



NEUROBLASTOMA

What is cancer?

The body is made up of hundreds of millions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells.

Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues are what makes a cell a cancer cell.

Cells become cancer cells because of damage to DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell doesn't die like it should. Instead, this cell goes on making new cells that the body does not need. These new cells will all have the same damaged DNA as the first cell does.

People can inherit damaged DNA, but most DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in our environment. Sometimes the cause of the DNA damage is something obvious, like cigarette smoking. But often no clear cause is found.

In most cases the cancer cells form a tumor. Some cancers, like leukemia, rarely form tumors. Instead, these cancer cells involve the blood and blood-forming organs and circulate through other tissues where they grow.

Cancer cells often travel to other parts of the body, where they begin to grow and form new tumors that replace normal tissue. This process is called metastasis. It happens when the cancer cells get into the bloodstream or lymph vessels of our body.

No matter where a cancer may spread, it is always named for the place where it started. For example, breast cancer that has spread to the liver is still called breast cancer, not liver cancer. Likewise, prostate cancer that has spread to the bone is metastatic prostate cancer, not bone cancer.

Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer.

Not all tumors are cancerous. Tumors that aren't cancer are called benign. Benign tumors can cause problems -- they can grow very large and press on healthy organs and tissues. But they cannot grow into (invade) other tissues. Because they can't invade, they also can't spread to other parts of the body (metastasize). These tumors are almost never life threatening.

What are the differences between cancers in adults and children?

The types of cancers that develop in children are different from the types that develop in adults. Although there are exceptions, childhood cancers tend to respond better to chemotherapy. Children's bodies also tend to tolerate chemotherapy better than adults' bodies do. But because chemotherapy can have some long-term side effects, children who survive their cancer need careful attention for the rest of their lives.

Since the 1960s, most children and adolescents with cancer have been treated at specialized centers designed for them. Being treated in these centers offers children the advantage of a team of specialists who know the differences between adult and childhood cancers, as well as the unique needs of children with cancers. This team usually includes pediatric oncologists, pathologists, surgeons, radiation oncologists, pediatric oncology nurses, and nurse practitioners.

These centers also have psychologists, social workers, child life specialists, nutritionists, rehabilitation and physical therapists, and educators who can support and educate the entire family.

Most children with cancer in the United States are treated at a center that is a member of the Children's Oncology Group (COG). All of these centers are associated with a university or children's hospital. As we have learned more about treating childhood cancer, it has become even more important that treatment be given by experienced experts.

What is neuroblastoma?

Neuroblastoma is a form of cancer that starts in certain types of very primitive nerve cells found in an embryo or fetus. (The term *neuro* refers to nerves, while *blastoma* refers to a cancer that affects immature or developing cells). This type of cancer occurs in infants and young children. It is rarely found in children older than 10 years.

To understand neuroblastoma, it helps to know something about the normal structure and function of the sympathetic nervous system, which is where these tumors start.

About the sympathetic nervous system

The nervous system consists of the brain, spinal cord, and the nerves that reach out from them to all areas of the body. The nervous system is essential for thinking, sensation, and movement, among other things.

Part of the nervous system also controls body functions we are rarely aware of, such as heart rate, breathing, blood pressure, digestion, and other functions. This part of the nervous system is known as the *autonomic nervous system*.

The *sympathetic nervous system* is a part of the autonomic nervous system. It includes:

- Nerve fibers that run along either side the spinal cord.
- Clusters of nerve cells called ganglia (plural of ganglion) at certain points along the path of the nerve fibers.
- Nerve-like cells found in the medulla (center) of the adrenal glands. The adrenals are small glands that sit on top of each kidney. These glands make the hormone adrenaline (epinephrine).

The main cells that make up the nervous system are called *nerve cells* or *neurons*. These cells communicate with other types of cells in the body by releasing tiny amounts of chemicals (hormones). This is important, because neuroblastoma cells often release certain hormones that can cause symptoms (see the section, "How is neuroblastoma diagnosed?").

Neuroblastomas

Neuroblastomas are cancers that start in early nerve cells of the sympathetic nervous system (sympathetic neuroblasts), so they can be found anywhere along this system.

A little more than 1 out of 3 neuroblastomas start in the adrenal glands. About 1 out of 3 begins in the sympathetic nerve ganglia of the abdomen. Most of the rest start in sympathetic ganglia near the spine in the chest or neck or in the pelvis.

In rare cases, a neuroblastoma may have spread so widely by the time it is found that doctors can't tell exactly where it started.

Neuroblastomas can behave strangely. For example, sometimes the cancer cells die without any cause and the tumor goes away on its own. This is much more common in very young infants than in older children. In other cases, the cells sometimes mature spontaneously into normal ganglion cells and stop dividing. This causes the tumor to become a ganglioneuroma (see below).

Other autonomic nervous system tumors

Not all childhood autonomic nervous system tumors are malignant (cancerous).

Ganglioneuroma is a benign (non-cancerous) tumor made up of mature ganglion and nerve sheaths.

Ganglioneuroblastoma is a tumor that has both malignant and benign parts. It contains neuroblasts (immature nerve cells) that can grow and spread abnormally, as well as areas of more mature tissue that are similar to ganglioneuroma.

Ganglioneuromas are usually removed by surgery and looked at carefully under a microscope to be certain they do not have areas of ganglioneuroblastoma. If the final diagnosis is ganglioneuroma, no other treatment is needed. In contrast, ganglioneuroblastomas are treated the same as neuroblastomas (see the section, "How is neuroblastoma treated?").

What are the key statistics about neuroblastoma?

Neuroblastoma is by far the most common cancer in infants (less than 1 year old). It accounts for about 7% of all cancers in children. There are about 650 new cases of neuroblastoma each year in the United States. This number has remained about the same for many years.

The average age at the time of diagnosis is about 1 to 2 years. In rare cases, neuroblastoma is detected by ultrasound even before birth. Nearly 90% of cases are diagnosed by age 5. Neuroblastoma is extremely rare in people over the age of 10 years.

In about 2 of 3 cases, the disease has already spread (metastasized) to other parts of the body when it is diagnosed.

What are the risk factors for neuroblastoma?

A risk factor is anything that affects your chance of getting a disease such as cancer.

Lifestyle-related risk factors are important in many cancers in adults. Examples of lifestyle-related risks include obesity, unhealthy diets, not getting enough exercise, smoking, and drinking too much alcohol. But unlike many adult cancers, lifestyle-related risk factors do not seem to play a large role in childhood cancers, including neuroblastomas.

Heredity

In rare cases (about 1% to 2% of all neuroblastomas), children may inherit an increased risk of developing neuroblastoma. But the vast majority of neuroblastomas do not seem to be inherited.

Children with the *familial* form of neuroblastoma (those with an inherited tendency to develop this cancer) usually come from families with one or more affected members who had neuroblastoma as infants. The average age at diagnosis of familial cases is earlier than the age for *sporadic* (not inherited) cases.

Children with familial neuroblastoma may develop 2 or more of these cancers in different organs (for example, in both adrenal glands or in more than one sympathetic ganglion). It is important to distinguish neuroblastomas developing in several organs from neuroblastomas that have started in one organ and then spread to others (metastatic neuroblastomas). When tumors develop in several places at once it suggests a familial form. Metastases can occur with either the familial or sporadic forms.

Do we know what causes neuroblastoma?

The causes of neuroblastoma are not completely known. But researchers have found important differences between neuroblastoma cells and the normal neuroblasts (primitive nerve cells) they develop from. They have also found differences between neuroblastomas likely to respond to treatment and those that have a poor prognosis (outlook). These differences (known as *prognostic markers*) are useful in selecting treatment for some patients (see the section, "How is neuroblastoma staged?").

For many years, scientists have known that both nerve cells and cells of the medulla (center) of the adrenal gland develop from cells in the fetus called neuroblasts. Many researchers think that neuroblastomas develop when normal fetal neuroblasts fail to become mature nerve cells or adrenal medulla cells. Instead, they continue to grow and divide.

Neuroblasts may not have completely matured in babies by the time they are born. In fact, studies have shown that there are small clusters of neuroblasts in the adrenal glands of some infants less than 3 months old. Most of these eventually mature into nerve cells or simply disappear and do not form neuroblastomas. Sometimes, neuroblasts remaining in very young infants continue to grow and then form tumors and may even spread to other parts of the body. But many of these tumors will still eventually mature into nerve tissue or go away on their own.

However, as children get older, it becomes less likely that these cells will mature and more likely that they will continue to grow into a cancer. By the time neuroblastomas are large enough to be felt or cause symptoms, most can no longer mature on their own and will grow and spread unless treated.

This failure to mature and to stop growing is due to abnormal DNA in the neuroblasts. DNA is the chemical in each of our cells that makes up our *genes* -- the instructions for how our cells function. DNA is found in each cell's nucleus (control center), in long string-like structures called *chromosomes*. We usually look like our parents because they are the source of our DNA, but DNA affects more than how we look. It can also influence our risk for developing certain diseases, such as some kinds of cancer.

Some genes contain instructions for controlling when our cells grow, divide, and die. Certain genes that speed up cell division are called *oncogenes*. Others that slow down cell division, or cause cells to die at the right time, are called *tumor suppressor genes*. Cancers can be caused by DNA changes (mutations) that turn on oncogenes or turn off tumor suppressor genes.

For example, neuroblastoma cells sometimes contain higher than normal levels of an oncogene called MYCN, which may be responsible for their uncontrolled growth. A tumor suppressor gene called TrkA is sometimes less active than usual in neuroblastoma cells, which may be another reason for uncontrolled growth.

