



Neuroblastoma

What is cancer?

The body is made up of trillions of living cells. Normal body cells grow, divide to make new cells, and die in an orderly way. 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. In most cases the cancer cells form a tumor. 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 often the DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in our environment. In adults, sometimes the cause of the DNA damage is something obvious, like cigarette smoking. But often no clear cause is found.

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.

Different types of cancer can behave very differently. 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 often different from the types that develop in adults. Childhood cancers are often the result of DNA changes in cells that take place very early in life, sometimes even before birth. Unlike many cancers in adults, childhood cancers are not strongly linked to lifestyle or environmental risk factors.

There are exceptions, but childhood cancers tend to respond better to treatments such as chemotherapy. Children's bodies also tend to tolerate chemotherapy better than adults' bodies do. But cancer treatments such as chemotherapy and radiation therapy can have some long-term side effects, so children who survive their cancer need careful attention for the rest of their lives.

Since the 1960s, most children and teens with cancer have been treated at specialized centers designed for them. Being treated in these centers offers 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 cancer and their families. This team usually includes pediatric oncologists, surgeons, radiation oncologists, pathologists, 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 experts in this area.

Any time a child is diagnosed with cancer, it affects every family member and nearly every aspect of the family's life. You can read more about coping with all these changes in our documents about children with cancer. See the "Additional resources" section for a list of titles.

What is neuroblastoma?

Neuroblastoma is a type of cancer that starts in certain very early forms of 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 most often in infants and young children. It is rarely found in children older than 10 years.

To understand neuroblastoma, it helps to know about 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 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 hormones (such as adrenaline [epinephrine]) that help control heart rate, blood pressure, blood sugar, and how the body reacts to stress.

The main cells that make up the nervous system are called *nerve cells* or *neurons*. These cells interact 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, “Signs and symptoms of neuroblastoma”).

Neuroblastomas

Neuroblastomas are cancers that start in early nerve cells (called *neuroblasts*) of the sympathetic nervous system, 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 4 begin in sympathetic nerve ganglia in the abdomen. Most of the rest start in sympathetic ganglia near the spine in the chest or neck, or in the pelvis.

Rarely, a neuroblastoma has spread so widely by the time it is found that doctors can't tell exactly where it started.

There is a wide range in how neuroblastomas behave. Some grow and spread quickly, while others grow slowly. Sometimes, in very young children, the cancer cells die for no reason

and the tumor goes away on its own. In other cases, the cells sometimes mature on their own into normal ganglion cells and stop dividing. This makes the tumor a ganglioneuroma (see below).

Other autonomic nervous system tumors in children

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

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

Ganglioneuroblastoma is a tumor that has both malignant and benign parts. It contains neuroblasts (immature nerve cells) that can grow and spread abnormally, similar to neuroblastoma, 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 sure they don't have areas of malignant cells (which would make the tumor a ganglioneuroblastoma). If the final diagnosis is ganglioneuroma, no other treatment is needed. If it's found to be a ganglioneuroblastoma, it's treated the same as a neuroblastoma.

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 6% of all cancers in children. There are about 700 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 very rare in people over the age of 10 years.

In about 2 of 3 cases, the disease has already spread to the lymph nodes or to other parts of the body when it is diagnosed.

Statistics related to survival are discussed in the section "Survival rates for neuroblastoma based on risk groups."

What are the risk factors for neuroblastoma?

A risk factor is anything that affects your chance of getting a disease such as cancer. Different cancers have different risk factors.

Lifestyle-related risk factors such as body weight, physical activity, diet, and tobacco use play a major role in many adult cancers. But these factors usually take many years to

influence cancer risk, and they are not thought to play much of a role in childhood cancers, including neuroblastomas.

No environmental factors (such as exposures during the mother's pregnancy or in early childhood) are known to increase the chance of getting neuroblastoma.

Age

Neuroblastoma is most common in very young children, but it is still rare even in this age group. It is very rare in people over the age of 10 years.

Heredity

In about 1% to 2% of all neuroblastomas, children inherit an increased risk of developing neuroblastoma from a parent. But most 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 members who had neuroblastoma as infants. The average age at diagnosis of familial cases is younger than the age for *sporadic* (not inherited) cases.

Children with familial neuroblastoma sometimes develop 2 or more of these cancers in different organs (for example, in both adrenal glands or in more than one sympathetic ganglion). It's important to distinguish neuroblastomas that start in more than one organ 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. This might mean that family members should consider genetic counseling and testing (see our document *Genetic Testing: What You Need to Know*). Both familial and sporadic neuroblastoma can spread to other organs.

Do we know what causes neuroblastoma?

The causes of most neuroblastomas are not known. But researchers have found important differences between neuroblastoma cells and the normal neuroblasts (early forms of nerve cells) from which they develop. They have also found differences between neuroblastomas that are likely to respond to treatment and those that have a poor prognosis (outlook). These differences (known as *prognostic markers*) are sometimes helpful in choosing the best treatment.

Both nerve cells and cells of the medulla (center) of the adrenal gland develop from neuroblasts in the fetus. 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 matured completely 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 die off and do not form neuroblastomas. Sometimes, neuroblasts remaining in very young infants continue to grow and then form tumors. Some can 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 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.

The failure of some neuroblasts to mature and to stop growing is due to abnormal DNA inside the cells. DNA is the chemical in each of our cells that makes up our *genes* – the instructions for how our cells function. The DNA inside our cells is in long string-like structures called *chromosomes*.

Some genes contain instructions for controlling when our cells grow, divide into new cells, and die. Certain genes that help cells grow, divide, or stay alive 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 that turn on oncogenes or turn off tumor suppressor genes. These gene changes can be inherited from a parent (as is sometimes the case with childhood cancers), or they may happen during a person's lifetime as cells in the body divide to make new cells.

In most cases, neuroblastoma cells have chromosome changes (such as having too many or too few chromosomes or missing part of a chromosome) that are likely to affect certain genes. Scientists are still trying to determine which genes are affected by these chromosome changes, as well as how these changes affect the growth of neuroblastoma cells.

In rare cases, neuroblastoma seems to occur because of gene changes inherited from a parent. Inherited changes in the *ALK* oncogene seem to account for most cases of hereditary neuroblastoma. A small number of inherited neuroblastomas are caused by changes in *PHOX2B*, a gene that normally helps nerve cells mature.

Still, most neuroblastomas are not caused by inherited DNA changes. They are the result of gene changes that happen early in the child's development, often before birth. These changes are found only in the child's cancer cells, so they will not be passed on to his or her children. For example, about 10% to 15% of sporadic (non-inherited) neuroblastomas have changes in the *ALK* gene. But in many neuroblastomas the exact genes affected are not known.

Some gene changes seem to affect how quickly a neuroblastoma is likely to grow. For example, neuroblastoma cells sometimes have extra copies of an oncogene called *MYCN*, which is often a sign that the tumor will grow quickly and be harder to treat. On the other hand, the *NTRK1* gene (which makes the TrkA protein) is often overactive in the cells of neuroblastomas that have a better outlook. Researchers recently found that neuroblastoma

cells in older children are more likely to have changes in the *ATRX* tumor suppressor gene. Tumors with this gene change tend to grow more slowly, but they are also harder to cure. This may help explain why younger children with neuroblastoma tend to do better long term than children who are older when they are diagnosed.

Researchers have found some of the gene changes that may lead to neuroblastoma, but it's still not clear what causes these changes. Some gene changes may be inherited. Some might have unknown outside causes, but others may just be random events that sometimes happen inside a cell, without having an outside cause. There are no known lifestyle-related or environmental causes of neuroblastomas at this time, so it's important to remember that there is nothing these children or their parents could have done to prevent these cancers.

Can neuroblastoma be prevented?

The risk of many adult cancers can be reduced with certain lifestyle changes (such as staying at a healthy weight or quitting smoking), but at this time there are no known ways to prevent most cancers in children.

The only known risk factors for neuroblastoma (age and heredity) cannot be changed. There are no known lifestyle-related or environmental causes of neuroblastomas at this time.

