Cancer - Unknown Primary

What is cancer?

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

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

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

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

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

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

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

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

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

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

What is a cancer of unknown primary?

Cancers often spread from their *primary site* (the part of the body where the cancer started) to one or more metastatic sites (other parts of the body). Cancers are named based on their primary site, regardless of where in the body they spread. For example, a lung cancer that spreads to the liver is still classified as lung cancer and not as liver cancer.

Sometimes it's not clear where a cancer may have started. When cancer is found in one or more metastatic sites but the primary site cannot be determined, it is called a *cancer of unknown primary* (CUP) or an *occult primary cancer*. This happens in a small portion of cancers.

Further tests may eventually find the primary site of some of these cancers. When this happens, they are no longer considered a cancer of unknown primary and are renamed and treated according to where they started.

As an example, a person has an enlarged lymph node on the side of their neck. When it is removed, cancer is found. But under the microscope it does not look like a cancer that normally starts in lymph nodes. At this point it might be considered a cancer of unknown primary. The way it looks under the microscope might suggest that the cancer started in the mouth, throat, or voice box (larynx). When this area is examined, a small cancer of the larynx might be found. From then on, the patient is said to have laryngeal cancer rather than a cancer of unknown primary and will get treated for that type of cancer.

In many cases, the source of the cancer is never determined. Even the most thorough search may not find the primary site. Even when doctors do autopsies on people who have died of cancer of unknown primary, they are often still unable to find the site where the cancer started.

When cancer is found, it is only natural to want to know where it came from. But the main reason to look for the primary site of a CUP is to guide treatment. Since a cancer that starts in

one place needs the same treatments when it spreads, knowing where a cancer started tells the doctor what types of treatments to use. This is especially important for certain cancers that respond well to specific chemotherapy or hormone drugs. When the types of cancer with the best hope for responding to treatment have been ruled out by certain tests, it usually becomes less important to find the exact origin or cancer type.

But even if the primary site is not known, treatment can still be successful. How the cancer looks under the microscope, the results of lab tests, and information about which organs it has already affected can help doctors predict what kinds of treatment might be helpful.

General cancer types

Cancers are classified based on their primary site, and they can also be grouped by the types of cells in them. This grouping is based on how the cancer cells look under the microscope and on certain lab tests of the cells. Knowing the type of cell might give doctors a clue as to where the cancer started.

Carcinomas

A carcinoma is a cancer that begins in the cells that line the inside or outside of a body organ. These cells are called *epithelial cells*. There are different types of carcinomas, depending on how the cancer cells look under the microscope. The 2 most common types are squamous cell carcinoma and adenocarcinoma.

Squamous cell cancers

Cancers formed by flat cells that look like cells normally found on the surface of the skin or the linings of certain organs are called *squamous cell cancers* or *squamous cell carcinomas*. Squamous cell cancers can start in the mouth, throat, esophagus, lungs, anus, cervix, vagina, and some other organs.

Adenocarcinomas

Cancers that develop from gland cells (cells that secrete a substance) are called *adenocarcinomas*. Gland cells are found in many organs of the body, including some that are not usually thought of as glands. For example, most cancers in the stomach, intestines, and colon are adenocarcinomas. About 4 of 10 lung cancers are adenocarcinomas. Adenocarcinomas can also develop in many other organs.

Other cancer types

Less common types of cancer can develop from other cell types.

- **Lymphomas** develop from cells of the immune system found in lymph nodes and several other organs.

- **Melanomas** develop from cells that produce the skin's tan or brown color.
- **Sarcomas** develop from connective tissue cells that usually are present in tendons, ligaments, muscle, fat, bones, cartilage, and related tissues.
- **Germ cell tumors** can develop in the testes (testicles) in men or the ovaries in women, or in the parts of the body where these organs developed in the fetus.

This list is not intended to include all types of cancers but merely to name the most common ones.

When the cancer cells closely resemble normal cells of the organ where they start, the cancer is called *well differentiated*. When the cells do not look much like normal cells, the cancers are called *poorly differentiated*. Cancers of unknown primary are often poorly differentiated.

Broad categories of cancers of unknown primary

When first looking at the cancer cells under a microscope, doctors usually classify a cancer of unknown primary (CUP) into 1 of 5 broad categories. Many of these cancers can be better classified later on, after more extensive testing.

Adenocarcinoma

As noted before, these cancers develop from gland cells. They make up about 6 of 10 cases of CUP.

Poorly differentiated carcinoma

When looking at these cancers under a microscope, there is enough detail to tell that they are carcinomas, but the cells are too irregular to classify them further. These cancers make up about 3 of 10 cases of CUP. On further testing, about 10% of these turn out to be lymphoma, melanoma, or sarcoma.

Squamous cell cancer

These cancers look like the flat cells on the surface of the skin or the linings of certain organs.

Poorly differentiated malignant neoplasm

These are clearly cancers, but the cells are so abnormal that the doctor can't tell what type of cell they may have started from. Most of them turn out to be lymphomas, sarcomas, or melanomas. Some turn out to be carcinomas upon further testing.

Neuroendocrine carcinoma

These rare cancers start from cells of the diffuse neuroendocrine system. This system has cells that are like nerve cells in certain ways and like hormone-making endocrine cells in other ways. These cells do not form an actual organ like the adrenal or thyroid glands. Instead, they are scattered throughout other organs like the esophagus, stomach, pancreas, intestines, and lungs. These cancers account for a small number of CUP cases. (Some poorly differentiated cancers are found to be neuroendocrine carcinomas upon further testing.)

Even when doctors don't know where the cancer started, they do their best to classify the type of cancer. This can help them select the best treatment. Some cancers respond very well to specific treatments, so it is very important to classify the cancer as much as possible. This is best done by looking at the cancer under a microscope and doing special tests in the lab (see the section "How is a cancer of unknown primary diagnosed?").

Other types

Lymphoma often does not have a clear primary site, but it's not considered a CUP.

Although the primary site of a melanoma may not be clear, once a cancer is classified as a melanoma, it's no longer called a CUP.

What are the key statistics about cancers of unknown primary?

The exact number of cancers of unknown primary (CUP) diagnosed each year is unknown, because some cancers start out being diagnosed as unknown primary, but the primary site is found later. Still, the American Cancer Society estimates that about 31,430 cases of cancer of unknown primary will be diagnosed in 2014 in the United States. This number represents less than 2% of all cancers. As more sophisticated lab tests become available to determine where a cancer started, the number of cancers of unknown primary may go down.