In most cases, some of the chromosomes in neuroblastoma cells have changes that likely affect other genes. Scientists are still trying to determine which genes are affected by these chromosome changes, as well as how these changes might affect the growth of neuroblastoma cells.

Some people who develop cancer have DNA mutations they inherited from a parent, which increases their risk for the disease. In rare cases, neuroblastoma seems to be due to inherited gene changes. Recent research suggests that inherited mutations in the ALK gene may account for most cases of hereditary neuroblastoma.

Still, the great majority of neuroblastomas are not caused by inherited DNA mutations. They are the result of mutations acquired early in the child's development. These changes are present only in the cancer cells, so they will not be passed on to his or her children.

Although some of the causes of DNA mutations in certain adult cancers are known (for example, cancer-causing chemicals in cigarette smoke), the reasons for DNA changes that cause neuroblastomas are not known.

Can neuroblastoma be prevented?

Because there are no avoidable risk factors for neuroblastoma, there is no proven way to prevent the disease.

Some studies suggest that having mothers take prenatal multi-vitamins or folic acid might lower the risk of neuroblastoma, but further research is needed to confirm this.

If there is a history of neuroblastoma in your family, you may want to talk with a genetic counselor about your children's risks of developing the disease. It is important to remember, though, that familial neuroblastoma is very rare.

Can neuroblastoma be found early?

Researchers have studied whether screening infants for neuroblastoma might result in earlier diagnosis and better treatment results. Screening is testing for a disease, such as cancer, in people without symptoms. One way to screen for neuroblastoma is to test children's urine for certain substances made by neuroblastoma tumors. (For more information on this urine test, see the section, "How is neuroblastoma diagnosed?")

Studies have not found neuroblastoma screening to be helpful. Testing infants when they were 6 months old did find a large number of tumors that wouldn't have normally been diagnosed. But most of these tumors were of a type that would probably go away or mature into a benign tumor on their own and would likely never have caused any problems. The screening didn't lower the number of cases found at advanced stages or save lives.

What's more, only half of children identified by screening tests as possibly having neuroblastoma actually have a tumor that would cause serious problems. These "false positive" results may needlessly frighten parents and can lead to unnecessary tests and surgery in children whose tumors would regress naturally.

For these reasons, most experts do not recommend screening for neuroblastoma in infants at average risk of the disease.

In rare instances, neuroblastoma is found before birth during an ultrasound, a test that uses sound waves to create an image of the internal organs of a fetus. Ultrasounds are usually

done to estimate the age of a fetus, predict the date of birth, and look for certain common birth defects. Improvements in ultrasound technology or other methods may lead to more accurate prenatal (before birth) testing for this disease.

Neuroblastoma is sometimes found by accident in young children without any symptoms during tests done to find other childhood diseases. These children will usually have a good outcome and may not even need treatment. However, in most cases, neuroblastoma is detected because it causes certain symptoms that show the child is ill (see the section, "How is neuroblastoma diagnosed?").

How is neuroblastoma diagnosed?

Neuroblastomas are usually found as a result of signs or symptoms that a child is having. If a tumor is suspected, tests will be needed to confirm the diagnosis.

Signs and symptoms

The signs and symptoms of neuroblastoma can vary widely depending on the size and location of the original tumor, the extent of spread to other parts of the body, and whether or not the tumor cells secrete hormones.

Signs or symptoms caused by the main tumor

One of the most common signs of a neuroblastoma is an unusual lump or mass. These are usually found in the child's abdomen, causing it to swell. The child may not want to eat (which can lead to weight loss) or may complain of feeling full or having discomfort or pain. But the lump itself is usually not tender to the touch. Masses can also occur in other places such as the neck.

Sometimes, swelling from the tumor may affect parts of the body that do not contain any cancer cells, especially the legs and, in males, the scrotum. This happens when tumors in the abdomen or chest press against or invade and clog the blood and lymph vessels, preventing fluids from circulating back to the heart.

In some cases the pressure from a growing tumor can affect the child's bladder or bowel, which can cause problems with urination or bowel movements.

Pressure from the tumor on the superior vena cava (the large vein in the chest that returns blood from the head and neck to the heart) can cause swelling in the face or throat. This may make it hard for the child to breathe or swallow.

Neuroblastomas that press on certain nerves in the chest or neck can sometimes cause other symptoms, such as drooping eyelids and small pupils (the black areas in the center of the eyes). Pressure on other nerves near the spine may affect the child's ability to feel or move the arms or legs.

Signs or symptoms caused by the spread of the tumor

About 2 out of 3 cases of neuroblastoma have spread to other parts of the body by the time they are found.

Neuroblastoma frequently spreads to bones. A child who can talk may complain of pain in the bones. The pain may be so bad that the child limps or refuses to walk. If it spreads to the backbone, tumors may press on the spinal cord and cause weakness, numbness, or paralysis in the arms or legs.

Blue or purple bumps that look like small blueberries may indicate spread to the skin. Sometimes there is bruising around the eyes. In some cases the neuroblastoma may spread to the back of the eye, causing it to protrude (stick out slightly).

If the bone marrow (the inner parts of certain bones that make blood cells) is affected, the child may not have enough red blood cells, white blood cells, or blood platelets. These shortages of blood cells can result in tiredness, irritability, weakness, frequent infections, and excessive bleeding from small cuts or scrapes.

Rarely, bleeding can be caused by loss of clotting factors in the blood, which is due to clotting and excessive breakdown of tissue inside a large tumor. This is known as a *consumption coagulopathy* and can be life threatening.

A special widespread form of neuroblastoma (known as stage 4S) occurs only during the first few months of life. In this special form, the neuroblastoma has spread to the liver, to the skin, and/or to the bone marrow (in small amounts). The liver can become very large. Despite the fact that the cancer is already widespread when it is found, stage 4S neuroblastoma is very treatable, and almost all children can be cured, usually with minimal treatment.

Signs or symptoms caused by hormones from the tumor

Neuroblastoma is one of the few cancers in children that release hormones that can cause strange changes in the body. These changes are called *paraneoplastic syndromes*.

Symptoms of paraneoplastic syndromes can include:

- Fever (in about 1 out of 4 children)
- Constant diarrhea
- High blood pressure (causing irritability)
- Rapid heartbeat

- Reddening (flushing) of the skin
- Sweating

An uncommon symptom is called the *opsoclonus-myoclonus-ataxia* syndrome or "dancing eyes, dancing feet." In this situation, the child has irregular, rapid eye movements (opsoclonus), twitch-like muscle spasms (myoclonus), and appears uncoordinated when standing or walking (ataxia). He or she may also have trouble speaking. For unknown reasons, neuroblastoma tumors that cause this syndrome tend to be less life-threatening than other forms of the disease.

Medical history and physical exam

If your child has signs or symptoms that may suggest a neuroblastoma, the doctor will want to take a complete medical history to learn more about the symptoms. A physical exam can provide information about signs of a neuroblastoma and other health problems. For example, the doctor may find a child has high blood pressure or may be able to see or feel an abnormal mass in the body.

If symptoms and/or the results of the physical exam suggest a neuroblastoma (or other tumor), other tests will likely be done. These might include blood and urine tests, imaging tests, and biopsies. These tests are important because many of the symptoms and signs of neuroblastoma can also be caused by other cancers or by non-cancerous diseases.

Blood and urine tests

Blood or urine catecholamine tests

Neuroblastoma can often be found by detecting substances called catecholamines in the blood or urine. Sympathetic nerve cells normally release catecholamines, such as epinephrine (adrenaline). Eventually the body breaks these down into metabolites (smaller pieces), which are then passed out of the body in the urine.

In most cases, neuroblastoma cells make enough catecholamines to be detected by blood or urine tests. The 2 catecholamine metabolites most often measured are:

- Homovanillic acid (HVA)
- Vanillylmandelic acid (VMA)

Other lab tests

Your child's doctor will probably also order blood tests to check blood cell counts, liver and kidney function, and the balance of salts (electrolytes) in the body. A urinalysis (urine test) may also be done to further check kidney function.

Imaging tests

Imaging tests use x-rays, magnetic fields, sound waves, or radioactive substances to create pictures of the inside of the body. Imaging tests may be done for a number of reasons, including:

- To help find out whether a suspicious area might be cancerous
- To learn how far cancer may have spread
- To help determine if treatment has been effective

Most patients who have or may have cancer will have one or more of these tests.

Neuroblastoma patients are generally quite young, so it can be difficult to do some of these tests. Parents and medical staff need to be very patient.

X-rays

X-rays can be useful to see if cancer has spread to the bones. An x-ray of the head may be done to see if cancer has spread to the skull bones. A bone scan (described below) is usually better for looking at the bones in the rest of the body, but x-rays may be used in infants, where a bone scan might not be possible. A standard chest x-ray may be done if doctors suspect that the tumor has invaded the lungs, but a CT or MRI scan of the chest can show the area in more detail.

Computed tomography (CT or CAT) scan

CT scans can be useful to look for neuroblastoma in the abdomen, pelvis, and chest.

The CT scan is an x-ray test that produces detailed cross-sectional images of parts of the body. Instead of taking one picture, like a regular x-ray, a CT scanner takes many pictures as it rotates around your child while he or she lies on a table. A computer then combines these pictures into images of slices of the part of the body being studied. Unlike a regular x-ray, a CT scan creates detailed images of the soft tissues in the body.