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 find these tumors earlier and lead to better treatment results. Screening is testing for a disease, such as cancer, in people who don't have any 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 many tumors that wouldn't have normally been diagnosed. But most of these tumors were of a type that probably would have gone away or matured into benign (non-cancerous) tumors on their own. These tumors probably would never have caused any problems. The screening didn't lower the number of cancers found at advanced stages or save lives.

What's more, finding tumors that would never cause serious problems may needlessly frighten parents and can lead to unnecessary tests and surgery in children whose tumors would have gone away or matured on their own if left alone.

For these reasons, most experts do not recommend screening for neuroblastoma in infants who are not at increased 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 tests may lead to more accurate prenatal (before birth) testing for this disease.

Neuroblastoma is sometimes found incidentally in young children without any symptoms during tests done to find other childhood diseases. These children will usually have a good outcome, and some may not even need treatment.

But most often, neuroblastoma is first detected because of signs or symptoms the child is having.

Signs and symptoms of neuroblastoma

The signs and symptoms of neuroblastoma vary widely, depending on the size of the tumor, where it is, how far it has spread, and if the tumor cells secrete hormones.

Many of the signs and symptoms below are more likely to be caused by something other than neuroblastoma. Still, if your child has any of these symptoms, check with your doctor so the cause can be found and treated, if needed.

Signs or symptoms caused by the main tumor

Tumors in the abdomen (belly) or pelvis: One of the most common signs of a neuroblastoma is a large lump or swelling in the child's abdomen. The child might not want to eat (which can lead to weight loss). If the child is old enough, he or she may complain of feeling full or having belly pain. But the lump itself is usually not painful to the touch.

Sometimes, a tumor in the abdomen or pelvis can affect other parts of the body. For example, tumors that press against or grow into the blood and lymph vessels in the abdomen or pelvis can stop fluids from getting back to the heart. This can sometimes lead to swelling in the legs and, in boys, the scrotum.

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

Tumors in the chest or neck: Tumors in the neck can often be seen or felt as a hard, painless lump.

If the tumor is in the chest, it might press on the superior vena cava (the large vein in the chest that returns blood from the head and neck to the heart). This can cause swelling in the face, neck, arms, and upper chest (sometimes with a bluish-red skin color). It can also cause headaches, dizziness, and a change in consciousness if it affects the brain. The tumor might also press on the throat or windpipe, which can cause coughing and trouble breathing or swallowing.

Neuroblastomas that press on certain nerves in the chest or neck can sometimes cause other symptoms, such as a drooping eyelid and a small pupil (the black area in the center of the eye). Pressure on other nerves near the spine might affect the child's ability to feel or move their arms or legs.

Signs or symptoms caused by cancer spread to other parts of the body

About 2 out of 3 neuroblastomas have already spread to the lymph nodes or other parts of the body by the time they are found.

Lymph nodes are bean-sized collections of immune cells found throughout the body. Cancer that has spread to the lymph nodes can cause them to swell. These nodes can sometimes be felt as lumps under the skin, especially in the neck, above the collarbone, under the arm, or in the groin. Enlarged lymph nodes in children are much more likely to be a sign of infection than cancer, but they should be checked by a doctor.

Neuroblastoma often spreads to bones. A child who can talk may complain of bone pain. The pain may be so bad that the child limps or refuses to walk. If it spreads to the bones in the spine, tumors can press on the spinal cord and cause weakness, numbness, or paralysis in the arms or legs. Spread to the bones around the eyes is common and can lead to bruising around the eyes or cause an eyeball to stick out slightly. The cancer can also spread to other bones in the skull, causing bumps under the scalp.

If the cancer spreads to the bone marrow (the inner part of certain bones that makes blood cells), 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 excess bruising or bleeding from small cuts or scrapes.

Rarely, large tumors can start to break down, leading to a loss of clotting factors in the blood. This can result in a high risk of serious bleeding, which 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). Blue or purple bumps that look like small blueberries may be a sign of spread to the skin. The liver can become very large and can be felt as a mass on the right side of the belly. Sometimes it can grow large enough to push up on the lungs, which can make it hard for the child to breathe. Despite the fact that the cancer is already widespread when it is found, stage 4S neuroblastoma is very treatable, and often

shrinks or goes away on its own. Almost all children with this form of neuroblastoma can be cured.

Signs or symptoms caused by hormones from the tumor

Neuroblastomas sometimes release hormones that can cause problems with tissues and organs in other parts of the body, even though the cancer has not spread to those tissues or organs. These problems are called *paraneoplastic syndromes*.

Symptoms of paraneoplastic syndromes can include:

- Constant diarrhea
- Fever
- High blood pressure (causing irritability)
- Rapid heartbeat
- Reddening (flushing) of the skin
- Sweating

An uncommon set of symptoms is called the *opsoclonus-myoclonus-ataxia syndrome* or “dancing eyes, dancing feet.” 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 reasons that are not clear, neuroblastomas that cause this syndrome tend to be less life-threatening than other forms of the disease.

How is neuroblastoma diagnosed?

Neuroblastomas are usually found when a child is brought to the doctor because of signs or symptoms he or she is having. If a tumor is suspected, tests will be needed to confirm the diagnosis.

Medical history and physical exam

If your child has signs or symptoms that might be caused by a neuroblastoma (or another tumor), the doctor will want to get a complete medical history to learn more about the symptoms. The doctor might also ask if there's a family history of any type of cancer.

The doctor will examine your child for possible signs of a neuroblastoma and other health problems. For example, the doctor may be able to see or feel an abnormal mass or swelling in the body or may find a child has lumps or bumps under the skin or high blood pressure.

Neuroblastomas can sometimes grow close to the spinal cord, which can affect movement and strength in the child's arms and legs, so the doctor will pay close attention to these.

Some signs that could be caused by neuroblastoma, such as fever and enlarged lymph nodes, are much more likely to be caused by an infection, so the doctor might look for other signs of infection at first.

If the history and exam suggest a child might have a neuroblastoma (or another type of tumor), other tests will be done. These could 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 diseases, such as infections, or even other types of cancer.

Blood and urine catecholamine tests

Sympathetic nerve cells normally release hormones called *catecholamines*, such as epinephrine (adrenaline) and norepinephrine, which enter the blood. Eventually the body breaks these down into metabolites (smaller pieces), which then pass out of the body in the urine.

Neuroblastoma cells can also make these hormones. 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

If neuroblastoma is suspected or has been found, your child's doctor will probably 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 can be done for a number of reasons, including:

- To help find out if a suspicious area might be cancerous
- To learn how far cancer has spread

- To help determine if treatment has been effective

Most children who have or might have neuroblastoma will have one or more of these tests.

Children with neuroblastoma are often very young, so it can be hard to do some of these tests.

Ultrasound

Ultrasound is often one of the first tests done in small children if a tumor is suspected, because it is fairly quick and easy, it does not use radiation, and it can often give the doctor a good view inside the body, especially in the abdomen (belly).

This test uses sound waves to create pictures of organs or masses inside the body. For this test, your child lies on a table (or sits on your lap) while a small wand called a *transducer* is placed on the skin over the belly (which is first lubricated with gel). The wand gives off sound waves and picks up the echoes as they bounce off organs. The echoes are converted by a computer into a black and white image on a screen. The test is not usually painful, but it might cause some discomfort if the transducer is pressed down hard on the belly.

Ultrasound is used most often to look for tumors in the abdomen. (It's not used to look in the chest because the ribs block the sound waves.) Ultrasound can detect if kidneys have become swollen because the outflow of urine has been blocked by enlarged lymph nodes or a mass. It can also be used to help guide a biopsy needle into a suspected tumor to get a sample for testing. It is particularly useful in checking to see if tumors in the abdomen are shrinking.

The pictures from ultrasound aren't as detailed as those from some other tests, so even if a tumor is found, CT or MRI scans (described below) might still be needed.