What are the risk factors for a cancer of unknown primary?

A risk factor is anything that affects a person's chance of getting a disease such as cancer. Different cancers have different risk factors. For example, exposing skin to strong sunlight is a risk factor for skin cancer. Smoking is a risk factor for cancer of the lung and many other cancers.

But risk factors don’t tell us everything. Having a risk factor, or even several, does not mean that a person will get the disease, and many people get cancer without having any known risk factors.

Since the exact type of cancer is not known, it’s hard to identify factors that might affect risk for cancer of unknown primary (CUP). These cancers are also a very diverse group, making this issue even more complicated. But there is research that provides some information about CUP risk factors.

Smoking is probably an important risk factor for CUP. More than half of patients with CUP have a history of smoking. When autopsy studies are done, many cancers of unknown primary are found to have started in the pancreas, lungs, kidneys, throat, larynx, or esophagus. Smoking increases the risk for all of these cancers.

Some other cancers of unknown primary are eventually found to have started in the stomach, colon, rectum, or ovaries. Diet, nutrition, and weight are factors that have been linked to these cancers. (For more information, see our documents on these cancer types.)

Melanoma (an aggressive type of skin cancer) is another source of cancer of unknown primary. An important melanoma risk factor is exposure to ultraviolet radiation in sunlight.

Overall, however, there are no factors that specifically increase the risk of cancer of unknown primary. Even in people who may have one or more of the risk factors above, it’s not possible to know for sure if these factors contributed to the cancer.

Do we know what causes a cancer of unknown primary?

Cancers of unknown primary (CUP) include a variety of cancers, which may each have a number of different causes. This is why it’s hard to assign a particular cause to CUP.

Cancer is the result of changes in a cell’s DNA. DNA is the chemical in each of our cells that makes up our genes – the instructions for how our cells function. It’s packaged in chromosomes – long strands of DNA in each cell. We normally have 23 pairs of chromosomes in each cell in our body (one set of chromosomes comes from each parent). We usually look like our parents because they are the source of our DNA. But DNA affects more than how we look.

Some genes control when our cells grow, divide, and die. Certain genes that promote cell division or make cells live longer than they should are called *oncogenes*. Others that slow down cell division, or make cells die at the right time, are called *tumor suppressor genes*. Cancers can be caused by DNA mutations (changes) that “turn on” oncogenes or “turn off” tumor suppressor genes. In most cases, a number of mutations are needed before a cell becomes cancerous.

Most of the DNA mutations related to CUP probably occur during a person's lifetime rather than having been inherited before birth. These acquired mutations may sometimes result from known exposures such as tobacco smoke, ultraviolet light, radiation, or certain cancer-causing chemicals, but often they occur for no apparent reason.

As scientists learn more about how cancers develop, they are also beginning to understand why some cancers tend to grow and spread so quickly that they are diagnosed as cancers of unknown primary.

Can a cancer of unknown primary be prevented?

Cancer of unknown primary (CUP) represents a number of different cancers, so there is no known way to prevent it. Still, certain lifestyle changes may reduce the risk of many types of cancer. This might in turn reduce a person's risk of CUP.

Smoking is one of the most significant risk factors that a person can control. About 1 out of 3 cancer deaths is thought to be the direct result of smoking. Quitting or never starting reduces the risk of cancers of many types, including those of unknown primary. Please call us if you need help quitting tobacco. You can also learn more in *Questions About Smoking, Tobacco, and Health*, our *Guide to Quitting Smoking*, and our *Guide to Quitting Smokeless Tobacco*. All of these, and a lot more information about tobacco, can be read online or mailed to you.

Factors linked with body weight, physical activity, and nutrition are also thought to cause about 1 out of 3 cancer deaths. Staying at a healthy weight throughout life, being physically active, eating a healthy diet with an emphasis on plant-based foods, and limiting alcohol intake can all help reduce your risk of cancer.

Because the exact type and the origin of a CUP are unknown, it's not possible to say how any particular case might have been prevented. It is important to realize that many people with cancer have no apparent risk factors, and there's nothing they could have done to avoid the disease.

Can a cancer of unknown primary be found early?

Cancers of unknown primary (CUP) have always spread outside the organ they started in by the time they are diagnosed. If they had been found early, we would know where they started and they would not be classified as a cancer of unknown primary.

Screening tests

The American Cancer Society has specific recommendations about tests that may help detect breast, prostate, cervical, and colorectal cancers early, before they cause any symptoms. The Society also recommends routine cancer-related checkups that may detect skin, thyroid, mouth, and some other cancers at an early stage.

But these cancers account for a fairly small portion of cancers of unknown primary. No screening tests have been proven to be effective in the early detection of many of the cancers that are likely to be diagnosed as cancer of unknown primary, such as pancreatic, stomach, and kidney cancers.

Signs and symptoms of a cancer of unknown primary

The signs and symptoms of a cancer of unknown primary vary depending on which organs it has spread to. It's important to note that none of the symptoms listed below is caused only by CUP. In fact, they are more likely to be caused by something other than cancer. Still, if you have symptoms that suggest that something abnormal may be going on, consult a doctor so that the cause can be evaluated and treated, if needed.

Some possible symptoms of CUP include:

Swollen, firm, non-tender lymph nodes

Normal lymph nodes are bean-sized collections of immune system cells located throughout the body that are important in fighting infections. Cancers often spread to the lymph nodes, which become swollen and firmer. A person might notice a lump (enlarged lymph node) under the skin on the side of the neck, above the collarbone, under the arms, or in the groin area. Sometimes, a doctor notices them first during a routine checkup.

A mass in the abdomen that can be felt or a feeling of "fullness"

A mass is an abnormal area such as a swelling or firm area that can be caused by a tumor. This can be caused by cancer growing in the liver or less often, the spleen.

Sometimes the cancer cells grow on the surface of many organs in the abdomen. This may cause *ascites*, the buildup of fluid inside the abdomen. The fluid buildup can swell the abdomen. It can sometimes lead to a feeling of fullness or bloating.

Shortness of breath

This symptom may be caused by cancer that has spread to the lungs or by the build-up of fluid and cancer cells in the space around the lungs (a *pleural effusion*).

