregivers too

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

If the family of a patient diagnosed with cancer is able to express feelings openly and solve problems effectively, both the patient and family members will have less depression. Good communication within the family reduces anxiety.

**Seeking help**

The 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 (734) 232-6366.

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 2000 Americans annually, but they are spread throughout the country.
Therefore, you will find pheochromocytoma resources most commonly on the internet and in large academic healthcare centers that have specialized Endocrine Cancer Clinics.

Web Resources

• University of Michigan Endocrine Oncology Program
  www.umadrenalcancer.org

• All About Pheochromocytoma
  → Go to the American Cancer Society site at: www.cancer.org
  → Click on: "Choose a cancer topic" under “Learn about Cancer”
  → Select "Pheochromocytoma" from the list and click "Go”
  → Click on: "All About Adrenal Cortical Cancer"

• Pheochromocytoma Disease Menu on cancer.gov
  www.cancer.gov/cancerinformation/cancertype/pheochromocytoma/

• University of Michigan Comprehensive Cancer Center Multidisciplinary Adrenal Cancer Clinical
  www.cancer.med.umich.edu/cancertreat/endocrine/the_clinic.shtml

  This site has information about the Multidisciplinary Adrenal Cancer Clinic at the University of Michigan. The “Resources” page has links to additional resources that may be of interest to people with adrenal cancer.

• Your Adrenal Glands www.endocrineweb.com/adrenal.html

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A Section of EndocrineWeb.com site, this page reviews the anatomy of the adrenal glands and links to information on pheochromocytomas and adrenal cancer.

- Von Hippel Lindau disease – the VHL family alliance: http://www.vhl.org/

Pheochromocytomas Fast Facts

• Pheochromocytomas are tumors that arise from the adrenal medulla or inner layer of the adrenal gland

• They are rare and occur in about 5 persons in every million.

• Pheochromocytomas have been clearly associated with several hereditary disorders including Type MEN type 2 (multiple endocrine neoplasia), von Hippel Lindau disease, Neurofibromatosis Type 1 and the Familial Paraganglioma Syndrome. Therefore, physicians regularly recommend genetic testing for everybody with a pheochromocytoma.

• SYMPTOMS: Cardinal symptoms are paleness, high blood pressure, fast heart beat, headache and high blood sugar. Symptoms can be episodic, of sudden onset or constant and persisting.

• DIAGNOSIS: Diagnosis is made by measuring hormones that are secreted by the pheochromocytoma in the blood or urine. Once doctors know a pheochromocytoma is present they proceed with further radiological and nuclear medicine imaging to find out more about the localization and extent of the tumor.

• TREATMENT: Surgery is the treatment of choice. Before surgery the blood pressure of pheochromocytoma patients needs to be well controlled with special medications. There are also treatment options for advanced pheochromocytoma, such as chemotherapy. They are mainly available through clinical trials.

• PROGNOSIS: Pheochromocytomas have a 98% cure rate with surgery alone. Patients with a history of a genetic mutation or whose pheochromocytoma was outside of the adrenal gland have a higher risk of recurrence (the cancer returning).
• FOLLOW-UP: Patients with pheochromocytomas are followed annually for the rest of their lives. Follow-up involves imaging and blood tests to evaluate presence of recurrent disease.