X-rays

The doctor may order an x-ray of the chest or another part of the body as an early test if a child is having symptoms but it's not clear what might be causing them. But the images might not always be detailed enough to spot tumors.

If neuroblastoma has already been diagnosed, x-rays can be useful to see if cancer has spread to certain bones. An x-ray of the head may be done to see if cancer has spread to the skull bones. An MIBG scan or 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 these scans 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 are often used 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 showing 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.

Before the test, your child may be asked to drink a contrast solution and/or get an IV (intravenous) injection of a contrast dye. 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. A CT scanner has been described as a large donut, with a narrow table in the middle opening. Your child will need to lie still on the table while the scans are being done. During the test, the table slides in and out of the scanner. Younger children may be sedated (given medicine to make them sleepy) before the test to reduce movement and help make sure the pictures come out well.

CT-guided needle biopsy: CT scans can also be used to help guide a biopsy needle into a tumor. For this procedure, the child lies 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 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. These scans are very helpful in looking at the brain and spinal cord. They may be slightly better than CT scans for seeing the extent of a neuroblastoma tumor, especially around the spine, but this test can be harder to do in small children.

MRI scans use radio waves and strong magnets to create the images instead of x-rays, so there is no radiation. A contrast material called *gadolinium* may be injected into a vein before the scan to better see details, but this is needed less often than with a CT scan. It usually does not cause allergic reactions, but it can cause other problems in children with kidney disease, so doctors are careful when they use it.

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. 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. The MRI machine also makes loud buzzing and clicking noises that may be disturbing. Younger children are often given medicine to help keep them calm or even asleep during the test.

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 hormone made by sympathetic nerve cells. It is injected into a vein and travels through the blood, 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 helps doctors tell where the neuroblastoma is and whether it has spread to the bones and/or other parts of the body.

This test is preferred by many doctors as a standard test in 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).

Positron emission tomography (PET) scan

For a PET scan, a radioactive substance (usually a type of sugar related to glucose, known as *FDG*) is injected into the blood. The amount of radioactivity used is very low and will pass out of the body within a day or so. Because cancer cells in the body are growing quickly, they absorb large amounts of the radioactive sugar. After about an hour, your child will be moved onto a table in the PET scanner. He or she will lie on the table for about 30 minutes while a special camera creates a picture of areas of radioactivity in the body. Younger children may be given medicine to help keep them calm or even asleep during the test. The picture from a PET scan is not as detailed as a CT or MRI scan, but it can provide helpful information about the whole body.

Some newer machines can do a PET and CT scan at the same time (PET/CT scan). This lets the doctor compare areas of higher radioactivity on the PET scan with the more detailed appearance of that area on the CT scan.

Bone scan

A bone scan can help show if a cancer has spread to the bones, and can provide a picture of the entire skeleton at once. Neuroblastoma often causes bone damage, which a bone scan can find. This test used to be done routinely, but in some centers it has been replaced by use of MIBG or PET scans.

For this test, a small amount of low-level radioactive material (technetium-99) is injected into a vein. (The amount of radioactivity used is very low and will pass out of the body within a day or so.) The substance settles in areas of damaged bone throughout the 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. Younger children may be given medicine to help keep them calm or even asleep during the test.

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

Biopsies

Exams and tests might strongly suggest a child has neuroblastoma, but a biopsy (removing some of the tumor for viewing under a microscope and other lab testing) is often done to be sure.

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 or surgical) biopsy:** This type of biopsy is done by removing a piece of the tumor through an incision (cut) in the skin. For tumors deep in the body this may be done laparoscopically using long, thin surgical tools inserted through small cuts in the skin.
- **Needle (closed) biopsy:** For this type of biopsy, a thin, hollow needle is placed through the skin and into the tumor to remove a small sample. If the tumor is deep within the body, CT scans or ultrasound can be used to help guide the needle into the tumor.

The biopsy samples are sent to a lab, where they are viewed under a microscope by a pathologist (a doctor with special training in identifying cancer cells). Some neuroblastomas are easily recognized when looked at by experienced doctors. But some may be hard to tell apart from other types of children’s cancers. In these cases, special lab tests must be done to show the tumor is a neuroblastoma.

Other 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 (without getting a biopsy of the main tumor). If neuroblastoma has already been diagnosed by a biopsy done elsewhere in the body, bone marrow tests are 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.

Even when the area is numbed with local anesthetic, these tests can be painful, so in most cases the child is also given other medicines to reduce pain or even be asleep during the procedure.

For a bone marrow *aspiration*, a thin, hollow needle is inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow.

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 pushed down into the bone. Once the biopsy is done, pressure is applied to the site to help stop any bleeding.

Samples from the bone marrow are sent to a lab, where they are looked at and tested for the presence of cancer cells. You can read more about testing tissue samples in our document *Testing Biopsy and Cytology Specimens for Cancer*.

How is neuroblastoma staged?

The stage of a cancer describes how far it has spread. Your child's treatment and prognosis (outlook) depend, to a large extent, on the cancer's stage.

The stage of the neuroblastoma is based on results of physical exams, imaging tests, and biopsies of the main tumor and other tissues (which were described in the section, "How is neuroblastoma diagnosed?"). The results of surgery are sometimes used in staging as well.

For neuroblastoma, several other factors also affect prognosis, including a child's age and certain tests of blood and tumor specimens. These prognostic factors are not used to determine the stage of the cancer, but they are used along with the stage to determine which risk group a child falls into, which in turn affects treatment options. These prognostic factors and risk groups are also described below and in the "Risk groups" section.

The stages and risk groups for neuroblastoma are complex and can be confusing. If you are unsure about what these mean for your child, ask your child's doctor to explain them to you in a way you can understand.

International Neuroblastoma Staging System

A staging system is a standard way for the cancer care team to sum up the extent of the cancer. Since the mid-1990s, most cancer centers have used the International Neuroblastoma Staging System (INSS) to stage neuroblastoma. This system takes into account the results of surgery to remove the tumor. 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 has been removed completely by surgery (although looking at the

tumor's edges under the microscope after surgery may show some cancer cells). Lymph nodes outside the tumor are free of cancer (although nodes enclosed within the tumor may contain neuroblastoma cells).

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 could be removed by surgery. Lymph nodes outside the tumor are free of cancer (although nodes enclosed within the tumor may contain neuroblastoma cells).

Stage 2B: The cancer is on one side of the body, and may or may not have been removed completely 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 removed completely 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 is growing toward both sides (either directly or by spreading to nearby lymph nodes) and cannot be removed completely 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 might 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 are cancerous, and imaging tests such as an MIBG scan do not show that the cancer has spread to the bones or the bone marrow.

Recurrent: While not formally part of the staging system, this term is used to describe cancer that has come back (recurred) after it has been treated. The cancer might come back in the area where it first started or in another part of the body.

International Neuroblastoma Risk Group Staging System

A risk-group staging system now coming into use is known as the International Neuroblastoma Risk Group Staging System (INRGSS). It is similar to the INSS, but it does not use the results of surgery to help define the stage. This lets doctors determine a stage before surgery, based on the results of imaging tests (usually a CT or MRI scan, and an MIBG scan), as well as exams and biopsies. The stage can then be used to help predict how resectable the tumor is – that is, how much of it can be removed with surgery.

The INRGSS uses image-defined risk factors (IDRFs), which are factors seen on imaging tests that might mean the tumor will be harder to remove. This includes things like the tumor growing into a nearby vital organ or growing around important blood vessels.

The INRGSS divides neuroblastomas into 4 stages:

L1: A tumor that has not spread from where it started and has not grown into vital structures as defined by the list of IDRFs. It is confined to one body compartment, such as the neck, chest, or abdomen.

L2: A tumor that has not spread far from where it started (for example, it may have grown from the left side of the abdomen into the left side of the chest), but that has at least one IDRF.

M: A tumor that has spread (metastasized) to a distant part of the body (except tumors that are stage MS).