Pain in the chest or abdomen

This may be caused by cancer growing around nerves or by tumors pressing against internal organs.

Bone pain

Cancer that has spread to the bones can sometimes cause severe pain. Common areas of pain include the back and the legs and hips, but any bone can be affected. The bones may be weakened by the cancer's spread, and can break from minor injuries or even the normal stress of supporting the body's weight. This can lead to a sudden severe pain or worsening of pain that was already there.

Skin tumors

Some cancers that start in internal organs can spread through the bloodstream to the skin. Because bumps in the skin are easily seen, skin metastases are sometimes the first sign of spread from a CUP.

Low red blood cell counts (anemia)

Cancer that started in the gastrointestinal system (such as esophagus, stomach, small intestines, or colon) can bleed. Often this occurs at a slow rate, so that the blood isn't visible in the stool. Eventually, this can lead to low red blood cell counts.

Red blood cell counts can also become low if the cancer spreads to the bone marrow and crowds out the normal blood forming cells.

Weakness, fatigue, poor appetite, and weight loss

These symptoms are often seen with more advanced cancers. They may occur because the cancer has spread to specific organs or systems such as the bone marrow or digestive system. Some cancers also release substances into the bloodstream that can affect metabolism and cause these problems.

This is by no means a complete list of symptoms that might be caused by CUPs. Again, most of the symptoms above are more likely to be caused by conditions other than cancer, Still, if

you have any of these problems, it’s important to see your doctor right away so the cause can be found and treated, if needed.

How is a cancer of unknown primary diagnosed?

Cancers of unknown primary (CUP) are usually found as the result of signs or symptoms a person is having.

Medical history and physical exam

If you have any signs or symptoms that suggest you might have cancer, your doctor will want to take a complete medical history to check for symptoms and risk factors, including your family history. This will be followed by a physical exam that will pay special attention to any parts of the body where there are symptoms.

Approach to diagnosing a cancer of unknown primary

If your symptoms and the results of your physical exam suggest cancer may be the cause, the doctor may use different types of tests to look for cancer, see what kind it is, and find out where it is located (and where it may have started):

- Imaging tests such as x-rays, ultrasound, or CT (computed tomography) or MRI (magnetic resonance imaging) scans
- Endoscopy exams, in which organs are looked at through a lighted tube placed into a body opening such as the mouth, nose, or anus
- Blood tests
- Biopsies, in which samples of tissues or cells are removed and looked at under a microscope or tested in the lab

Imaging tests and endoscopy exams

Imaging tests use sound waves, x-rays, magnetic fields, or radioactive substances to create pictures of the inside of your body. Imaging tests may be done for a number of reasons, including to look more closely at an abnormal area that might be a cancer, to learn how far cancer may have spread, to try to see where a cancer has started, and to help determine if treatment has been effective.

X-rays

X-rays are tests that use low doses of radiation to help doctors see bones and some aspects of certain organs. They can sometimes help when looking for cancer, but other tests like CT and MRI scans often provide better views of soft tissues in the body.

A chest x-ray is a simple test that lets the doctor to look at the lungs, heart, and bones of the upper body. It can help show if the cancer started in the lung or has spread to the lung. This test can be done in a doctor's office or any outpatient facility.

If your doctor suspects your cancer came from somewhere in your digestive tract, such as your esophagus, stomach, or large intestine, he or she may x-ray these organs. A liquid contrast material called *barium* can help outline the organs on the x-rays. You will be asked to drink it before having the x-rays if the esophagus and stomach are being looked at (called *an upper GI series*). If the large intestine is to be looked at (*a lower GI series* or *barium enema*), the barium is given as an enema before the test. Endoscopy is used more often than barium x-rays to look for CUP.

X-rays of bones can help evaluate pain that might come from cancer that has spread to the bones.

Computed tomography (CT) scan

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

A CT scanner has been described as a large donut, with a narrow table in the middle opening. You will need to lie still on the table while the scan is being done. CT scans take longer than regular x-rays, and you might feel a bit confined by the ring while the pictures are being taken.

Before any pictures are taken, you may be asked to drink 1 to 2 pints of a liquid called *oral contrast*. This helps outline the intestine so that certain areas are not mistaken for tumors. You may also receive an IV (intravenous) line through which a different kind of contrast dye (IV contrast) is injected. This helps better outline structures in your body.

The injection can 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 you have ever had a reaction to any contrast material used for x-rays. The contrast can also sometimes affect the kidneys, so usually a blood test to check kidney function is done before the contrast is given.

CT-guided needle biopsy: CT scans can also be used to guide a biopsy needle precisely into a tumor. For this procedure, you stay 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 doctors are sure that the needle is within the mass. A fine needle biopsy sample (tiny fragment of tissue) or a core needle biopsy sample (a thin cylinder of tissue about 1/2-inch long and less than 1/8-inch in diameter) is then removed and looked at under a microscope.

Magnetic resonance imaging (MRI) scan

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

MRI scans are a little more uncomfortable than CT scans. First, they take longer – often up to an hour. Second, you have to lie inside a narrow tube, which is confining and can upset people with claustrophobia (a fear of enclosed spaces). If this is severe, you may need to have the scan on an “open” MRI machine. These machines are less enclosed, but the scans may not be as good. Also, MRI machines make buzzing and clicking noises that you may find disturbing. Some centers provide headphones with music to block this noise out.

Ultrasound

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

Ultrasound is a fairly quick and easy procedure that doesn’t use radiation, which is why it is often one of the first tests done if an internal mass is suspected. For most ultrasound exams, you simply lie on a table and a technician moves the transducer on the skin over the part of the body being examined. Usually, the skin is lubricated with gel first.

Ultrasound can be useful to look at organs in the abdomen and pelvis to see if they have been affected by cancer.

Positron emission tomography (PET) scan

PET scans inject glucose (a form of sugar) that contains a radioactive atom into the blood. The amount of radioactivity used is very low. Because cancer cells in the body are growing rapidly, they absorb large amounts of the radioactive sugar. A special camera can then create

a picture of areas of radioactivity in the body. The picture is not finely detailed like a CT or MRI scan, but it can provide helpful information about the whole body.

A PET scan can be useful if you have cancer in lymph nodes in your neck. It may be able to find the source of the cancer somewhere in your head or neck. It can also help tell if an abnormal area on a chest x-ray is cancer.