Your child may be asked to drink a contrast solution and/or receive an IV (intravenous) line through which a contrast dye is injected. This helps better outline structures in the body. The contrast may cause some flushing (a feeling of warmth, especially in the face). Some people are allergic and get hives. Rarely, more serious reactions like trouble breathing or low blood pressure can occur. Be sure to tell the doctor if your child has any allergies or has ever had a reaction to any contrast material used for x-rays.

CT scans take longer than regular x-rays, but not as long as MRI scans. Your child will need to lie still on a table while they are being done. During the test, the table moves in and out of

the scanner, a ring-shaped machine that completely surrounds the table. Some people feel a bit confined by the ring they have to lie in while the pictures are being taken. In some cases, your child may be sedated (given medicine to make them sleepy) before the test to reduce movement and help make sure the pictures come out well.

Spiral CT (also known as helical CT) is now available in many medical centers. This type of CT scan uses a faster machine. The scanner part of the machine rotates around the body continuously, allowing doctors to collect the images much more quickly than with a standard CT. This lowers the chance of blurred images occurring as a result of breathing motion. It also lowers the dose of radiation received during the test. The biggest advantage may be that the slices it images are thinner, which yields more detailed pictures.

CT-guided needle biopsy: CT scans can also be used to precisely guide a biopsy needle into a tumor. For this procedure, the patient remains on the CT scanning table while a radiologist advances a biopsy needle through the skin and toward the mass. CT scans are repeated until the needle is within the mass. A fine needle biopsy sample or a larger core needle biopsy sample is then removed and looked at under a microscope. In children, this procedure is always done under general anesthesia (where the child is asleep).

Magnetic resonance imaging (MRI) scan

MRI scans provide detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays, so there is no radiation involved. The energy from the radio waves is absorbed by the body and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body. A contrast material called gadolinium may be injected into a vein before the scan to better see details, but contrast is needed less often than with a CT scan.

MRI scans are most helpful in looking at the brain and spinal cord. MRI may be slightly better than CT at evaluating the extent of neuroblastoma, but it can be more difficult for the child.

MRI scans take longer than CT scans, often up to an hour. For most MRI machines, your child has to lie inside a narrow tube, which is confining and can be distressing. The MRI machine makes loud buzzing and clicking noises that your child may find disturbing. Newer, more open MRI machines may be an option in some cases, but they still require the child to stay still for long periods of time, so sedation is often needed.

Ultrasound

Ultrasound uses sound wave echoes to produce pictures of internal organs or masses. A small microphone-like instrument called a transducer emits sound waves and picks up the echoes as they bounce off body tissues. The echoes are converted by a computer into a black and white image that is displayed on a computer screen.

Ultrasound is a fairly quick and easy test that involves no radiation, which is why it is often one of the first tests done if an internal mass is suspected. To have an ultrasound exam, the child simply lies on a table (or the parent holds the child) and a technician moves the transducer across the skin over the part of the body being examined. Usually, the skin is lubricated with gel first.

Sometimes an ultrasound is used to find masses in the abdomen. (It's not used for masses in the chest because the ribs block the sound waves.) It can also detect if kidneys have become swollen because the outflow of urine has been blocked by enlarged lymph nodes or a mass. It is particularly useful in checking to see if tumors in the abdomen are shrinking.

MIBG scan

This scan uses a form of the chemical meta-iodobenzylguanidine (MIBG) that contains a small amount of radioactive iodine. MIBG is similar to norepinephrine, a chemical made by sympathetic nerve cells. It is injected into a vein and travels through the bloodstream, and in most patients it will attach to neuroblastoma cells anywhere in the body. Several hours or days later, the body is scanned with a special camera to look for areas that picked up the radioactivity. This allows doctors to find the neuroblastoma and spot whether it has spread to the bones and/or other parts of the body.

This test is preferred by many doctors as a standard way to evaluate children with neuroblastoma. It can be repeated after treatment to see if it has been effective. It is also good to know if the tumor takes up the MIBG because in some cases, this radioactive molecule can be used (at higher doses) to treat the neuroblastoma (see the radiation therapy section in "How is neuroblastoma treated?").

Positron emission tomography (PET) scan

For a PET scan, a chemical like glucose (a form of sugar) that contains a radioactive atom is injected into the blood. The amount of radioactivity used is very low. Because cancer cells in the body are growing quickly, they absorb large amounts of the radioactive sugar. A special camera can then create a picture of areas of radioactivity in the body. The picture is not finely detailed like a CT or MRI scan, but it can provide helpful information about the whole body.

Some newer machines are able to perform both a PET and CT scan at the same time (PET/CT scan). This allows the doctor to compare areas of higher radioactivity on the PET with the more detailed appearance of that area on the CT.

Bone scan

A bone scan can help show if a cancer has metastasized (spread) to the bones, and can provide a picture of the entire skeleton at once.

For this test, a small amount of low-level radioactive material (technetium-99) is injected into a vein. The substance settles in areas of damaged bone throughout the entire skeleton over the course of a couple of hours. Your child then lies on a table for about 30 minutes while a special camera detects the radioactivity and creates a picture of the skeleton. (This may require sedation for smaller children.)

Areas of active bone changes attract the radioactivity and appear as "hot spots" on the skeleton. These areas may suggest the presence of cancer, but other bone diseases can also cause the same pattern. To distinguish between these conditions, other imaging tests such as plain x-rays or MRI scans, or even a bone biopsy might be needed.

Neuroblastoma often causes bone damage, which a bone scan can find. This used to be a standard test, but it has been largely replaced by the MIBG scan.

Biopsies

Signs and symptoms, lab tests, and imaging tests may strongly suggest a neuroblastoma, but a biopsy (removing some of the tumor for viewing under a microscope and other lab testing) is the only way to be certain.

During a biopsy, the doctor removes a sample of the tumor mass. In adults, biopsies are sometimes done using local anesthetic (numbing medicine), but in children they are more often done while the child is under general anesthesia (asleep). There are 2 main types of biopsies:

- **Incisional (open) biopsy:** This type of biopsy is done by cutting away a piece of the tumor through an opening on the skin.
- **Needle (closed) biopsy:** For this type of biopsy, a hollow needle is placed through the skin and into the tumor. If the tumor is deep within the body, CT scans or ultrasound may be used to help guide the needle into the tumor.

The biopsy samples are then viewed under a microscope by a pathologist. Some cases of neuroblastoma are easily recognized when looked at by doctors experienced in testing children's tumor samples. But some cases may be hard to tell apart from other types of children's cancers.

In these situations, special tests such as *immunohistochemistry* must be done. For this test, a portion of the sample is treated with special proteins (antibodies) that attach to substances in neuroblastoma cells but not other cancers. Chemicals (stains) are then added so that cells containing these substances change color and can be easily seen under a microscope. This lets the pathologist know that the tumor is a neuroblastoma.

Other types of lab tests may also be done on neuroblastoma samples to help determine how quickly the tumor is likely to grow. Some of these are described in the section, "How is neuroblastoma staged?"

Bone marrow aspiration and biopsy

Neuroblastoma often spreads to the bone marrow (the soft inner parts of certain bones). If blood or urine levels of catecholamines are increased, then finding cancer cells in a bone marrow sample is enough to diagnose neuroblastoma. If neuroblastoma has already been diagnosed by a biopsy done elsewhere in the body, bone marrow testing is done to help determine the extent of the disease.

A bone marrow aspiration and biopsy are usually done at the same time. In most cases the samples are taken from the back of both of the pelvic (hip) bones.

For a bone marrow *aspiration*, the child lies on a table (on his or her side or belly). After cleaning the skin over the hip, the doctor numbs the area and the surface of the bone with local anesthetic, which may cause a brief stinging or burning sensation. A thin, hollow needle is then inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow. Even with the local anesthetic, most patients still have some brief pain when the marrow is removed.

A bone marrow *biopsy* is usually done just after the aspiration. A small piece of bone and marrow is removed with a slightly larger needle that is twisted as it is pushed down into the bone. The biopsy may also cause some brief pain. Once the biopsy is done, pressure will be applied to the site to help stop any bleeding.

In many cases, the child is also given other medicines to reduce pain or may even be asleep during the bone marrow aspiration and biopsy.

Samples from the bone marrow are sent to a pathology lab, where they are looked at and tested for the presence of cancer cells.

How is neuroblastoma staged?

Staging is the process of finding out how far a cancer has spread. The outlook (prognosis) for people with cancer depends, to a large extent, on the cancer's stage. The stage of a cancer is one of the most important factors in choosing treatment.

The stage of the neuroblastoma is based on results of imaging tests and biopsies of the main tumor and other tissues, which were described in the section, "How is neuroblastoma diagnosed?"

For neuroblastoma, several other factors also affect prognosis, including a child's age and certain tests of blood and tumor specimens. While these prognostic factors are not included in determining the stage of the cancer, they are used along with the stage to determine which risk group a child falls into. These prognostic factors and risk groups are also described below.

International Neuroblastoma Staging System

A staging system is a standardized way for the cancer care team to describe the extent of the cancer. Since the mid-1990s, most cancer centers have used the International Neuroblastoma Staging System (INSS) to stage neuroblastoma. In simplified form, the stages are:

Stage 1: The cancer is still in the area where it started. It is on one side of the body (right or left). All visible tumor can be totally removed by surgery (although looking at the tumor's edges under the microscope after surgery may show some cancer cells). Lymph nodes enclosed within the tumor may contain neuroblastoma cells, but lymph nodes outside of the tumor should be free of cancer.