MS: Metastatic disease in children younger than 18 months with cancer spread only to skin, liver, and/or bone marrow. No more than 10% of marrow cells are cancerous, and an MIBG scan does not show spread to the bones and/or the bone marrow.

Prognostic markers

Prognostic markers are 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 said to have an *unfavorable histology*.

DNA ploidy

The amount of DNA in each cell, known as *ploidy* or the *DNA index*, can be measured using special lab tests, such as flow cytometry or imaging cytometry. Neuroblastoma cells with about the same amount of DNA as normal cells (a DNA index of 1) are classified as *diploid*. Cells with increased amounts of DNA (a DNA index higher than 1) 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. Ploidy is not as useful a factor in older children.

***MYCN* gene amplifications**

MYCN is an oncogene, a gene that helps regulate cell growth. Changes in oncogenes can make cells grow and divide too quickly, as with cancer cells.

Neuroblastomas with too many copies (amplification) of the *MYCN* oncogene tend to grow quickly 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 at this time, but they are still important and may influence the treatment of a child with neuroblastoma.

Chromosome changes: Tumor cells that are missing certain parts of chromosomes 1 or 11 (known as *1p deletions* or *11q deletions*) may predict a less favorable prognosis. It is thought that these chromosome parts, which are missing in many neuroblastomas, 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 mature.

Neuroblastomas that have more of certain 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 some 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 important in treating neuroblastoma (see the section, “What’s new in neuroblastoma research and treatment?”).

Neuroblastoma risk groups

Children’s Oncology Group (COG) risk groups

The Children’s Oncology Group (COG) uses the major prognostic factors discussed in the previous section, combined with the INSS stage of the disease, to place children into 3 different risk groups: low, intermediate, and high. These risk groups are used to help predict how likely it is that a child can be cured. For example, a child in a low-risk group can often be cured with limited treatment, such as surgery alone. With children in higher risk groups, the chance of cure is not as great, so more intensive treatment is often needed.

These risk groups are based on what is now known about neuroblastoma and how it is treated. As new research provides more information, these risk groups may change over time. For example, in recent treatment recommendations the age cut-off for some of these categories has been revised from up to 12 months (365 days) to up to 18 months (547 days).

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 4S (younger than age 1), whose cancer has favorable histology, is hyperdiploid (excess DNA) and has *no* extra copies of the *MYCN* gene

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 age 1, 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
- 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 extra copies of the *MYCN* gene
- Any child who is Stage 3, older than 18 months of age, whose cancer has unfavorable histology
- Any child who is Stage 4, whose cancer has extra copies of the *MYCN* gene regardless of age
- Any child who is Stage 4 and older than 18 months
- Any child who is Stage 4 and between 12 and 18 months old whose cancer has extra copies of the *MYCN* gene, unfavorable histology, and/or normal DNA ploidy (a DNA index of 1)
- Any child who is Stage 4S (younger than age 1), whose cancer has extra copies of the *MYCN* gene

International Neuroblastoma Risk Group (INRG) classification

As with the staging system described in the previous section, a newer risk group classification system, the International Neuroblastoma Risk Group (INRG) classification, is now being studied and may soon replace the COG system above. This system is based on the newer INRGSS staging system, which includes the image-defined risk factors (IDRFs), as well as many of the prognostic factors listed in the previous section, such as:

- The child's age
- Tumor histology (how the tumor looks under the microscope)
- The presence or absence of *MYCN* gene amplification
- Certain changes in chromosome 11 (known as an 11q aberration)
- DNA ploidy (the total number of chromosomes in the tumor cells)

The INRG classification uses these factors to put children into 16 different pre-treatment groups (lettered A through R). Each of these pretreatment groups falls into 1 of 4 overall risk groups:

- Very low risk
- Low risk
- Intermediate risk
- High risk

This system has not yet been widely adopted, but it is being researched in new treatment protocols.

Survival rates for neuroblastoma based on risk groups

Survival rates are a way to get an idea of the outlook for children with a certain type 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. If you would rather not read about survival rates, please skip to the next section.

The 5-year survival rate refers to the percentage of children 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).

In order to get 5-year survival rates, doctors have to look at children who were treated at least 5 years ago. Improvements in treatment since then may result in a better outlook for children now being diagnosed with neuroblastoma.

Survival rates are based on previous outcomes of large numbers of people who had the disease, but they cannot predict what will happen in any particular child's case. The risk group of a child's cancer is important in estimating their outlook. But many other factors can also affect a child's outlook, such as their age, the location of the tumor, and how well the cancer responds to treatment. Your child's doctor can tell you how the numbers below might apply to your child, as he or she knows your situation best.

Survival by Children's Oncology Group (COG) risk group

Low-risk group: Children in the low-risk group have a 5-year survival rate that is higher than 95%.

Intermediate-risk group: In children in the intermediate-risk group, the 5-year survival rate is around 90% to 95%.

High-risk group: The 5-year survival rate in children in the high-risk group is around 40% to 50%.

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.

Children with neuroblastoma and their families have special needs. These needs can be met best by cancer centers for children, working closely with the child's primary care doctor. These centers have teams of specialists who understand the differences between cancers in adults and those in children, as well as the unique needs of younger people with cancer.

Treating neuroblastoma is complex and often requires the expertise of many different doctors, nurses, and other health professionals. The doctors on the treatment team often include:

- A pediatric cancer surgeon
- A pediatric oncologist (doctor who uses chemotherapy and other medicines to treat childhood cancers)
- A pediatric radiation oncologist (doctor who uses radiation therapy to treat cancer in children)

Many other specialists may be involved in your child's care as well, including physician assistants, nurse practitioners, nurses, psychologists, social workers, rehabilitation specialists, and other health professionals. You can read more about this in our document *Children Diagnosed With Cancer: Understanding the Health Care System*.

Treatment of neuroblastoma depends on the stage of the cancer, the child's age, and other factors such as the prognostic markers mentioned previously. The types of treatment used can include:

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

Some children will get more than one type of treatment. Your child's cancer care team will discuss the treatment options with you. It's important to discuss these options and their possible side effects with your child's doctors so you can make an informed decision. (For a list of some questions to ask, see the section "What should you ask your child's doctor about neuroblastoma?")

The next few sections describe the types of treatment used for neuroblastomas. This is followed by a discussion of when these treatments are used in different situations.

Neuroblastoma 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

In many cases, doctors need to get a sample of the tumor to be sure it is a neuroblastoma before deciding which treatment might work best. Tumor samples are removed during a surgical biopsy to be looked at under a microscope and for other lab tests.

If the tumor is in the abdomen (belly), 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 put 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 pieces 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 cure.

During the operation, the surgeon looks carefully for signs of tumor spread to other organs. Nearby lymph nodes (small collections of immune system cells to which cancers often spread first) are removed and looked at under a microscope for cancer cells.

If possible, the surgeon will remove the entire tumor. This is less likely if the tumor is near vital structures or wrapped around large blood vessels. Even if some of the tumor is left behind, treatment with chemotherapy (and sometimes radiation therapy) after surgery may still 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 large, chemotherapy may be used before surgery to shrink the tumor and make it easier to remove.

Possible risks and side effects of surgery

The risks from surgery depend on the location and extent of the operation and the child's health beforehand. Serious complications, although rare, can include problems with anesthesia, excess bleeding, infections, and damage to blood vessels, kidneys, other organs, or nerves. Complications are more likely if the tumor is large and growing into blood vessels or nerves. Most children will have some pain for a while after the operation, but this can usually be helped with medicines if needed.

Chemotherapy for neuroblastoma

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

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

Chemo for neuroblastoma usually includes a combination of drugs. The main chemo drugs used include:

- Cyclophosphamide or ifosfamide
- Cisplatin or carboplatin
- Vincristine
- Doxorubicin (Adriamycin)
- Etoposide
- Topotecan
- Busulfan and melphalan (sometimes used during stem cell transplant)

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

Doctors give chemo in cycles, which consist of treatment on a few days in a row, followed by time off to allow the body time to recover. The cycles are typically repeated every 3 or 4 weeks. The total length of treatment depends on which risk group the child is in – higher risk groups usually require longer treatment.