Often, a PET scan is combined with a CT scan using a machine that can do both scans at the same time (PET/CT scan). This lets the doctor compare areas of higher radioactivity on the PET with the appearance of that area on the CT. PET/CT can be useful in finding the primary site in CUP. It is also helpful in locating other areas where the cancer has spread.

Somatostatin receptor scintigraphy

Somatostatin receptor scintigraphy (SRS), also known as *OctreoScan,* can be very helpful in diagnosing neuroendocrine tumors (NETs), including neuroendocrine carcinomas. It uses a hormone-like substance called *octreotide* that has been bound to radioactive indium-111. Octreotide attaches to proteins on the tumor cells of many NETs. To do this test, a small amount of this substance is injected into a vein. It travels through the blood and is attracted to NETs. About 4 hours after the injection, a special camera can be used to show where the radioactivity has collected in the body. Additional scans may be done on the following few days as well. This test is useful not only in finding some NETs, but also with determining treatment. If a tumor is seen on SRS, it is likely to respond to treatment with certain drugs.

Endoscopy

Endoscopy is a medical procedure in which tube-like instruments (called *endoscopes*) are used to look inside of the body. Some endoscopes are hollow so the doctor can see directly into the body, while others use fiber optics (flexible glass or plastic fibers that transmit light). Still others have a small video camera on the end for viewing.

Endoscopes are named for the part of the body they examine. For example, an endoscope that looks at the main airways in the lungs is called a *bronchoscope* and the procedure is called a *bronchoscopy*. The endoscope used to look at the inside of the colon is called a *colonoscope*.

Common types of endoscopy include:

- Laryngoscopy – to look at the larynx (voice box)
- Esophagogastroduodenoscopy (EGD, also called *upper endoscopy*) to look at the esophagus (the tube that connects the throat to the stomach), the stomach, and the duodenum (the first part of the small intestine)
- Bronchoscopy – to look at the lungs
- Colonoscopy – to look at the large intestine (colon)

- Cystoscopy – to look at the bladder

Depending on the area of the body being looked at, the endoscope may be inserted through an opening like the mouth, nose, or anus. Most endoscopies are done after you have been sedated (made sleepy) and is often painless.

Endoscopy is commonly used to look at the esophagus and stomach, the large intestine, the lungs, and the throat and larynx (voice box). If something suspicious is seen during the exam, biopsy samples may be removed with special tools used through the endoscope. The samples will then be viewed under a microscope to see if cancer cells are present.

Endoscopic ultrasound: This test is done with an ultrasound probe attached to an endoscope. It's most often used to get pictures of the pancreas and tumors of the esophagus. Patients are first sedated (given medicine to make them sleepy). The probe is then passed through the mouth or nose, to the esophagus. In the esophagus it can be used to look closer at any tumors present. When there are no esophagus tumors, the endoscope travels through the esophagus and the stomach, and into the first part of the small intestine. The probe can then be pointed toward the pancreas, which sits next to the small intestine. The probe is on the tip of the endoscope, so it's a very good way to look at the pancreas. It's better than CT scans for spotting small tumors in the pancreas. If a tumor is seen, it can be biopsied during this procedure.

A form of endoscopic ultrasound also can be used to look more closely at tumors of the rectum. For this procedure, the endoscope is passed through the anus and into the rectum.

Endoscopic retrograde pancreatography (ERCP): For this procedure, the endoscope is passed down the patient's throat, through the esophagus and stomach, and into the first part of the small intestine. The doctor can see through the endoscope to find the ampulla of Vater (the place where the common bile duct is connected to the small intestine). The doctor guides a catheter (a very small tube) from the end of the endoscope into the common bile duct. A small amount of dye (contrast material) is then injected through the tube into the common bile duct and x-rays are taken. This dye helps outline the bile duct and pancreatic duct. The x-ray images can show narrowing or blockage of these ducts that might be due to pancreatic cancer. The doctor doing this test can also put a small brush through the tube to remove cells to view under a microscope to see if they look like cancer. This procedure is usually done while you are sedated (given medicine to make you sleepy).

More information about these tests can be found in our document *Endoscopy*.

Blood tests

If signs and symptoms suggest you may have cancer, blood tests will probably be done to examine the number and type of blood cells and to measure levels of certain blood chemicals.

Complete blood count

The complete blood count (CBC) is a test that measures the different cells in the blood, such as the red blood cells, the white blood cells, and the platelets. Lower than normal numbers of different blood cell types may suggest that a CUP has spread to bones and replaced much of the normal bone marrow, where new blood cells are made.

Anemia (lower than normal numbers of red blood cells) might also mean there's stomach or intestinal bleeding caused by the cancer. This could point to somewhere in the stomach or intestine as the site of its origin.

Blood chemistry tests

Tests of chemical levels in the blood can show how well certain organs are functioning, and in some cases they might give a clue as to where cancer may be found in the body.

For example, abnormal liver function tests in a person with CUP may suggest cancer is in the liver. The cancer may have started in the liver or may have spread from another part of the body. Other blood tests can tell how well the kidneys are working and whether or not cancer has have invaded the bones.

Serum tumor markers

Some types of cancer release certain substances into the bloodstream that are known as tumor markers. There are many different tumor markers, but only a few of them are helpful in figuring out the origin of a cancer, such as:

- **Prostate-specific antigen (PSA):** A high PSA level in a man suggests that a CUP may have started in the prostate gland.
- **CA-125**: A high CA-125 level in a woman suggests ovarian, fallopian tube, or primary peritoneal cancer may be the cause.
- **Human chorionic gonadotropin (HCG):** High levels of HCG suggest a germ cell tumor, a type of cancer that can begin in the testicles, ovaries, the mediastinum (area between the lungs), or the retroperitoneum (area behind the intestines).
- **Alpha-fetoprotein (AFP):** This substance is produced by some germ cell tumors as well as by some cancers that start in the liver.
- **Chromogranin A (CgA):** CgA levels can go up with neuroendocrine cancers
- **CA 19-9**: High levels of this tumor marker suggest that the cancer started in the pancreas or bile ducts.

There are many other tumor markers, but they are less useful in patients with CUP because their levels go up with many different cancers. For example, *carcinoembryonic antigen* (CEA) can go up in the presence of an adenocarcinoma of any source. Cancers of the colon, lung, ovaries, pancreas, stomach and many others can be adenocarcinomas and cause the CEA level to rise.