Stage 2A: The cancer is still in the area where it started and on one side of the body, but not all of the visible tumor can be removed by surgery. Lymph nodes enclosed within the tumor may contain neuroblastoma cells, but lymph nodes outside of the tumor should be free of cancer.

Stage 2B: The cancer is on one side of the body, and may or may not be able to be totally removed by surgery. Nearby lymph nodes outside the tumor contain neuroblastoma cells, but the cancer has not spread to lymph nodes on the other side of the body or elsewhere.

Stage 3: The cancer has not spread to distant parts of the body, but one of the following is true:

- The cancer cannot be completely removed by surgery and it has crossed the midline (defined as the spine) to the other side of the body. It may or may not have spread to nearby lymph nodes.
- The cancer is still in the area where it started and is on one side of the body. It has spread to lymph nodes that are relatively nearby but on the other side of the body.
- The cancer is in the middle of the body and growing toward both sides (either directly or by spreading to nearby lymph nodes) and cannot be completely removed by surgery.

Stage 4: The cancer has spread to distant sites such as distant lymph nodes, bone, liver, skin, bone marrow, or other organs (but the child does not meet the criteria for stage 4S).

Stage 4S (also called "special" neuroblastoma): The child is younger than 1 year old. The cancer is on one side of the body. It may have spread to lymph nodes on the same side of the body but not to nodes on the other side. The neuroblastoma has spread to the liver, skin, and/or the bone marrow. However, no more than 10% of marrow cells may be cancerous, and imaging tests do not show spread to the bones.

Recurrent: This term is used to describe cancer that has come back (recurred) after it has been treated. It may come back in the area where it first started or in another part of the body.

Prognostic markers

Prognostic markers are specific features that help predict whether the child's outlook for cure is better or worse than would be predicted by the stage alone. The following markers are used to help determine a child's prognosis.

Age

Younger children (under 12-18 months) are more likely to be cured than older children.

Tumor histology

Tumor histology is based on how the neuroblastoma cells look under the microscope. Tumors that contain more normal-looking cells and tissues tend to have a better prognosis and are said to have a *favorable histology*. Tumors whose cells and tissues look more abnormal under a microscope tend to have a poorer prognosis and are labeled as having an *unfavorable histology*.

DNA ploidy

The amount of DNA in each cell, known as ploidy, can be measured by special lab techniques, such as flow cytometry or imaging cytometry. Neuroblastoma cells with about the same amount of DNA as normal cells are classified as *diploid*. Cells with increased amounts of DNA are termed *hyperdiploid*.

In infants, hyperdiploid cells tend to be associated with earlier stages of disease, respond better to chemotherapy, and usually predict a more favorable prognosis (outcome) than diploid cells.

MYCN gene amplifications

MYCN is an oncogene, a gene that is important in regulating growth of cells. Alterations of these genes can make cells grow and divide too quickly, as with cancer cells.

Researchers have found that neuroblastomas with too many copies (amplification) of the MYCN oncogene tend to grow more rapidly and are less likely to mature. Children whose neuroblastomas have this feature tend to have a worse prognosis than other children with neuroblastoma.

Other markers

These markers are not used to help determine risk groups (see below), but they are still important and may influence a doctor's decision on how to treat a child with neuroblastoma.

Cytogenetics: In this lab test, the number of chromosomes in each cell is counted under a microscope, and the abnormalities of any chromosome are described. Normal cells have 46 chromosomes (2 sets of 23), which are made of DNA and protein. Neuroblastomas with normal chromosome numbers tend to grow and spread more quickly than those with extra chromosomes.

Cells that are missing certain parts of chromosomes 1 or 11 (known as 1p deletions or 11q deletions) may also predict a less favorable prognosis. It is thought that these chromosome parts -- missing in many neuroblastoma patients -- may contain important tumor suppressor genes, but more studies are needed to verify this.

Having an extra part of chromosome 17 (17q gain) is also linked with a worse prognosis; this probably means that there is an oncogene in this part of chromosome 17.

Understanding the importance of chromosome deletions/gains is an active area of neuroblastoma research.

Neurotrophin (nerve growth factor) receptors: These are substances on the surface of normal nerve cells and on some neuroblastoma cells. They normally allow the cells to recognize neurotrophins -- hormone-like chemicals that help the nerve cells to mature.

Neuroblastomas with more neurotrophin receptors, especially the nerve growth factor receptor called TrkA, may have a better prognosis.

Serum markers: Serum (blood) levels of certain substances can be used to help predict prognosis.

Neuroblastoma cells release ferritin, a chemical that is an important part of the body's normal iron metabolism, into the blood. Patients with high ferritin levels tend to have a worse prognosis.

Neuron-specific enolase (NSE) and lactate dehydrogenase (LDH) are made by several types of normal cells as well as by neuroblastoma cells. Increased levels of NSE and LDH in the blood are often linked with a worse outlook in children with neuroblastoma.

A substance on the surface of many nerve cells known as ganglioside GD2 is often increased in the blood of neuroblastoma patients. Although the usefulness of GD2 in predicting prognosis is unknown, it may turn out to be more useful in treating neuroblastoma (see "What's new in neuroblastoma research and treatment?").

Risk groups

The major prognostic factors above are combined with the stage of the disease to form 3 different risk groups: low, intermediate, and high. These risk groups are used to help predict how likely a child can be cured. For example, a child in a low-risk group can often be cured with simple treatment, such as surgery alone. With children in higher risk groups, the chance of cure is not as high, so more intensive treatment is often needed.

These risk groups are based on what is currently known about clinical and biologic features of neuroblastoma and how it is treated. As new research provides more information, these risk groups may change over time.

Low risk

- All children who are Stage 1
- Any child who is Stage 2A or 2B and younger than age 1
- Any child who is Stage 2A or 2B, older than age 1, whose cancer has *no* extra copies of the MYCN gene
- Any child who is Stage 2A or 2B, older than age 1, whose cancer has extra copies of the MYCN gene *but* has a favorable histology (appearance under the microscope)
- Any child who is Stage 4S (younger than age 1), whose cancer has favorable histology, is hyperdiploid (excess DNA) and has no MYCN amplification

Intermediate risk

- Any child who is Stage 3, younger than age 1, whose cancer has *no* extra copies of the MYCN gene
- Any child who is Stage 3, older than age 1, whose cancer has *no* extra copies of the MYCN gene and has favorable histology (appearance under the microscope)
- Any child who is Stage 4, younger than 18 months, whose cancer has *no* extra copies of the MYCN gene

- Any child who is Stage 4S (younger than age 1), whose cancer has *no* extra copies of the MYCN gene and has normal DNA ploidy (number of chromosomes) and/or has unfavorable histology

High risk

- Any child who is Stage 2A or 2B, older than age 1, whose cancer has extra copies of the MYCN gene and unfavorable histology (appearance under the microscope)
- Any child who is Stage 3, younger than age 1, whose cancer has extra copies of the MYCN gene
- Any child who is Stage 3, older than age 1, whose cancer has *no* extra copies of the MYCN gene but has unfavorable histology
- Any child who is Stage 3, older than age 1, whose cancer has extra copies of the MYCN gene
- Any child who is Stage 4, younger than 18 months, whose cancer has extra copies of the MYCN gene
- Any child who is Stage 4 and older than 18 months
- Any child who is Stage 4S (younger than age 1), whose cancer has extra copies of the MYCN gene

5-year survival rates based on risk groups

Survival rates are a way to get a general idea of the outlook for children with a certain type and stage of cancer. Some parents may want to know the statistics for children in similar situations, but others may not find the numbers helpful, or may even not want to know them. Whether or not you want to read about the survival statistics below for neuroblastoma is up to you.

The 5-year survival rate refers to the percentage of patients who live *at least 5 years* after their cancer is diagnosed. Of course, many children live much longer than 5 years (and many are cured). These numbers are based on children treated several years ago; improvements in treatment since then may result in a more favorable outlook for children now being diagnosed with the neuroblastoma.

Survival rates are typically based on previous outcomes of large numbers of children who had the disease, but they cannot predict what will happen in any particular child's case. Many

other factors may affect a child's outlook, such as how well the cancer responds to treatment. Your child's doctor can tell you if the numbers below may apply, as he or she is familiar with the aspects of your child's particular situation.

Survival by risk group

Low-risk group: Children in the low-risk group have a 5-year survival rate of around 90% to 95%.

Intermediate-risk group: In children in the intermediate-risk group, the 5-year survival rate is around 80% to 90%.

High-risk group: The 5-year survival rate in children in the high-risk group is around 20% to 40%.

How is neuroblastoma treated?

This information represents the views of the doctors and nurses serving on the American Cancer Society's Cancer Information Database Editorial Board. These views are based on their interpretation of studies published in medical journals, as well as their own professional experience.

The treatment information in this document is not official policy of the Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your doctor.

Your doctor may have reasons for suggesting a treatment plan different from these general treatment options. Don't hesitate to ask him or her questions about your treatment options.

The approach to treatment of neuroblastoma depends on the stage of the cancer, the child's age, and other factors such as the prognostic markers mentioned above. The types of treatment used may include:

- Surgery
- Chemotherapy
- Retinoid therapy
- Radiation therapy
- High-dose chemotherapy/radiation therapy and stem cell transplant
- Immunotherapy

In many cases, more than one type of treatment is needed.

This section describes the types of treatment used for neuroblastomas. This is followed by a discussion of when these treatments are used in different situations.