Possible side effects of chemotherapy

Chemo drugs attack 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 (where new blood cells are made), the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemo, which can lead to side effects.

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

- Hair loss
- Mouth sores
- Loss of appetite
- Nausea and vomiting
- Diarrhea or constipation
- Increased chance of infections (from having too few white blood cells)
- Easy bruising or bleeding (from having too few blood platelets)
- Fatigue (from having too few red blood cells)

Most of these side effects are short-lived 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 ask your child's doctor or nurse about medicines to help reduce side effects, and let him or her know if your child has side effects so they can be managed.

Along with the effects listed above, some drugs can have specific side effects. For example:

Cyclophosphamide and ifosfamide can damage the bladder, which can cause blood in the urine. The risk of this can be lowered 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, which could affect fertility (the ability to have children).

Doxorubicin can cause heart damage. Doctors try to reduce this risk as much as possible by limiting the 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 while it is being given.

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

Vincristine can damage nerves. Some patients may have tingling, numbness, weakness, or pain, particularly in the hands and feet.

Chemotherapy can also have some longer-term side effects. For example, some drugs can increase the risk of later developing another type of cancer (such as leukemia). While this is a serious risk, it is not common, and the small increase in risk has to be weighed against the importance of chemotherapy in treating neuroblastoma. (See *Second Cancers Caused by Cancer Treatment* to find out more about this.) For more on the possible long-term effects of treatment, see the section, “Late and long-term effects of neuroblastoma and its treatment.”

If you’d like more information on a drug used in your child’s treatment or a specific drug mentioned in this section, see our Guide to Cancer Drugs, or call us with the names of the medicines. For more information on chemotherapy in general, see the “Chemotherapy” section of our website, or our document *A Guide to Chemotherapy*.

Radiation therapy for neuroblastoma

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

External beam radiation therapy

External radiation therapy focuses the radiation on the cancer from a source outside the body. This type of treatment 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
- 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

Most often, the radiation is aimed only at the tumor, but in some cases it may also target other parts of the body to reduce the risk of cancer spread. When radiation is aimed at the whole body, it is known as *total body irradiation* (TBI).

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.

Radiation therapy is much like getting an x-ray, but the dose of radiation is much higher. Your child might be fitted with a plastic mold resembling a body cast to keep him or her in the same position during each treatment so that the radiation can be aimed more accurately.

The number of radiation treatments given depends on the situation. For each treatment session, your child lies on a special table while a machine delivers the radiation from a precise angle. The treatment is not painful. 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 medicine to make them sleep so they will not move during the treatment.

Possible side effects: Radiation therapy is sometimes an important part of treatment, but young children's bodies are very sensitive to it, so doctors try to use as little radiation as possible to help avoid or limit any problems. Radiation can cause both short-term and long-term side effects, which depend on the dose of radiation and where it is aimed.

Possible short-term effects:

- Effects on skin areas that receive radiation can range from mild sunburn-like changes and hair loss to more severe skin reactions.
- Radiation to the abdomen (belly) can cause nausea or diarrhea.
- Radiation therapy can make a child tired, especially toward the end of treatment.

Radiation can also make the side effects of chemotherapy worse. Talk with your child's doctor about the possible side effects because there are ways to relieve some of them.

Possible long-term effects:

- Radiation therapy can slow the growth of normal body tissues (such as bones) that get radiation, especially in younger children. In the past this led to problems such as short bones or a curving of the spine, but this is less likely with the lower doses of radiation used today.
- Radiation that reaches the chest area can affect the heart and lungs. This does not usually cause problems right away, but in some children it may eventually lead to heart or lung problems as they get older.
- Radiation to the abdomen in girls can damage the ovaries. This might lead to abnormal menstrual cycles or problems getting pregnant or having children later on.
- Radiation can damage the DNA inside cells. As a result, radiation therapy slightly increases the risk of developing a second cancer in the areas that get radiation, usually many years after the radiation is given.

Close follow-up with doctors is important as children grow older so that any problems can be found and treated as soon as possible. For more on the possible long-term effects of treatment, see the section “Late and long-term effects of neuroblastoma and its treatment.”

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 blood 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 children with advanced neuroblastoma, often along with other treatments. Once injected into the blood, the MIBG goes to tumors anywhere in the body and delivers its radiation. The child will need to stay in a special hospital room for a few days after the injection until most of the radiation has left the body. Most of the radiation leaves the body in the urine, so younger children might need to have a catheter in the bladder to help urine leave the body, usually for a couple of days.

Possible side effects: Most of the radiation from MIBG therapy stays in the area of the neuroblastoma, so most children do not have serious side effects from this treatment. MIBG therapy can sometimes cause mild nausea and vomiting. It can also make some children feel tired or sluggish. Some children might have swollen cheeks from the MIBG because it can affect the salivary glands. In rare cases it may cause high blood pressure for a short period of time.

High-dose chemotherapy/radiation therapy and stem cell transplant for neuroblastoma

This type of treatment is often used in children with high-risk neuroblastoma who are unlikely to be cured with other treatments.

Giving higher doses of chemotherapy (and sometimes radiation) might be more effective in treating these cancers, but normally this can't be done because it would cause severe damage to the bone marrow, where new blood cells are made. This could lead to life-threatening shortages of blood cells.

Doctors can sometimes get around this problem by giving the high-dose treatments, then replacing the patient's bone marrow cells by giving them new blood-making cells (called *stem cells*). This is known as a *stem cell transplant* (SCT).

In the past, the stem cells were often collected from the child's own bone marrow before treatment, which required drilling small holes in certain bones. The treatment was commonly referred to as a *bone marrow transplant*.

But doctors have found that stem cells can be collected 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. This process may be repeated over a few days. The stem cells are then frozen until the transplant.

How the transplant is done

Typically, the child will be admitted to the stem cell transplant unit of the hospital on the day before the high-dose chemo begins. He or she will usually stay in the hospital until after the chemo and the stem cells have been given, and until the stem cells have started making new blood cells again (see below).

The child gets high-dose chemotherapy, often along with radiation. This destroys the cancer cells in the body, as well as the normal cells in the bone marrow. After treatment, the frozen stem cells are thawed and given as a blood transfusion. The stem cells travel through the bloodstream and settle in the child's bone marrow.

Usually within a couple of weeks, the stem cells begin making new white blood cells. This is later followed by new platelet production and new red blood cell production. 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 help lower the risk of infection, the child stays in a special hospital room, and visitors must wear protective clothing. Blood and platelet transfusions and treatment with IV antibiotics may also be used to help prevent or treat infections or bleeding problems.

The child usually stays in the hospital room until part of the white blood cell count (known as the *absolute neutrophil count*, or *ANC*) rises to a safe level. The child is then seen in an outpatient clinic almost every day for several weeks. Because platelet counts often take longer to return to a safe level, the child may get platelet transfusions as an outpatient. Patients may need to make regular visits to the outpatient clinic for about 6 months, after which time their care may be continued by their regular doctors.

Practical points

A stem cell transplant is a complex treatment that can cause life-threatening side effects. If the doctors think your child can benefit from a transplant, the best place to have this done is at a nationally recognized cancer center where the staff has experience with the procedure and with managing the recovery period.

A stem cell transplant often requires a long hospital stay and can be very expensive (costing well over \$100,000). Be sure to get a written approval from your insurer if the procedure is recommended for your child. Even if the transplant is covered by your health insurance, co-pays or other costs could easily amount to many thousands of dollars. Find out what your

insurer will cover before the transplant so you will have an idea of what you might have to pay.

Possible side effects

The possible side effects from SCT are generally divided into early and long-term effects.