Biopsies

Physical exams, imaging tests, and blood tests can sometimes strongly suggest a cancer is present, but in most cases a biopsy (removing some of the tumor for viewing under a microscope and other lab testing) is needed to know for certain that cancer is present. A biopsy is also usually needed to tell what kind of cancer it is (like adenocarcinoma or squamous cell carcinoma) and can give clues about where the cancer started. A biopsy is needed to diagnose CUP.

Different types of biopsies may be done depending on where a suspected tumor is located.

Fine needle aspiration (FNA) biopsy

In an FNA biopsy, the doctor uses a thin, hollow needle attached to a syringe to aspirate (withdraw) a few drops of fluid containing cells and tiny fragments of tissue. Local anesthetic (numbing medication) may be used on the skin where the needle will be inserted.

If a lymph node or tumor is near the skin's surface, the doctor can guide the placement of the needle by touch. If the mass is deeper inside the body, the doctor can use an imaging test like an ultrasound or a CT scan to guide the placement of a longer needle.

FNA biopsies are quick, cause little discomfort, have few complications, and are useful in determining if a lump is cancerous. But in many cases, an FNA biopsy will not remove enough tissue for all of the tests needed to identify some cancers of unknown primary. When that is the case, other types of biopsies may be needed.

Core needle biopsy

A core biopsy uses a slightly larger needle to remove more tissue – usually one or more cylinders of tissue about 1/16-inch across and 1/2- to 1-inch long. Like FNA biopsies, core biopsies can be done by touch or guided by imaging tests, depending on the tumor's location. They are usually done with local anesthesia (where you are awake but the area is numbed) in an outpatient setting.

A core needle biopsy removes larger pieces of tissue so it's more likely than an FNA biopsy to provide a clear diagnosis.

Excisional biopsy

During an excisional biopsy, a surgeon cuts through the skin to remove the entire tumor nodule or lymph node. Doctors often prefer this type of biopsy for a CUP because it allows them to get as much tissue as possible to help make the right diagnosis.

If the node or tumor is near the skin surface, this is a simple operation that can usually be done with local anesthesia. If the node or tumor nodule is inside the chest or abdomen, deep sedation or general anesthesia is needed (you will be asleep).

Sometimes this type of biopsy can be done using a laparoscope. A laparoscope is a thin, lighted tube called that is inserted through a small cut in the abdominal wall. This is used to see the contents of the abdomen and guide instruments to do surgery. Because laparoscopic surgery only requires a few small incisions (cuts), recovery time is often shorter than with regular, open surgery.

Thoracoscopy is similar to laparoscopy, but is used for surgery of the chest.

If a tumor is deep inside the body and removing it would require major surgery, doctors often try a fine needle or core needle biopsy first.

Incisional biopsy

This procedure is similar to an excisional biopsy except that it removes only a part of the tumor or mass. It is useful in sampling large tumors, when removing the entire mass might cause serious complications, side effects, or the need for a prolonged recovery. An incisional biopsy, like an excisional biopsy, can often be done with local anesthesia if the tumor is near the surface, but it requires deep sedation or general anesthesia if the tumor is deeper in the body.

Endoscopic biopsy

If anything abnormal is seen during endoscopy, it can often be biopsied at that time. Needle biopsies can be done using endoscopic ultrasound, and cells can also be sampled through the endoscope during an ERCP procedure.

Thoracentesis or paracentesis

If you have have large amounts of fluid inside your chest in the area around your lungs (known as a *pleural effusion*) or in your abdomen (*ascites*), samples of the fluid can be removed with a long, hollow needle. Often, ultrasound is used to guide the needle. The fluid is then looked at under a microscope to see if it contains cancer cells and, if so, to determine the type of cancer that is present. *Thoracentesis* is the medical term for removing fluid from the chest cavity. *Paracentesis* refers to removing fluid from the abdomen. These procedures are usually done under local anesthesia (numbing medicine), with you are awake.

Bone marrow aspiration and biopsy

These tests may be done to see if cancer has spread to the bone marrow, the soft inner part of certain bones where new blood cells are made.

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

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

A bone marrow biopsy is usually done just after the aspiration. A small piece of bone and marrow (about 1/16 inch in diameter and 1/2 inch long) is removed with a slightly larger needle that is twisted as it is pushed down into the bone. The biopsy may also cause some brief pain. Once the biopsy is done, pressure will be applied to the site to help stop any bleeding.

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

Lab tests of biopsy samples

All biopsy samples are first looked at under a microscope by a pathologist, a doctor who has special training in laboratory diagnosis of cancers. How the cancer looks under the microscope will often provide clues to its origin. If the diagnosis isn’t clear, then further testing might help.

Immunohistochemistry

For this test, very thin slices of the tissue from the biopsy are attached to glass microscope slides. The samples are then treated with special proteins (antibodies) designed to attach only to a specific substance found in certain cancer cells. If the patient’s cancer contains that substance, the antibody will attach to the cells. Chemicals are then added so that cells with antibodies attached to them change color. The doctor who looks at the sample under a microscope can see this color change. Doctors often need to use many different antibodies to try to determine what type of cancer is on the slides.

Flow cytometry

In flow cytometry, cells from a biopsy sample are treated with special antibodies, each of which sticks only to certain types of cells. The cells are then passed in front of a laser beam. If the antibodies have stuck to the cells, the laser causes them to give off a colored light that

is measured and analyzed by a computer. This test is probably most useful in helping to determine whether cancer in a lymph node is a lymphoma or some other cancer. It also can help determine the exact type of lymphoma so doctors can select the best treatment.

Cytogenetic testing

Cytogenetic tests look at a cell's chromosomes (pieces of DNA) under a microscope to find any changes. Normal human cells contain 46 chromosomes. Some types of cancer have characteristic abnormalities in their chromosomes. Finding these changes helps identify certain types of cancer. Several types of chromosome changes can be found in cancer cells.

- A *translocation* means a part of one chromosome has broken off and is now located on another chromosome.
- An *inversion* means that part of a chromosome is upside down (now in reverse order) but still attached to the original chromosome.
- A *deletion* indicates part of a chromosome has been lost.
- A *duplication* happens when all or part of a chromosome has been copied so that there are too many copies of it in the cell.