Surgery

Surgery can be used both to help diagnose neuroblastoma and to treat it. For smaller tumors that have not spread, surgery is often the only treatment that is needed.

Surgical (open) biopsy

Before treatment begins, doctors may do a surgical biopsy to remove tumor samples to be looked at under a microscope and for other lab tests. If the tumor is in the abdomen, the surgeon may do the biopsy with the aid of a laparoscope. This is a long, thin tube with a tiny video camera on the end. It is inserted into the abdomen through a small incision to allow the surgeon to see inside. The surgeon then makes a second small incision to reach inside the abdomen with long, thin instruments and remove a small piece of tumor.

Surgery as treatment

After neuroblastoma is diagnosed, surgery is often used to try to remove as much of the tumor as possible. In some cases, surgery can remove the entire tumor and bring about a complete cure.

During the operation, the surgeon looks carefully for signs of tumor spread to other organs. Nearby lymph nodes are removed and looked at under a microscope for cancer cells.

If possible, the surgeon will remove the entire tumor. This is less likely to be possible if the tumor is wrapped around large blood vessels. Even if the tumor cannot be completely taken out, treatment with chemotherapy (and sometimes radiation therapy) after removing most of the cancer may result in a cure. Sometimes surgery is repeated after other treatments (chemotherapy and/or radiation therapy) to check the results of therapy and to remove any remaining cancer if possible.

If the tumor is very big, chemotherapy may be used before surgery. This can shrink the tumor and make it easier to remove completely.

Possible risks and side effects of surgery

Like all forms of treatment, surgery poses some risk of complications. These can include reactions to anesthesia, excess bleeding, and damage to blood vessels, kidneys, other organs, or nerves. Most complications are minor, but serious ones are possible. Complications are more likely if the tumor is large and growing into blood vessels or nerves.

Chemotherapy

Chemotherapy is the use of anti-cancer drugs, which are usually given into a vein. The drugs enter the bloodstream and circulate throughout the body to reach and destroy cancer cells. This makes chemotherapy useful for treating neuroblastoma that has spread to the lymph nodes, bone marrow, liver, lungs, or other organs.

Some cases of neuroblastoma are treated with chemotherapy given along with surgery, either before (neoadjuvant chemotherapy) or after (adjuvant chemotherapy). In other cases, especially when the cancer has spread too far to be completely removed by surgery, chemotherapy is the main treatment.

Most children with neuroblastoma will need to have chemotherapy. In most cases, a combination of medicines are given. The main drugs used to treat children with neuroblastoma include:

- Cyclophosphamide or ifosfamide
- Cisplatin or carboplatin
- Vincristine
- Doxorubicin (Adriamycin)
- Etoposide
- Topotecan

The most common combination of drugs to treat neuroblastoma consists of carboplatin (or cisplatin), cyclophosphamide, doxorubicin, and etoposide, but others may be used. For children in the high-risk group, larger combinations of drugs are used, and the drugs are given at higher doses, which may be followed by a stem cell transplant (see below).

Possible side effects of chemotherapy

Chemotherapy drugs work by attacking cells that are dividing quickly, which is why they work against cancer cells. But other cells in the body, such as those in the bone marrow, the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to side effects.

Children seem to have an advantage over adults when it comes to chemotherapy. They tend to have less severe side effects and recover from side effects more quickly. One benefit of this is that doctors can give high doses of chemotherapy that are necessary to kill the tumor.

The side effects of chemotherapy depend on the type and dose of drugs given and the length of time they are taken. General side effects of chemotherapy drugs can include:

- Hair loss
- Mouth sores
- Loss of appetite
- Nausea and vomiting
- Increased chance of infections (due to low white blood cell counts)

- Easy bruising or bleeding (due to low blood platelet counts)
- Fatigue (due to low red blood cell counts)

Most of these side effects are short-term and tend to go away after treatment is finished. There are often ways to lessen these side effects. For example, drugs can be given to help prevent or reduce nausea and vomiting. Be sure to discuss any questions you have about side effects with the cancer care team.

Along with the effects listed above, some side effects are specific to certain medicines:

Cyclophosphamide and ifosfamide can damage the bladder. This can be avoided or minimized by giving the drugs with plenty of fluids and with a drug called mesna, which helps protect the bladder. These drugs can also damage the ovaries or testicles and may affect fertility (the ability to have children).

Doxorubicin can cause heart damage. Doctors try to reduce this risk as much as possible by not giving more than the recommended doses of doxorubicin and by checking the heart with a test called an echocardiogram (an ultrasound of the heart) during treatment. This drug can also cause skin damage if it should leak out of the vein during administration.

Cisplatin and carboplatin can affect the kidneys. Giving plenty of fluids can help reduce this risk. These drugs can also affect hearing in some cases. Your child's doctor may check this with hearing tests (audiograms) during or after treatment.

Vincristine can damage nerves. Some patients may notice tingling and numbness, particularly in the hands and feet.

Chemotherapy may also have longer-term side effects in some cases. For example, some drugs used to treat neuroblastoma can increase the risk of later developing a cancer of white blood cells known as acute myeloid leukemia (AML). While this is a serious risk, it is not common, and the importance of chemotherapy in treating neuroblastoma far outweighs this risk. For more on the possible long-term effects of treatment, see the section, "What happens after treatment for neuroblastoma?"

Retinoid therapy

Retinoids are chemicals that are related to vitamin A. They are known as differentiating agents because they are thought to help some cancer cells to mature (differentiate) into normal cells.

In children with high-risk neuroblastoma, treatment with a retinoid called 13-cis-retinoic acid (isotretinoin) reduces the risk of recurrence after high-dose chemotherapy and stem cell transplant. Most doctors now recommend 6 months of 13-cis-retinoic acid (taken as a capsule) once therapy is completed.

Researchers are now trying to develop more effective retinoids and to define the exact role of this approach in the treatment of neuroblastoma.

Possible side effects

The most common side effect of 13-cis-retinoic acid is drying and cracking of the lips. Dry skin or eyes are also possible, as are nosebleeds and changes in the nails.

Radiation therapy

Radiation therapy uses high-energy rays or particles to kill cancer cells. Radiation is sometimes a necessary part of treatment, but because of the possible long-term side effects in children, it is avoided when possible. Two types of radiation therapy can be used to treat children with retinoblastoma.

External beam radiation therapy

This type of radiation therapy focuses radiation on the cancer from a source outside the body. There are several situations in which this type of radiation therapy might be used:

- To destroy neuroblastoma cells that remain behind after surgery and chemotherapy
- To try to shrink tumors before surgery, making them easier to remove at the time of surgery
- To treat larger tumors that are causing serious problems (such as trouble breathing) and do not respond quickly to chemotherapy
- As part of the treatment regimen (along with high-dose chemotherapy) before a stem cell transplant in children with high-risk neuroblastoma
- To help relieve pain caused by advanced neuroblastoma

The radiation is typically directed at the tumor itself, but in some cases it may also target other parts of the body to reduce the risk of cancer spread. When radiation is delivered throughout the body, it is known as total body irradiation (TBI).

External radiation therapy is much like getting an x-ray, but the radiation is more intense. The procedure itself is painless.

Before treatments start, the radiation team takes careful measurements with imaging tests such as MRI scans to determine the correct angles for aiming the radiation beams and the proper dose of radiation.

Each actual treatment lasts only a few minutes, but the setup time -- getting your child into place for treatment -- usually takes longer. Young children may be given medication to make them fall asleep so they will not move during the treatment. Most often, radiation treatments are given 5 days a week for several weeks.

Possible side effects: Short-term side effects of external radiation therapy may include mild skin reactions, nausea, diarrhea, or fatigue. Often these go away after a short while. Talk with your child's doctor about these side effects because there are ways to relieve some of them. Radiation may also make the side effects of chemotherapy worse.

Radiation therapy can interfere with the growth of normal body tissues, and may increase the risk of developing other cancers later on. The actual effects depend on the part of the body getting radiation.

MIBG radiotherapy

As described in the section "How is neuroblastoma diagnosed?", MIBG is a chemical similar to norepinephrine, which is made by sympathetic nerve cells. A slightly radioactive form of MIBG is sometimes injected into the bloodstream as part of an imaging test to look for neuroblastoma cells in the body.

A more highly radioactive form of MIBG is also used to treat some patients with advanced neuroblastoma, often along with other treatments. Once injected into the bloodstream, the MIBG goes to the sites of tumors anywhere in the body, where it delivers its radiation. The child will need to stay in a special room for a few days after the injection until most of the radiation has left the body.

Possible side effects: MIBG therapy can sometimes cause nausea and vomiting. It can also lower blood cell counts because of its effects on the bone marrow. In rare cases it may cause high blood pressure for a short period of time. MIBG may build up in the thyroid gland in the neck, which can sometimes result in low levels of thyroid hormone in the body.

High-dose chemotherapy/radiation therapy and stem cell transplant

This type of treatment is sometimes used in children with high-risk neuroblastoma who are unlikely to be cured with other treatments. It involves giving high doses of chemotherapy (higher than could safely be given otherwise) and/or radiation therapy (total body irradiation or high-dose MIBG), and then replacing the body's bone marrow cells, which were killed by the treatment. In the past, this type of treatment was commonly referred to as a *bone marrow transplant*.

The bone marrow is the soft, inner part of some bones where new red blood cells, white blood cells, and platelets are formed. Red blood cells carry oxygen to all parts of the body.

White blood cells are part of the immune system, which fights off infections. Platelets are needed to stop bleeding caused by cuts and scrapes.