Early or short-term side effects

The early complications and side effects are basically the same as those caused by high-dose chemotherapy or radiation therapy and can be severe. They are caused by damage to the bone marrow and other quickly growing tissues of the body, and can include:

- Low blood cell counts (with fatigue and increased risk of infection and bleeding)
- Nausea and vomiting
- Loss of appetite
- Mouth sores
- Diarrhea
- Hair loss

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

Late or long-term side effects

Some complications and side effects can last for a long time or might not occur until months or years after the transplant. These can include:

- Radiation damage to the heart or lungs
- Problems with the thyroid or other hormone-making glands
- Problems with fertility
- Damage to bones or problems with bone growth
- Development of another cancer (including leukemia) years later

Be sure to talk to your child's doctor before the transplant to learn about possible long-term effects your child might have. For more on the possible long-term effects of this and other treatments, see the section, "Late and long-term effects of neuroblastoma and its treatment."

For more information on stem cell transplants in general, see our document *Stem Cell Transplant (Peripheral Blood, Bone Marrow, and Cord Blood Transplants)*.

Retinoid therapy for neuroblastoma

Retinoids are chemicals that are related to vitamin A. They are known as *differentiating agents* because they are thought to help some cancer cells 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 the cancer coming back after high-dose chemotherapy and stem cell transplant. Most doctors now recommend 6 months of 13-cis-retinoic acid after the transplant. This drug is taken as a capsule, twice a day for 2 weeks, followed by 2 weeks off.

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

Possible side effects

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

Immunotherapy for neuroblastoma

Immunotherapy is the use of medicines to help a patient's own immune system recognize and destroy cancer cells more effectively. Several types of immunotherapy are now being studied for use against neuroblastoma (some of which are described in the section "What's new in neuroblastoma research and treatment?").

Monoclonal antibodies are man-made versions of immune system proteins that can be made to attack a very specific target. They can be injected into the body to seek out and attach to cancer cells.

A monoclonal antibody called *ch14.18* attaches to GD2, a substance found on the surface of many neuroblastoma cells. This antibody can be given together with cytokines (immune system hormones) such as GM-CSF and interleukin-2 (IL-2) to help the child's immune system 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.

Possible side effects

Side effects of ch.14.18 treatment can include nerve pain (which can sometimes be severe), leaking of fluid in the body (which can lead to low blood pressure, fast heart rate, shortness of breath, and swelling), and allergic reactions.

Clinical trials for neuroblastoma

You may have had to make a lot of decisions since you've been told your child has cancer. One of the most important decisions you will make is deciding which treatment is best. You may have heard about clinical trials being done for neuroblastoma. 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. These studies are done to get a closer look at promising new treatments or procedures.

Clinical trials are one way to get state-of-the-art cancer care for your child. Sometimes they may be the only way to get access to some newer treatments. They are also the only way for doctors to learn better methods to treat cancer. Still, they might not be right for every child.

If you would like learn more about clinical trials your child may be eligible for, start by asking your doctor if your clinic or hospital conducts clinical trials. Children's cancer centers often conduct many clinical trials at any one time, and most children treated at these centers take part in a clinical trial as part of their treatment.

You can also call our clinical trials matching service for a list of clinical trials that meet your child's needs. You can reach this service at 1-800-303-5691 or on our website at www.cancer.org/clinicaltrials. You can also get a list of current clinical trials by calling the National Cancer Institute toll free at 1-800-4-CANCER (1-800-422-6237) or by visiting the NCI clinical trials website at www.cancer.gov/clinicaltrials.

Your child will have to meet certain requirements to take part in any clinical trial. If your child does qualify for a clinical trial, you will have to decide whether or not to enter (enroll) your child into it. Older children, who can understand more, usually must also agree to take part in the clinical trial before the parents' consent is accepted.

You can get a lot more information on clinical trials in our document *Clinical Trials: What You Need to Know*. You can read it on our website or call our toll-free number (1-800-227-2345) to have it sent to you.

Complementary and alternative therapies for neuroblastoma

When your child has cancer you are likely to hear about ways to treat his or her cancer or relieve symptoms that your doctor hasn't mentioned. Everyone from friends and family to Internet groups and websites might offer ideas for what might help. These methods can include vitamins, herbs, and special diets, or other methods such as acupuncture or massage, to name a few.

What exactly are complementary and alternative therapies?

Not everyone uses these terms the same way, and they are used to refer to many different methods, so it can be confusing. We use *complementary* to refer to treatments that are used *along with* your regular medical care. *Alternative* treatments are used *instead of* a doctor's medical treatment.

Complementary methods: Most complementary treatment methods are not offered as cures for cancer. Mainly, they are used to help the person with cancer feel better. Some methods that are used along with regular treatment are: art therapy or play therapy to reduce stress; acupuncture to help relieve pain; or peppermint tea to relieve nausea. Some complementary methods are known to help, while others have not been tested. Some have been proven not to be helpful, and a few have even been found harmful.

Alternative treatments: Alternative treatments may be offered as cancer cures. These treatments have not been proven safe and effective in clinical trials. Some of these methods may pose danger, or have life-threatening side effects. But the biggest danger in most cases is that your child may lose the chance to be helped by standard medical treatment. Delays or interruptions in your child's medical treatments may give the cancer more time to grow and make it less likely that treatment will help.

Finding out more

It is easy to see why parents who have children with neuroblastoma might think about alternative methods. You want to do all you can to help fight the cancer, and the idea of a treatment with few or no side effects sounds great. Sometimes medical treatments like chemotherapy can be hard to take, or they may no longer be working. But the truth is that most alternative methods have not been tested and proven to work in treating cancer.

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

- Look for red flags that suggest fraud. Does the method promise to cure all or most cancers? Are you told not to use regular medical treatments? Is the treatment a "secret" that can only be given by certain providers or in another country?
- Talk to your child's doctor or nurse about any method you are thinking about.
- Contact us at 1-800-227-2345 to learn more about complementary and alternative methods in general or read our document *Complementary and Alternative Methods and Cancer*. To find out about any specific methods you are looking at, you can call us or read about them in the Complementary and Alternative Methods section of our website.

The choice is yours

You always have a say in how your child is treated. If you want to use a non-standard treatment, learn all you can about the method and talk to your child's doctor about it. With

good information and the support of the health care team, you may be able to safely use the methods that can help 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 usually don't need very intensive treatment to cure the neuroblastoma. In fact, some children might not need to be treated at all because some of these neuroblastomas will mature or go away on their own.

Many children can have surgery as their only treatment. Even if 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.

If much of the tumor can't be removed or if it has some unfavorable features, chemotherapy is typically given after surgery. A common chemo 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 low-risk tumor that can't safely be treated right away with surgery, a short course of chemotherapy might be given first. 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 might be needed if chemotherapy doesn't shrink the tumor fast enough.

Infants with stage 4S disease and no symptoms can often be watched carefully with no treatment, because these cancers typically mature or go away on their own. If the tumor causes problems such as an enlarged liver, which can be life-threatening for very young infants, chemotherapy that is less intense may be used to shrink the tumor. Radiation therapy may be used if chemo does not shrink the liver right away.

Recent research has also shown that infants younger than 6 months with small adrenal tumors (which are assumed to be neuroblastomas) can often be watched closely without needing surgery or other treatments. Many of these tumors will mature or go away on their own, but if a tumor keeps growing or is causing symptoms, surgery can be done to remove it.

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 chemo drugs used usually include carboplatin, cyclophosphamide, doxorubicin, and etoposide. 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 might be followed by radiation therapy, if needed.

Doctors are now looking at the possibility of not giving chemo after surgery in some infants whose tumors are not causing symptoms. These children might just be watched closely after surgery and would only get further treatment if the tumor begins growing or causing symptoms. This approach is now being studied.

High risk

Children at high risk require more aggressive treatment, which often includes chemotherapy, surgery, and radiation. Treatment is often divided into 3 phases.

Induction: The goal of this phase is to get the cancer into remission by destroying or removing as much of it as possible. Treatment usually starts with chemotherapy, using alternating regimens of several drugs (typically cisplatin, etoposide, vincristine, cyclophosphamide, doxorubicin, and topotecan) given at higher doses than what is used in other risk groups. Surgery is usually done after this to try to remove any tumors that are still visible.