One drawback of cytogenetic testing is that it usually takes about 3 weeks to get results. This is because the cancer cells must grow in lab dishes for about 2 weeks before their chromosomes are ready to be viewed under the microscope. Another form of chromosome testing is called *fluorescence in situ hybridization (FISH)*. FISH uses special fluorescent dyes to recognize specific chromosome changes in certain types of cancer. An advantage of FISH is that it takes less time than standard cytogenetic testing. The disadvantage is that it only looks for specific genes and chromosome changes, so doctors must have an idea of what they are looking for ahead of time.

Molecular genetic testing

Testing cancer cells' DNA using methods like polymerase chain reaction (PCR) can find some genes and chromosome changes that can't be seen under a microscope in cytogenetic tests. PCR testing can find some translocations in parts of chromosomes too small to be seen with usual cytogenetic testing, but like FISH it requires that the doctors know what they are looking for. It can also be used to look for a certain viruses. For example, it can be used to find the Epstein-Barr virus, which is seen in nasopharyngeal cancer. Finding this virus in cancer cells from an enlarged neck lymph node can mean that it's a nasopharyngeal cancer.

This sophisticated testing is not needed in most cases, but it's sometimes helpful in classifying some cancers when other tests have not provided clues regarding their origin.

Gene expression profiling

With advances in technology, some newer lab tests are able to look at the activity of many genes in the cancer cells at the same time. By comparing the pattern of gene activity in the CUP sample to the patterns of activity seen with known types of cancer, doctors can sometimes get a better idea of where a cancer started. These tests can sometimes help your doctor discover where the cancer may have started, but so far, they haven't been linked to better outcomes in patients.

Electron microscopy

Most microscopes use a beam of ordinary light to view specimens. A much more complex, larger, and more expensive instrument called an *electron microscope* uses beams of electrons. The electron microscope's magnifying power is hundreds of times greater than that of an ordinary light microscope. This sometimes helps find very tiny details of cancer cell structure that can provide clues to the tumor type or origin.

Using the results of these tests, the appearance of the cancer under the microscope, the location of its metastasis, and other information about the patient (age, gender, etc.), it's often possible to find the source of the cancer or to classify the cancer in a way that can help guide treatment.

Classifying cancers of unknown primary

After initial lab tests, the pathologist classifies a cancer of unknown primary into 1 of the 5 main types:

- Squamous cell carcinoma
- Adenocarcinoma
- Poorly differentiated carcinoma
- Neuroendocrine carcinoma
- Poorly differentiated malignant neoplasm

Approaches to testing for cancer of unknown primary by location

Based on the classification and the location of the metastatic cancer, doctors decide which additional tests should be done. For example, a poorly differentiated malignant neoplasm may be tested further to try to classify it more precisely as a melanoma, lymphoma, sarcoma, small cell carcinoma, germ cell tumor, etc. The classification and location also help the doctor decide what other imaging tests may be helpful in looking for the primary site.

Some of the more common ways in which cancer of unknown primary may appear are listed with a brief description of what testing may be done.

Cancer in lymph nodes in the neck

Cancer that has spread to neck nodes usually comes from cancers of the mouth, throat, sinuses, salivary glands, larynx (voice box), thyroid, or lung. Tests will be done to look at these areas thoroughly for signs of where the cancer may have started.

The type of cancer is also a clue about where the cancer might have started. Most cancers of the mouth, throat, and larynx are squamous cell carcinomas. Lung cancer and cancer of the sinuses can be squamous cell carcinomas or adenocarcinomas. Salivary gland cancers are often a type of adenocarcinoma. Thyroid cancer can spread to neck lymph nodes. When it looks similar to normal thyroid tissue, it's easy to know where it came from. It can also look like adenocarcinoma. Cancers from all of these sites can also be poorly differentiated carcinomas or even poorly differentiated malignant neoplasms.

The base of the tongue, the throat, and the larynx are deep inside the neck and not seen easily. Indirect pharyngoscopy and laryngoscopy use small mirrors to look at these areas. A fiberoptic laryngoscope (a flexible, lighted, tube inserted through the mouth or nose) can be also be used to look in those areas, as well as deeper in the throat, if needed.

If the cancer is likely to have started in the head and neck area, the mouth, throat, larynx, esophagus (tube that connects the mouth to the stomach), trachea (wind pipe), and bronchi (tubes leading from the trachea to the lungs) will be examined very thoroughly. This exam, called *panendoscopy*, is done in the operating room while you are under general anesthesia (asleep).

Imaging tests like CT or MRI scans of the sinuses and neck area may be used to look for small cancers that may have already spread to lymph nodes in the neck. A PET scan (or combined PET/CT scan) may be done as well.

A chest CT scan and bronchoscopy (viewing the air passages through a flexible lighted tube) are often recommended to find suspected lung cancers that may have been missed by a routine chest x-ray.

Ultrasound or CT of the neck may be used to look for thyroid cancer.

Women with adenocarcinoma in lymph nodes under the arm

In women, cancer that has spread to underarm (axillary) nodes is most likely to have started in the breast, so a thorough breast physical exam is always done. Then diagnostic mammography (breast x-ray) and breast ultrasound are often the first tests ordered. If no tumor is found on these tests, an MRI of the breasts may be very useful.

Lab tests on the tumor cells can determine if they have estrogen receptors (ER) and/or progesterone receptors (PR). These receptors are often found in breast cancers, and finding them may help confirm the diagnosis of breast cancer. The presence of these receptors is also important in planning treatment, as cancers containing these receptors are likely to respond to hormone therapy.

If a breast cancer diagnosis cannot be confirmed, tests to look for lung cancer may be done. Lung cancer is the most common cause of cancer spread to underarm lymph nodes in men, and can also be the cause in women.

Cancer in lymph nodes in the groin

The most likely starting places of these cancers are the vulva, vagina, cervix, penis, skin of the legs, anus, rectum, or bladder, but other places are also possible.

- In women, a Pap test and pelvic exam (to look at the vulva, vagina, and cervix, and check for enlarged ovaries) are recommended. A CA-125 blood test may be done to see if ovarian cancer might be the source.
- In men, the penis and scrotum should be carefully examined. A blood test for prostate-specific antigen (PSA) can help tell if the cancer may have started in the prostate.
- In men and women, a proctoscopy (exam of the anus and the rectum through a lighted tube), skin exam, microscopic exam of urine, and abdominal and pelvic CT scans may be useful. If they are having urinary symptoms or have even a trace of blood in the urine, an exam of the bladder (cystoscopy) may be done as well.