Both chemotherapy and some types of radiation can affect blood-forming stem cells in the bone marrow. (These are the cells that make the different types of blood cells.) Even though more intensive treatments might be more effective in treating tumors, they can't be given because they would cause severe damage to the bone marrow, leading to life-threatening shortages of blood cells.

Doctors try to get around this problem by giving the child an infusion of blood-forming stem cells after treatment. This is known as a *peripheral blood stem cell transplant* (PBSCT).

What it involves

The first step in a PBSCT is to collect, or "harvest," the child's own blood-producing stem cells to use later. In the past, the stem cells were often taken from the child's bone marrow, which was done by drilling small holes in certain bones. But doctors have found that these cells can be taken from the bloodstream during a procedure known as *apheresis*. This is similar to donating blood, but instead of going into a collecting bag, the blood goes into a special machine that filters out the stem cells and returns the other parts of the blood back to the person's body. The stem cells are then frozen until the transplant.

After the harvest, the child gets high-dose chemotherapy and/or radiation. When treatment is complete, the patient's stem cells are thawed and returned to the body in a process similar to a normal blood transfusion. The stem cells travel through the bloodstream and settle in the bone marrow. Over the next 3 or 4 weeks, the stem cells start to make new, healthy blood cells in the child's bone marrow.

Until this happens, the child is at high risk of infection because of a low white blood cell count, as well as bleeding because of a low platelet count. To avoid infection, protective measures are taken, such as using special air filters in the hospital room and having visitors wear protective clothing. Blood and platelet transfusions and treatment with IV antibiotics may also be used to prevent or treat infections or bleeding problems.

A peripheral blood stem cell transplant is a complex treatment. If the doctors think your child may benefit from a transplant, the best place to have this done is at a nationally recognized cancer center where the staff has experience in performing the procedure and managing the recovery period.

A stem cell transplant is also very expensive (costing more than \$100,000) and often requires a lengthy hospital stay. Because the procedure is so expensive, you should have an idea of how the costs might be covered beforehand. Be sure to get a written approval from your insurer if the procedure is recommended for your child.

Possible side effects

Possible early complications and side effects are basically the same as those caused by any other type of high-dose chemotherapy (see the "Chemotherapy" section of this document) or radiation therapy, and are due to damage to the bone marrow and other quickly dividing tissues of the body. They can include low blood cell counts (with increased risk of infection and bleeding), nausea, vomiting, loss of appetite, mouth sores, and hair loss.

One of the most common and serious short-term effects is an increased risk for infection. Antibiotics are often given to try to prevent this from happening. Other side effects, like low red blood cell and platelet counts, may require blood product transfusions or other treatments.

Some complications and side effects can persist for a long time or may not occur until years after the transplant. Be sure to talk to your child's doctor before the transplant to learn about possible long-term effects your child may have.

For more information on stem cell transplants, see our document, *Bone Marrow & Peripheral Blood Stem Cell Transplants*.

Immunotherapy

Monoclonal antibodies are man-made versions of immune system proteins that can be made to attack a very specific target. These molecules can be injected into the body to seek out and attach to cancer cells. A monoclonal antibody called ch14.18 has been developed to attach to the ganglioside GD2, a substance found on the surface of many neuroblastoma cells. This antibody is often given together with cytokines (immune system hormones) such as GM-CSF and interleukin-2. This combination can help the child's immune system to recognize and destroy neuroblastoma cells.

This antibody is now part of the routine treatment for many children with high-risk neuroblastoma, often after a stem cell transplant.

Side effects may include pain, buildup of fluid in the body, and allergic reactions.

Clinical trials

You may have had to make a lot of decisions since you've been told you have cancer. One of the most important decisions you will make is choosing which treatment is best for you. You may have heard about clinical trials being done for your type of cancer. Or maybe someone on your health care team has mentioned a clinical trial to you.

Clinical trials are carefully controlled research studies that are done with patients who volunteer for them. They are done to get a closer look at promising new treatments or procedures.

If you would like to take part in a clinical trial, you should start by asking your doctor if your clinic or hospital conducts clinical trials. You can also call our clinical trials matching service for a list of clinical trials that meet your medical needs. You can reach this service at 1-800-303-5691 or on our Web site at <http://clinicaltrials.cancer.org>. You can also get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll-free at 1-800-4-CANCER (1-800-422-6237) or by visiting the NCI clinical trials Web site at www.cancer.gov/clinicaltrials.

There are requirements you must meet to take part in any clinical trial. If you do qualify for a clinical trial, it is up to you whether or not to enter (enroll in) it.

Clinical trials are one way to get state-of-the-art cancer treatment. They are the only way for doctor's to learn better methods to treat cancer. Still, they are not right for everyone.

You can get a lot more information on clinical trials, in our document called *Clinical Trials: What You Need to Know*. You can read it on our Web site or call our toll-free number and have it sent to you.

Complementary and alternative therapies

When your child has cancer you are likely to hear about ways to treat his or her cancer or relieve symptoms that are different from mainstream (standard) medical treatment. These methods can include vitamins, herbs, and special diets, or methods such as acupuncture or massage -- among many others. You may have a lot of questions about these treatments. Here are some you may have thought of already:

- How do I know if a non-standard treatment is safe?
- How do I know if it works?
- Should we try one or more of these treatments?
- What does my doctor know/think about these methods? Should I tell the doctor that I'm thinking about trying them?
- Will these treatments cause a problem with my child's standard medical treatment?
- What is the difference between "complementary" and "alternative" methods?
- Where can I find out more about these treatments?

The terms can be confusing

Not everyone uses these terms the same way, so it can be confusing. The American Cancer Society uses *complementary* to refer to medicines or methods that are used *along with* regular medical care. *Alternative* medicine is a treatment used *instead of* standard medical treatment.

Complementary methods: Complementary treatment methods, for the most part, are not presented as cures for cancer. Most often they are used to help you feel better. Some methods that can be used in a complementary way are meditation to reduce stress, acupuncture to relieve pain or peppermint tea to relieve nausea. There are many others. Some of these methods are known to help, while others have not been tested. Some have been proven not be helpful. A few have even been found harmful. However, some of these methods may add to your comfort and well-being.

There are many complementary methods that can be safely used right along with medical treatment to help relieve symptoms or side effects, to ease pain, and to help your child enjoy life more. For example, some people find methods such as aromatherapy, massage therapy, meditation, or yoga to be useful.

Alternative treatments: Alternative treatments are those that are used instead of standard medical care. These treatments have not been proven safe and effective in clinical trials. Some of these methods may even be dangerous and some have life-threatening side effects. The biggest danger in most cases is that your child may lose the chance to benefit from standard treatment. Delays or interruptions in standard medical treatment may give the cancer more time to grow.

Deciding what to do

It is easy to see why people with cancer may consider alternative methods. You want to do all you can to fight the cancer. Sometimes mainstream treatments such as chemotherapy can be hard to take, or they may no longer be working.

Sometimes people suggest that their method can cure your cancer without having serious side effects, and it's normal to want to believe them. But the truth is that most non-standard methods of treatment have not been tested and proven to be effective for treating cancer.

As you consider your options, here are 3 important steps you can take:

- Talk to your doctor or nurse about any method you are thinking about using.
- Check the list of "red flags" below.
- Contact the American Cancer Society at 1-800-227-2345 to learn more about complementary and alternative methods in general and to learn more about the specific methods you are thinking about.

Red flags

You can use the questions below to spot treatments or methods to avoid. A "yes" answer to any one of these questions should raise a "red flag."

- Does the treatment promise a cure for all or most cancers?

- Are you told not to use standard medical treatment?
- Is the treatment or drug a "secret" that only certain people can give?
- Does the treatment require you to travel to another country?
- Do the promoters attack the medical or scientific community?

The decision is yours

Decisions about how to treat or manage your child's cancer are always yours to make. If you are thinking about using a complementary or alternative method, be sure to learn about the method and talk to your doctor about it. With reliable information and the support of your health care team, you may be able to safely use the methods that can help your child while avoiding those that could be harmful.

Treatment of neuroblastoma by risk group

Treatment for neuroblastoma is largely based on which risk group a child falls into.

Low risk

Children at low risk often require surgery as their only treatment. Even in cases where some neuroblastoma is left behind after surgery, the child can usually be watched carefully without further treatment because the remaining tumor will often mature or go away on its own.

Chemotherapy is typically given after surgery if less than half the tumor can be removed. A common chemotherapy regimen is a combination of carboplatin, cyclophosphamide, doxorubicin, and etoposide. But other combinations may be used.

For those few children that have symptoms from a tumor that can't safely be treated right away with surgery, a short course of chemotherapy might be given. For example, if the tumor is pressing on the spinal cord or affecting breathing, chemotherapy may be used to shrink the tumor to control the symptoms. Radiation therapy may be needed if chemotherapy doesn't shrink the tumor fast enough.

Infants with 4S disease and no symptoms can often be watched carefully with no treatment, because these cancers often mature or go away on their own.

Intermediate risk

Surgery is an important part of treatment for children at intermediate risk, but it is rarely enough on its own. Children are typically given 4 to 8 cycles (about 12 to 24 weeks) of chemotherapy before or after surgery. The chemotherapy drugs used are usually the same as for low-risk disease. Radiation therapy may be used if chemotherapy is not effective.

If chemotherapy is used after surgery, a "second look surgery" may be done to see if there is any cancer remaining and, if there is, remove it if possible. This may be followed by radiation therapy, if needed.