Consolidation: This phase uses more intensive treatment to try to get rid of any cancer cells that remain in the body. High-dose chemotherapy is given (sometimes along with radiation therapy), followed by a stem cell transplant.

Maintenance: The goal of this phase of treatment is to try to lower the chance that the cancer will come back. The retinoid drug 13-cis-retinoic acid (isotretinoin) is often given for 6 months after other treatments are completed. Immunotherapy with the monoclonal antibody ch14.18, along with immune-activating cytokines (GM-CSF and IL-2), is often given as well.

Recurrent neuroblastoma

If neuroblastoma comes back after initial treatment, it is known as a recurrence or relapse. Treatment of recurrent neuroblastoma depends on many factors, including the initial risk group, where the cancer recurs, and what treatments have been used.

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

For high-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). Chemotherapy might include drugs that weren't used during the initial treatment. Intensive treatment with high-dose chemotherapy/radiation therapy followed by a stem cell transplant might be another option. Because these cancers can be hard to treat, clinical trials of newer treatments, such as monoclonal antibodies or new

anti-cancer drugs, might be another reasonable option. (See the section “What’s new in neuroblastoma research and treatment?”)

Emotional and social issues in children with neuroblastoma

Most children with neuroblastoma are very young when they are diagnosed. Still, some children may have emotional or psychological issues that need to be addressed during and after treatment. Depending on their age, they may also have some problems with normal functioning and school work. These can often be overcome with support and encouragement. Doctors and other members of the health care team can also often recommend special support programs and services to help children during and after cancer treatment.

Parents and other family members can also be affected, both emotionally and in other ways. The family’s situation should be evaluated by the treatment center as soon as possible. Some common family concerns include financial stresses, traveling to and staying near the cancer center, the need for family members to take time off from work, the possible loss of a job, and the need for home schooling. Social workers and other professionals at cancer centers can help families sort through these issues. If family members have concerns, they can be addressed before they become a crisis. You can read more about financial concerns in our document *Children Diagnosed With Cancer: Financial and Insurance Issues*.

Centers that treat many patients with neuroblastoma may have programs to introduce new patients and their families to others who have finished their treatment. This can give parents an idea of what to expect during and after treatment, which is very important. Seeing another patient with neuroblastoma doing well is often helpful for the patient and family.

Many experts recommend that school-aged children attend school as much as possible. This can help them maintain a sense of daily routine and keep their friends informed about what is happening.

Friends can be a great source of support, but patients and parents should know that some people have misunderstandings and fears about cancer. Some cancer centers have a school re-entry program that can help in these situations. In this program, health educators visit the school and tell students about the diagnosis, treatment, and changes that the cancer patient may go through. They also answer any questions from teachers and classmates. (For more information, see our document *Children Diagnosed With Cancer: Returning to School*.)

During treatment, children and their families tend to focus on the daily aspects of getting through it and beating the cancer. But once treatment is finished and as children who have had neuroblastoma grow older, a number of emotional issues can arise. Some of these might last a long time. They can include things like:

- Dealing with physical changes or long-term side effects from the treatment
- Worries about the cancer returning or new health problems developing

- Feelings of resentment for having had cancer or having gone through treatment when others did not
- Concerns about being treated differently or discriminated against (by friends, classmates, coworkers, employers, etc.)
- Concerns about dating, marrying, and having a family later in life

No one chooses to have cancer, but for many survivors, the experience can eventually be positive, helping to establish strong self-values. Other survivors may have a harder time recovering, adjusting to life after cancer, and moving on. It is normal to have some anxiety or other emotional reactions after treatment, but feeling overly worried, depressed, or angry can affect many aspects of a young person's growth. It can get in the way of relationships, school, and other aspects of life.

With support from family, friends, other survivors, mental health professionals, and others, many people who have survived cancer can thrive in spite of the challenges they've had to face. If needed, doctors and other members of the health care team can often recommend special support programs and services to help children after cancer treatment.

More treatment information about neuroblastoma

For more details on treatment options – including some that may not be addressed in this document – the National Cancer Institute (NCI) and the Children's Oncology Group (COG) are good sources of information.

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

The COG is the world's largest organization devoted to childhood cancer research. The COG website, www.childrensoncologygroup.org, provides key information to help support children and their families from the time of diagnosis, through treatment, and beyond.

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

It is important to have open, honest discussions with your child's cancer care team. You should ask any question 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?

- What else can you tell about the cancer based on the lab tests?
- Do we need to have any other tests done before we discuss treatment?
- How much experience do you have treating this type of cancer?
- What other doctors will we need to see?
- What are our treatment options?
- 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 should we do to be ready for treatment?
- How long will treatment last? What will it be like? Where will it be done?
- How will treatment affect our daily activities?
- How long will it take my child to recover from treatment?
- What are the possible side effects from treatment? What can be done for them?
- Which side effects start shortly after treatment and which ones might develop later on?
- How might treatment affect my child's ability to learn, grow, and develop?
- Will treatment affect my child's ability to have children someday? Can we do anything about this?
- Will my child have a higher long-term risk of other cancers?
- What are the chances that the cancer will come back after treatment? What would we do if this happens?
- 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 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 short- and long-term effects of the tumor and its treatment, and concerns about the tumor coming back.

It is certainly normal to want to put the tumor and its treatment behind you and to get back to a life that doesn't revolve around cancer. 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 and tests

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, the size and location of the tumor, and other factors.

Because there is a chance that the cancer might return after 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 often at first. If nothing abnormal is found, the time between tests can then be extended.

A benefit of follow-up care is that it gives you a chance to discuss any questions and concerns that arise during and after your child's recovery. For example, almost any cancer treatment can have side effects. Some might last for only a short time, but others can last longer or might not show up until months or even years later. It's important to report any new symptoms to the doctor right away so that the cause can be found and treated, if needed.

It is also important to keep health insurance coverage. Tests and doctor visits cost a lot, and even though no one wants to think of the cancer coming back, this could happen.

Keeping good medical records for neuroblastoma

As much as you might want to put the experience behind you once treatment is done, it's 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. Gathering the details soon after treatment may be easier than trying to get them at some point in the future. There are certain pieces of information you should be sure your child's doctors have. These are:

- A copy of the pathology report(s) from any biopsies or surgeries
- If your child had surgery, a copy of the operative report(s)
- If your child stayed in the hospital, copies of the discharge summaries that doctors prepare when patients are sent home
- If your child received chemotherapy or other medicines for the cancer, a list of the drugs, drug doses, and when they were given
- If your child got radiation, a summary of the type and dose of radiation and when and where it was given

Late and 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 help keep their immune system in check.

Because of major advances in treatment, most children treated for neuroblastoma are now surviving into adulthood. Doctors have learned that the treatment can affect children's health later in life, so watching for health effects as they get older has become more of a concern in recent years.

Treating childhood cancer requires a very specialized approach, and so does the care and follow-up after treatment. The earlier any problems can be recognized, the more likely it is they can be treated effectively.

Neuroblastoma survivors are at risk, to some degree, for several possible late effects of their treatment. It's important to discuss what these possible effects might be with your child's medical team.

The risk of late effects depends on a number of factors, such as the specific cancer treatments the child received, doses of treatment, and age when getting the treatment. Late effects of treatment can include:

- Heart or lung problems (from certain chemotherapy drugs or radiation therapy)
- Slowed or decreased growth and development (especially after a stem cell transplant)
- Bone damage or thinning of bones (osteoporosis)
- Changes in sexual development and ability to have children (especially in girls)

- Changes in intellectual function with learning problems
- Development of second cancers, such as leukemia, later in life. These are not common, but they can occur.

There may be other possible late complications from treatment as well. Your child's doctor should carefully review any possible problems with you before your child starts treatment.

Along with physical side effects, survivors of childhood cancer may have emotional or psychological issues. They also may have some problems with normal functioning and school work. These can often be addressed with support and encouragement. Doctors and other members of the health care team can also often recommend special support programs and services to help children after cancer treatment.