Women with cancer throughout the pelvic cavity

The ovaries and fallopian tubes are the most likely source of a cancer that has spread in this way, but cancers from the breast, lung, or digestive tract can also spread here. Tests for CA-125 in the blood and tumor samples are positive in most ovarian and fallopian tube cancers, and can be used to help determine whether the primary tumor is likely to be from there or some other organ. CT scans of the abdomen and pelvis are also usually done.

Most cancers that start in the peritoneum (lining of the pelvis) look and behave like a cancer that started in the ovary and spread. They also cause the CA-125 level to go up. These cancers are called *primary peritoneal carcinoma* and are treated like ovarian cancer.

More information about ovarian, fallopian tube, and primary peritoneal cancers can be found in our document *Ovarian Cancer*.

Cancer in the retroperitoneum (back of the abdomen) or mediastinum (middle of the chest)

Germ cell tumors are one of the types of cancer that can start in these locations, especially in younger people. Most germ cell tumors develop from germ cells in the gonads (testicles or ovaries), but these cancers can sometimes start in other parts of the body, including the mediastinum (which is in the chest).

Results of blood tests and stains of the cancer cells for alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) are often positive in germ cell tumors. Cytogenetic or molecular studies may also find chromosomal changes that support a diagnosis of germ cell tumor.

In men, especially those who are younger or who have abnormal levels of AFP and/or HCG, ultrasound of the scrotum may be done to see if the cancer may have started in the testicles.

CT scans of the chest, abdomen, and pelvis are typically used to try to exclude other types of cancers (such as lung cancer). In women, tests may be done to see if the cancer started in the breast or ovaries.

It's important to identify germ cell tumors because they often respond well to certain combinations of chemotherapy drugs with good outcomes and sometimes, cures.

Melanoma in lymph nodes only

A thorough exam of the skin, nails, and other body surfaces such as the eye and the inside of the mouth is needed to look for the primary melanoma. Some primary melanomas that have already spread might be quite small or look like ordinary moles to the untrained examiner. Rarely, primary melanomas go away on their own without treatment after spreading, leaving behind only an area of slightly lighter colored skin.

Treatment of melanoma depends on whether it has spread only to lymph nodes or whether internal organs are also involved. Chest x-rays, CT scans of the head and abdomen, and blood tests are usually done to see if cancer can be found anywhere else in the body.

Cancer in other locations

The main goal in trying to determine the source of a CUP is to see if you have a cancer that may respond well to specific treatments. Some of the most important cancers to identify include thyroid, breast, and prostate cancers:

- Tests of the cancer cells for thyroglobulin can identify many thyroid cancers, which are often effectively treated with radioactive iodine injections.

- Tests of the cancer cells can help identify breast cancers containing estrogen receptors (ER) and progesterone receptors (PR), and these cancers can be treated with hormonal therapy.
- Blood tests and tests of cancer cells for prostate-specific antigen (PSA) can identify prostate cancer, which can be treated with hormone therapy.

Well differentiated neuroendocrine cancers can sometimes show up as liver metastases first (with no clear primary site). The source for these may be the pancreas (pancreatic neuroendocrine tumors), the gastrointestinal (GI) tract, or rarely, the lungs. These cancers tend to be slow growing and may respond to drug treatment.

More information about neuroendocrine cancers that start in the pancreas may be found in our document *Pancreatic Cancer*. Information about neuroendocrine cancers that start in the GI tract can be found in our document *Gastrointestinal Carcinoid Tumors*. Information about neuroendocrine tumors that start in the lungs can be found in our document *Lung Carcinoid Tumors*.

A type of poorly differentiated malignant neoplasm called *small cell carcinoma* or *poorly differentiated neuroendocrine carcinoma* can develop in the lungs and, less often, in other organs. Some of these cancers usually respond to certain chemotherapy combinations, although they are likely to come back (recur) at a later time.

How is a cancer of unknown primary staged?

Most types of cancer are given stages I, II, III or IV based on the size of the cancer, growth into nearby organs, and whether or not the cancer has spread to lymph nodes or distant organs in the body. Stage I is the least extensive, and the patients with this stage have the best outlook for a cure. Stage IV cancers have the most extensive spread and tend to have the poorest outlook.

For different types of cancer, each staging system is somewhat different. In order to know a cancer's stage, you first have to know where it started. Since the type of cancer is not known, it's not possible to accurately stage cancers of unknown primary (CUPs). Nonetheless, to be considered a CUP, the cancer must have spread beyond the primary site. **So all CUPs are at least a stage II, and most of them are stage III or IV.**

Even though a patient's exact stage may not be known, it's still possible to make some predictions about prognosis (outlook) based on which organs are affected by the cancer. For example, if the cancer is only found in lymph nodes in one area or in a single organ, the outlook tends to be better than if the cancer is found in many different organs. Of course, other factors, such as how the cancer cells look under a microscope, how well the cancer responds to treatment, and a person's overall health also play a role.

Survival statistics for cancer of unknown primary

Survival rates are often used by doctors as a standard way of discussing a person's prognosis (outlook). Some patients with cancer may want to know the survival statistics for people in similar situations, while others may not find the numbers helpful, or may even not want to know them. If you decide that you don't want to know them, stop reading here and skip to the next section.

CUP includes many different cancer types, so it's hard to provide meaningful survival statistics for these cancers as a group. In general, these are dangerous cancers for several reasons:

- When they are first diagnosed, these cancers have already spread beyond the site where they started. This means that the types of treatments that are most likely to be curative, such as surgery or radiation therapy, are not likely to result in a cure in most cases.
- Because the exact type of cancer is not known, it's harder for doctors to know what treatment is most likely to help the patient.
- Many cancers of unknown primary are fast-growing and/or fast-spreading cancers.

When all types of CUP are included, the average survival time is about 9 to 12 months after diagnosis. But this can vary widely depending on many factors, including the cancer cell type, where the cancer is found, how far the cancer has spread, a person's general health, the treatments received, and how well the cancer responds to treatment.