High risk

Children at high risk require more aggressive treatment, which often includes a combination of chemotherapy, surgery, and radiation. In many cases, high-dose chemotherapy followed by a stem cell transplant is used. Surgery and/or radiation may be part of this treatment regimen. The retinoid drug 13-cis-retinoic acid (isotretinoin) is often given for 6 months after other treatments are completed. Immunotherapy with a monoclonal antibody (ch14.18) and cytokines (immune system-activating hormones) is often given as well.

Recurrent neuroblastoma

Unfortunately, sometimes neuroblastoma can come back (known as a recurrence or relapse) after initial therapy. Treatment at this point will depend on many factors, including the initial risk group and where the cancer recurs.

For low- and intermediate-risk neuroblastomas that recur in the same area where they started, surgery with or without chemotherapy may be appropriate.

For higher-risk cancers or those that recur in distant parts of the body, treatment is usually more intense, and may include a combination of chemotherapy, surgery, and radiation therapy (such as MIBG radiotherapy). In some relapsed cases, intensive treatment with high-dose chemotherapy/radiation therapy, followed by a donor stem cell transplant, may be used. Because these cancers can be hard to treat, clinical trials of experimental treatments, such as monoclonal antibodies or new anti-cancer drugs, may be another reasonable option. (See "What's new in neuroblastoma research and treatment?")

More treatment information

For more details on treatment options -- including some that may not be addressed in this document -- the National Cancer Institute (NCI) is a good source of information.

The NCI provides treatment information via its telephone information center (1-800-4-CANCER) and its Web site (www.cancer.gov). Detailed information intended for use by cancer care professionals is also available on www.cancer.gov.

What should you ask your child's doctor about neuroblastoma?

As you deal with your child's cancer and the process of treatment, you need to have frank, open discussions with your cancer care team. You should feel free to ask any question that's on your mind, no matter how minor it might seem. Among the questions you might want to ask are:

- What is the stage (extent) of the neuroblastoma?
- Which risk group does my child's cancer fall into? What does this mean in my child's case?
- What else can you tell about the cancer based on the lab tests?
- Are there any other tests that need to be done before we discuss treatment?
- How much experience do you have treating this type of cancer?
- What treatment choices do we have?
- Does one type of treatment increase the chance of cure more than another?
- Are there any clinical trials we should consider?
- Which treatment do you recommend? Why?
- What are the possible side effects from treatment? What can be done for them?
- How long will treatment last? Will any of it need to be done in a hospital?
- How long will it take my child to recover from treatment?
- What are the chances that the cancer will recur? What would we do if this happens?
- Are there any long-term risks or complications from the disease or its treatment?
- What should I do to help my child be ready for treatment?
- What type of follow-up will my child need after treatment?
- Is there a support group for families who are coping with neuroblastoma or childhood cancer?

Along with these sample questions, be sure to write down some of your own. For instance, you might want more information about recovery times so you can plan your school or work schedules. You may also want to ask about getting a second opinion. Keep in mind, too, that doctors are not the only ones who can give you information. Other health care professionals, such as nurses and social workers, may have the answers you seek.

What happens after treatment for neuroblastoma?

Many children with neuroblastoma have a good chance of long-term survival following treatment.

After treatment for neuroblastoma, the main concerns for most families are the immediate and long-term effects of the tumor and its treatment, and concerns about possible recurrence of the tumor.

It is certainly understandable to want to put the tumor and its treatment behind you and to get back to a 'normal' life. But it's important to realize that follow-up care is a central part of this process that offers your child the best chance for recovery and long-term survival.

Follow-up exams

After treatment, the doctor will likely order follow-up tests, which may include lab tests and imaging tests (MIBG scans, PET scans, ultrasound, CT scans, and/or MRI scans) to see if there is any tumor remaining. The tests done will depend on the risk group and the size and location of the tumor.

Because there is a chance that the cancer may return after initial treatment, it is very important to keep all follow-up appointments and to report any new symptoms to your child's doctor right away. The health care team will discuss a follow-up schedule with you, including which tests should be done and how often. Doctor visits, lab tests, and imaging tests to look for signs of recurrence are done more frequently at first. If nothing abnormal is found, the time between tests can then be extended.

Keeping good medical records

As much as you may want to put the experience behind you once treatment is completed, it is also very important to keep good records of your child's medical care during this time. This can be very helpful for your child and his or her doctors later on as an adult. There are certain pieces of information you should be sure your child's doctors have. These are:

- A copy of the pathology report from any biopsies or surgeries
- If there was surgery, a copy of the operative report
- If there were hospitalizations, copies of the discharge summaries that doctors prepare when patients are sent home
- If there was chemotherapy treatment for the cancer, a list of the drugs, drug doses, and when they were given
- If there was radiation, a summary of the type and dose of radiation and when and where it was given

Long-term effects of neuroblastoma and its treatment

Both neuroblastoma itself and its treatment can sometimes result in long lasting effects.

In very rare instances and for unknown reasons, in some children with neuroblastoma the body's immune system attacks the child's normal nerve tissue. This can lead to problems such as learning disabilities, delays in muscle development, language problems, and behavioral problems. Children whose tumors arise in the neck or chest and who have problems with the eyes or with muscle twitches may need further treatment with corticosteroids or other hormones to suppress their immune system.

Because of major advances in treatment, more children treated for cancer are now surviving into adulthood. With childhood cancer survivors living longer, their health as adults has come more into focus in recent years. Researchers have learned that childhood cancer treatment may affect that child's health later in life.

Just as the treatment of childhood cancer requires a very specialized approach, so does aftercare and monitoring for late effects of treatment. Careful follow-up after cancer treatment allows for early recognition of and attention to the after-effects of treatment.

Childhood cancer survivors are at risk, to some degree, for several possible late effects of their cancer treatment. This risk depends on a number of factors, such as the type of cancer, the specific cancer treatments they received, doses of cancer treatment, and age when receiving the cancer treatment. Late effects of cancer treatment can include:

- Heart or lung problems (due to certain chemotherapy drugs or radiation therapy)
- Slowed or decreased growth and development (in the bones or overall)
- Changes in sexual development and ability to have children
- Changes in intellectual function with learning problems
- Development of second cancers

To help increase awareness of late effects and improve follow-up care of childhood cancer survivors throughout their lives, the Children's Oncology Group (COG) has developed long-term follow-up guidelines for survivors of childhood cancers. These guidelines, written for doctors and other health care professionals, describe in detail the suggested long-term follow-up care based on the treatments the child has received. It is very important to discuss possible long-term complications with your child's health care team, and to make sure there is a plan in place to watch for these problems and treat them, if needed. To learn more, ask your child's doctors about the COG survivor guidelines, and see our document, *Childhood Cancer: Late Effects of Cancer Treatment*.

What's new in neuroblastoma research and treatment?

Important research into neuroblastoma is under way right now in many university hospitals, medical centers, and other institutions around the world. Each year, scientists find out more about what causes the disease and how to improve treatment.

Classifying neuroblastomas

Researchers now have better tools to look for changes in the genes of neuroblastoma cells. They have made a great deal of progress in recent years in figuring out which neuroblastomas are likely to be cured with standard treatment, and which will need more aggressive treatment.

For example, using newer lab tests, researchers have found that certain DNA changes on the short arm of chromosome 6 (6p22) are more likely to be seen in neuroblastomas that grow more aggressively.

In the near future, doctors may be able to use these types of test results to aid in choosing the best treatments.

Treatment

Survival rates from childhood cancers have gotten better as doctors have found ways to improve on current treatments. Researchers continue to look for better ways to treat neuroblastoma.

Chemotherapy

Doctors continue to search for the best combinations of chemotherapy drugs to treat neuroblastoma.

Several chemotherapy drugs that are already used to treat other cancers, such as topotecan, irinotecan, and temozolomide, are now being studied for use against neuroblastoma. Some newer drugs that work in different ways from standard chemotherapy drugs are being studied against neuroblastoma as well. Examples include bortezomib, nifurtimox, and lestaurtinib.

Stem cell transplants

Doctors are also trying to improve the success rate with high-dose chemotherapy and stem cell transplants, using different combinations of chemotherapy, radiation therapy, retinoids, and other treatments. Some clinical trials are studying the use of more than one stem cell transplant in the same patient (known as a *tandem transplant*).

Retinoids

Retinoids such as 13-cis-retinoic acid (isotretinoin) have shown promise in reducing the risk of recurrence after treatment. Newer, potentially more effective retinoids, such as fenretinide, are now being studied in clinical trials.

Newer forms of treatment

Knowledge about what makes neuroblastoma cells different from normal cells may lead to new approaches to treating this disease. Several newer forms of therapy, which target neuroblastoma cells more specifically than standard treatments, are now being studied in clinical trials.

For example, doctors are now studying medicines that specifically target the machinery of neuroblastoma cells, such as inhibitors of the ALK pathway or aurora A pathway.

Some monoclonal antibodies that target substances on neuroblastoma cells are used routinely for children with high-risk neuroblastoma, to help immune system cells find and destroy the cancer cells. Clinical trials are now in under way to test the effectiveness of attaching radioactive particles or chemotherapy drugs these antibodies. By zeroing in on their targets, these antibodies may be able to deliver chemotherapy or radiation to the neuroblastoma cells with minimal damage to normal cells.

Forms of gene therapy and cancer vaccines are also being studied for use against neuroblastoma, although these treatments are still in the earliest stages of clinical trials.