Long-term follow-up guidelines

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 can help you know what to watch for, what type of screening tests should be done to look for problems, and how late effects can be treated.

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. You can also download them for free at the COG website: www.survivorshipguidelines.org. The guidelines are written for health care professionals. Patient versions of some of the guidelines are available (as "Health Links") on the site as well, but we urge you to review them with a doctor.

For more about some of the possible long-term effects of treatment, see our document *Children Diagnosed With 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.

Genetics of neuroblastomas

Researchers now have better lab tests 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. More recently, researchers have found that neuroblastoma cells in older children are more likely to have changes in the *ATRX* tumor suppressor gene. Tumors with this gene change tend to grow more slowly, but they are also harder to cure. This may help explain why younger children with neuroblastoma tend to do better in the long term than children who are older when they are diagnosed.

Doctors are now looking to use these and other findings to help choose the best treatments. Newer staging systems and risk group classifications, which take advantage of some of these findings, should be in use within the next few years.

Treatment

Survival rates for neuroblastoma have gotten better as doctors have found ways to improve on current treatments.

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.

Other studies are looking to see if children with low or intermediate risk neuroblastoma can be treated with less (or even no) chemotherapy. The goal is to still have the same good results, but with fewer side effects from treatment.

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*). Others are looking to see if using stem cells donated from another person (an *allogeneic stem cell transplant*) might help some children with hard-to-treat tumors.

Retinoids

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

Targeted drugs

Knowledge about what makes neuroblastoma cells different from normal cells may lead to new approaches to treating this disease. Newer drugs that target neuroblastoma cells more specifically than standard chemo drugs are now being studied in clinical trials. For example, doctors are now studying medicines that target the pathways inside neuroblastoma cells that help them grow, such as crizotinib (Xalkori) for the ALK pathway and alisertib (MLN8237) for the aurora A pathway.

Crizotinib is a drug that targets cells with changes in the *ALK* gene. Up to 15% of neuroblastomas have changes in this gene. In an early study, crizotinib was found to cause some neuroblastomas to shrink, although it's not clear how long this might last.

Some other drugs that work differently from standard chemo drugs are being studied against neuroblastoma as well. Examples include bortezomib, vorinostat, lenalidomide, temsirolimus, sorafenib, nifurtimox, and lestaurtinib.

Immunotherapy

Immunotherapy is the use of medicines to help a patient's own immune system fight cancer.

The monoclonal antibody ch14.18, which targets GD2 on neuroblastoma cells, is now used routinely for children with high-risk neuroblastoma, to help immune system cells find and destroy the cancer cells. Clinical trials are now testing the effectiveness of several other antibodies that target GD2. One example is hu14.18-IL2, an antibody that is linked to interleukin-2 (an immune-boosting cytokine). Early results have found that this antibody/cytokine combination may help some children in whom other treatments are no longer working.

Several cancer vaccines are also being studied for use against neuroblastoma. For these vaccines, modified neuroblastoma cells or other substances are injected into the body to try to get the child's own immune system to attack cancer cells. These treatments are still in the early stages of clinical trials.

Additional resources for neuroblastoma

More information from your American Cancer Society

Here is more information you might find helpful. You also can order free copies of our documents from our toll-free number, 1-800-227-2345, or read them on our website, www.cancer.org.

Children with cancer

[Children Diagnosed With Cancer: Dealing with Diagnosis](#) (also in Spanish)

[Pediatric Cancer Centers](#) (also in Spanish)

[Children Diagnosed With Cancer: Understanding the Health Care System](#) (also in Spanish)

[Children Diagnosed With Cancer: Financial and Insurance Issues](#)

[Children Diagnosed With Cancer: Returning to School](#)

[Children Diagnosed With Cancer: Late Effects of Cancer Treatment](#)

[Health Professionals Associated With Cancer Care](#)

[Talking With Your Doctor](#) (also in Spanish)

Coping with cancer

[After Diagnosis: A Guide for Patients and Families](#) (also in Spanish)

[Family and Medical Leave Act \(FMLA\)](#) (also in Spanish)

[Nutrition for Children With Cancer](#) (also 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](#) (booklet)

Cancer treatment information

[Understanding Cancer Surgery: A Guide for Patients and Families](#) (also in Spanish)

[A Guide to Chemotherapy](#) (also in Spanish)

[Understanding Radiation Therapy: A Guide for Patients and Families](#) (also in Spanish)

[Clinical Trials: What You Need to Know](#) (also in Spanish)

Fertility and Men With Cancer

Fertility and Women With Cancer

[Second Cancers Caused by Cancer Treatment](#)

[Stem Cell Transplant \(Peripheral Blood, Bone Marrow, and Cord Blood Transplants\)](#) (also in Spanish)

Cancer treatment side effects

[Caring for the Patient with Cancer at Home: A Guide for Patients and Families](#) (also in Spanish)

[Nausea and Vomiting](#)

[Guide to Controlling Cancer Pain](#) (also in Spanish)

[Anemia in People With Cancer](#)

[Fatigue in People With Cancer](#)

Books

Your American Cancer Society also has books that you might find helpful. Call us at 1-800-227-2345 or visit our bookstore online at cancer.org/bookstore to find out about costs or to place an order.

For family and friends of the child

American Cancer Society Complete Guide to Family Caregiving, Second Edition

Because... Someone I Love Has Cancer

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

For the child with cancer

Imagine What's Possible: Use the Power of Your Mind to Take Control of Your Life During Cancer (grades 4 through 6)

Let My Colors Out (picture book for ages 5 to 10)

The Long and the Short of It: A Tale About Hair (ages 7 and up)

National organizations and websites*

Along with the American Cancer Society, other sources of patient information and support include*:

American Childhood Cancer Organization (formerly Candlelighters)

Toll-free number: 1-855-858-2226

Website: www.acco.org

Offers information for children and teens with cancer, their siblings, and adults dealing with children with cancer. Also offers books and a special kit for children newly diagnosed with cancer, as well as some local support groups.

Children's Oncology Group (COG)

Website: www.childrensoncologygroup.org

Provides key information from the world's largest organization devoted to childhood cancer research to help support children and their families from the time of diagnosis, through treatment, and beyond. Also has a searchable database to find the COG center closest to you.

CureSearch for Children's Cancer

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

Website: www.curesearch.org

Provides up-to-date information about childhood cancer from pediatric cancer experts. Has sections on the website for patients, families, and friends to help guide them on how to support the child with cancer.

National Cancer Institute

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

TTY: 1-800-332-8615

Website: www.cancer.gov

Provides accurate, up-to-date information about cancer for patients and their families, including clinical trials information. Offers a special booklet for teen siblings of a child with cancer at: www.cancer.gov/cancertopics/when-your-sibling-has-cancer.

National Children's Cancer Society, Inc.

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

Website: www.children-cancer.org

Services include an online support network for parents of children with cancer, educational materials, and financial assistance for treatment-related expenses.

Websites for children and teens

Starlight Children's Foundation

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

Website: www.starlight.org

Website has animated stories and interactive programs to teach kids about chemo and procedures that may be done in the hospital; also has videos specifically for teens and provides a safe, monitored online support group for teens with cancer.

Group Loop (a subsite of the Cancer Support Community just for teens)

Toll-free number: 1-888-793-9355

Website: www.grouploop.org

An online place for teens with cancer or teens who know someone with cancer to connect with other teens – away from the pressures of classes, responsibilities, and treatment schedules. Has online support groups, chat rooms, information, and more.

SuperSibs! powered by Alex's Lemonade Stand

Toll-free number: 1-866-333-1213

Website: www.supersibs.org

Supports, honors, and recognizes 4- to 18-year-old brothers and sisters of children diagnosed with cancer so they may face the future with strength, courage, and hope. Alex's Lemonade Stand is restarting SuperSibs in 2014 so there may be some delays with resuming support services.

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

No matter who you are, we can help. Contact us anytime, day or night, for information and support. Call us at **1-800-227-2345** or visit www.cancer.org.

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