Additional resources

More information from your American Cancer Society

The following related information may also be helpful to you. These materials may be ordered from our toll-free number, 1-800-227-2345.

After Diagnosis: a Guide for Patients and Families

Childhood Cancer: Late Effects of Cancer Treatment

Children Diagnosed With Cancer: Dealing With Diagnosis (also available in Spanish)

Children Diagnosed With Cancer: Financial and Insurance Issues

Children Diagnosed With Cancer: Returning to School

Children Diagnosed With Cancer: Understanding the Health Care System (also available in Spanish)

Family and Medical Leave Act (FMLA)

Nutrition for Children With Cancer (also available in Spanish)

Psychosocial Issues of Children with Cancer (also available in Spanish)

Surgery (also available in Spanish)

Understanding Chemotherapy: A Guide for Patients and Families (also available in Spanish)

Understanding Radiation Therapy: A Guide for Patients and Families (also available in Spanish)

What Happened to You, Happened to Me (children's booklet)

When Your Brother or Sister Has Cancer (children's booklet)

When Your Child's Treatment Ends: a Guide for Families

The following books are available from the American Cancer Society. Call us at 1-800-227-2345 to ask about costs or to place your order.

Because Someone I Love Has Cancer

Cancer in the Family

Caregiving: a Step-By-Step Resource for Caring for the Person with Cancer at Home

Jacob has Cancer: His Friends Want to Help (coloring book for a child with a friend who has cancer)

National organizations and Web sites*

In addition to the American Cancer Society, other sources of patient information and support include*:

Cancer Kids

Web site: www.cancerkids.com

Candlelighters Childhood Cancer Foundation

Toll-free number: 1-800-366-2223 (1-800-366-CCCF)

Web site: www.candlelighters.org

CureSearch (National Childhood Cancer Foundation and Children's Oncology Group)

Toll-free number: 1-800-458-6223

Web site: www.curesearch.org

National Cancer Institute

Toll-free number: 1-800-422-6237 (1-800-4-CANCER)

Web site: www.cancer.gov

National Children's Cancer Society, Inc.

Toll-free number: 1-800-532-6459 (1-800-5-FAMILY)

Web site: www.children-cancer.org

Starlight Children's Foundation

Toll-free number: 1-800-315-2580

Web site: www.starlight.org

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

Other publications***For adults**

100 Questions & Answers About Your Child's Cancer, by William L. Carroll and Jessica Reisman. Jones and Bartlett Publishers, 2004.

Cancer & Self-Help: Bridging the Troubled Waters of Childhood Illness, by Mark A. Chester and Barbara K. Chesney. University of Wisconsin Press, 1995.

Care for Children and Adolescents with Cancer: Questions and Answers. National Cancer Institute. Available at: www.cancer.gov/cancertopics/factsheet/NCI/children-adolescents or call 1-800-332-8615.

Childhood Cancer: A Parent's Guide to Solid Tumor Cancers, by Honna Janes-Hodder and Nancy Keene. O'Reilly and Associates, 1999.

Childhood Cancer: A Handbook from St Jude Children's Research Hospital, by Grant Steen and Joseph Mirro (editors). Perseus Publishing, 2000.

Childhood Cancer Survivors: A Practical Guide to Your Future, by Nancy Keene, Wendy Hobbie, and Kathy Ruccione. O'Reilly and Associates, 2000.

Children with Cancer: A Comprehensive Reference Guide for Parents (2nd Edition), by Jeanne Munn Bracken and Pruden Pruden. Oxford University Press, 2005.

Educating the Child With Cancer: A Guide for Parents and Teachers, edited by Nancy Keene. Candlelighters Childhood Cancer Foundation, 2003.

Living with Childhood Cancer: A Practical Guide to Help Families Cope, by Leigh A. Woznick and Carol D. Goodheart. American Psychological Association, 2002.

Surviving Childhood Cancer: A Guide for Families, by Margo Joan Fromer. New Harbinger Publications, 1998.

When Bad Things Happen to Good People, by Harold Kushner. G.K. Hall, 1982.

When Someone You Love Is Being Treated for Cancer. National Cancer Institute. Available at: www.cancer.gov/cancertopics/when-someone-you-love-is-treated, or call 1-800-332-8615.

Young People with Cancer: A Handbook for Parents. National Cancer Institute, 2003. Available at: www.cancer.gov/cancertopics/youngpeople, or call 1-800-332-8615.

Your Child in the Hospital: A Practical Guide for Parents (2nd Edition), by Nancy Keene. O'Reilly & Associates. 1999. (Also available in Spanish.)

Books for teens and children

Although these books are intended for children, younger kids are helped more when an adult reads with and helps the child reflect about what different parts of the book mean to the child.

The Amazing Hannah, Look at Everything I Can Do! by Amy Klett. Candlelighters Childhood Cancer Foundation, 2002. For ages 1 to 6. (Also available in Spanish.)

Chemo, Crazyness and Comfort: My Book about Childhood Cancer by Nancy Keene. Candlelighters Childhood Cancer Foundation, 2002. Can be ordered from www.candlelighters.org. For ages 6 to 12.

Childhood Cancer Survivors: A Practical Guide to Your Future (2nd Edition), by Kathy Ruccione, Nancy Keene, and Wendy Hobbie. Patient Centered Guides, 2006. For older teens.

Going to the Hospital, by Fred Rogers. Paperstar Book, 1997. For children 4 to 8.

Life Isn't Always A Day at the Beach: A Book for All Children Whose Lives Are Affected by Cancer by Pam Ganz. High-Five Publishing, 1996. Workbook for ages 6 to 10.

Little Tree: A Story for Children with Serious Medical Problems, by Joyce C. Mills. Magination Press, 2003. For ages 4 to 8.

Living Well With My Serious Illness, by Marge Heegaard. Fairview Press, 2003. Ages 8 to 12.

Me and My Marrow, by Karen Crowe. Published by Fujsawa Healthcare, 1999. You can buy it as a book, but it's also available online at: www.meandmymarow.com/book/toc_ie.htm. For teens.

My Book for Kids with Cansur [sic], by Jason Gaes. Viking Penguin, 1998. For ages 4 to 8.

Oncology, Stupology...I Want to go Home! by Marilyn K. Hershey. Butterfly Press, 1999. For ages 8 to 12. (Also available in Spanish.)

What About Me? When Brothers and Sisters Get Sick, by Allan Peterkin and Frances Middendorf. Magination Press, 1992. For brothers and sisters (ages 4 to 8) of a child with cancer.

When Someone Has a Very Serious Illness: Children can learn to cope with loss and change, by Marge Heegaard. Woodland Press, 1991. For ages 6 to 12.

Why, Charlie Brown, Why? A Story About What Happens When a Friend is Very Ill, by Charles M. Schultz. Ballantine Publishing Group, 1990. For ages 6 to 12.

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

The American Cancer Society is happy to address almost any cancer-related topic. If you have any more questions, please call us at 1-800-227-2345 at any time, 24 hours a day.

References

American Cancer Society. *Cancer Facts & Figures 2009*. Atlanta, Ga: American Cancer Society; 2009.

Dome JS, Rodriguez-Galindo C, Spunt SL, Santana VM. Pediatric solid tumors. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, eds. *Abeloff's Clinical Oncology*. 4th ed. Philadelphia, Pa: Elsevier; 2008:2091-2096.

Goh YI, Bollano E, Einarson TR, Koren G. Prenatal multivitamin supplementation and rates of pediatric cancers: a meta-analysis. *Clin Pharmacol Ther*. 2007;81:685-691.

Goodman MT, Gurney JG, Smith MA, Olshan AF. Sympathetic nervous system tumors. In: Ries LAG, Smith MA, Gurney JG, et al, eds. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995, National Cancer Institute, SEER Program*. NIH Pub. No. 99-4649. Bethesda, MD, 1999. Accessed at <http://seer.cancer.gov/publications/childhood/sympathetic.pdf> on October 8, 2009.

Kushner BH. Neuroblastoma: a disease requiring a multitude of imaging studies. *J Nucl Med*. 2004;45:1172-1188.

Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. *Lancet*. 2007;369:2106-2120.

Maris JM, Mosse YP, Bradfield JP, et al. Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. *N Engl J Med*. 2008;358:2585-2593.

Mosse YP, Laudenslager M, Longo L, et al. Identification of ALK as a major familial neuroblastoma predisposition gene. *Nature*. 2008;455:930-935.

National Cancer Institute. Physician Data Query (PDQ). Neuroblastoma Treatment. 2008. Accessed at www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/healthprofessional on October 8, 2009.

Russell HV, Pappo AS, Nuchtern JG, et al. Solid tumors of childhood. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 8th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2008: 2044-2050.

Yamamoto K, Ohta S, Ito E, et al. Marginal decrease in mortality and marked increase in incidence as a result of neuroblastoma screening at 6 months of age: cohort study in seven prefectures in Japan. *J Clin Oncol*. 2002;20:1209-1214.

Yu AL, Gilman AL, Ozkaynak MF, et al. A phase III randomized trial of the chimeric anti-GD2 antibody ch14.18 with GM-CSF and IL2 as immunotherapy following dose intensive chemotherapy for high-risk neuroblastoma: Children's Oncology Group (COG) study ANBL0032. *J Clin Oncol*. 2009;27:15s (suppl; abstr 10067z).

Last Medical Review: 11/23/2009

Last Revised: 11/23/2009

2009 Copyright American Cancer Society

For additional assistance please contact your American Cancer Society
1 · 800 · ACS-2345 or www.cancer.org