Certain CUPs may have better predicted survival. For example, women who have cancer spread throughout the pelvic cavity may have a stage III or IV ovarian, fallopian tube, or primary peritoneal cancer. If treated like advanced ovarian cancer, these women can be expected to have the same survival. The relative 5-year survival for stage III ovarian cancer is 34% (for more information, see "Survival by ovarian cancer stage" in our document *Ovarian Cancer*).

Survival statistics can sometimes be useful as a general guide, but they may not accurately represent any one person's prognosis (outlook). Your doctor is likely to be a good source as to whether these numbers may apply to you, as he or she is familiar with the aspects of your situation.

How is a cancer of unknown primary 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.

General treatment information

After your cancer is diagnosed, your cancer care team will discuss your treatment options with you. Choosing a treatment plan is an important decision, so it's important to take time and think about all of the choices.

In creating your treatment plan, the most important factors to consider are the type of cancer and its location. Your cancer care team will also take into account your general state of health and your personal preferences.

Treatment for cancer of unknown primary (CUP) may include:

- Surgery
- Radiation therapy
- Chemotherapy
- Hormone therapy
- Targeted therapy
- Other drugs

It's important to discuss all of your treatment options, including their goals and possible side effects, with your doctors to help make the decision that best fits your needs. If time permits, it's often a good idea to get a second opinion. A second opinion can give you more information and help you feel confident about your chosen treatment plan.

Often, CUP is too advanced to be cured, and the goal may be to shrink the cancer for a time, in hopes of improving symptoms and helping you live longer. This treatment is considered palliative or supportive care, because it's meant to relieve symptoms such as pain, but is not expected to cure the cancer.

The next few sections describe the different types of treatment that may be used for CUP. This is followed by a discussion of the typical treatments used for some of the more common instances of CUP.

Surgery for cancer of unknown primary

Surgery is a common treatment for many types of cancer if they are found at an early stage. But because cancer of unknown primary (CUP) has already spread beyond the site where it started, surgery is less likely to be helpful.

Surgery may be an option if the cancer is found only in the lymph nodes or in one organ, where the surgeon may be able to remove it all. However, there's still a chance that the cancer may be elsewhere in the body. If you are considering surgery as a treatment option, it's important to understand how likely it is to help you.

The type and extent of surgery will depend on where the cancer is and how extensive it is. If surgery is used, it may be followed by radiation therapy and possibly chemotherapy to try to kill any remaining cancer cells in the body.

For more information on surgery, see our document *Understanding Cancer Surgery: A Guide for Patients and Families*.

Radiation therapy for cancer of unknown primary

Radiation therapy uses high-energy rays or particles to destroy cancer cells or slow their rate of growth. The goal of radiation therapy may change based on the situation.

For some cancers that have not spread too far from where they started, it can be used alone or with other treatments such as surgery with the goal of trying to cure the cancer.

If cancer has spread extensively, radiation can be used to relieve symptoms such as pain, bleeding, trouble swallowing, intestinal blockage, compression of blood vessels or nerves by tumors, and problems caused by metastases to bones.

External beam radiation therapy

The most common way to deliver radiation to a cancer is to carefully focus a beam of radiation from a machine outside the body. This is known as external beam radiation. To reduce the risk of side effects, doctors carefully figure out the exact dose and aim the beam as accurately as they can to hit the target.

External beam radiation therapy is much like getting a diagnostic x-ray, but the radiation is more intense. The procedure itself is painless. Each treatment lasts only a few minutes, although the setup time – getting you into place for treatment – usually takes longer. The radiation is usually divided into many treatments over several days or weeks.

Internal radiation therapy (brachytherapy)

Another method of delivering radiation is called *internal radiation*, *interstitial radiation*, or *brachytherapy*. Instead of using radiation beams aimed from a large machine, a radioactive material is placed directly into, or as close as possible to, the cancer. This type of radiation travels a very short distance in the body. The material itself may be left in the body for only a short time, or it may be left there permanently.

Internal radiation therapy lets your doctor give a dose of radiation to a smaller area and in a shorter time than is possible with external radiation treatment.

Sometimes, both internal and external beam radiation therapies are used together.

Possible side effects of radiation therapy

Side effects can vary from patient to patient and depend on the radiation dose and the part of your body treated. Some of the possible side effects are listed below:

General side effects

- Fatigue (feeling tired)
- Loss of appetite
- Low blood counts
- Skin changes (like a sunburn at the area where the radiation beams enter the body)
- Hair loss (at the site where the beams enter the body)

Side effects from radiation to the head and neck

Radiation therapy to the head and neck area often causes damage to the throat and salivary glands, which can result in:

- Throat pain
- Mouth sores
- Trouble swallowing
- Loss of taste
- Hoarseness
- Dry mouth,

Over the long term it can also lead to cavities in the teeth and thyroid problems (from damage to the thyroid gland). This might mean that you need pills to replace thyroid hormone.

Side effects from radiation to the chest

- Trouble and pain swallowing from irritation of the esophagus (the tube that connects the throat to the esophagus
- Lung irritation that can lead to cough and shortness of breath

Side effects from radiation to the abdomen

- Nausea

- Vomiting,
- Diarrhea
- Poor appetite

Side effects from radiation to the pelvis

- Bladder irritation, leading to symptoms like pain or burning with urination and feeling like you have to go often
- Irritation of the rectum and anus, which can lead to diarrhea, bleeding, and pain
- In women, vaginal irritation and discharge.

Most of these side effects go away after treatment ends, but some are long-term and may never go away completely.

If chemotherapy is given along with radiation, the side effects are often worse.

There are ways to relieve many of these side effects, so it's important to discuss any changes you notice with your cancer care team.

For more information on radiation therapy, see the "Radiation Therapy" section of our website, or our document *Understanding Radiation Therapy: A Guide for Patients and Families*.

Chemotherapy for cancer of unknown primary

Chemotherapy (chemo) uses anti-cancer drugs that are usually injected into a vein or taken by mouth. These drugs enter the bloodstream and can reach cancer that has spread. Because chemo reaches all parts of the body, it can sometimes be useful for cancers of unknown primary, as it may help kill cancer cells in areas where they haven't been detected.

Chemo can be used in a number of situations for cancer of unknown primary (CUP). If your doctor recommends chemo, it's important that you understand what the goals of your treatment are.

Chemo may be the main treatment for cancers that are clearly advanced and are unlikely to be helped by local treatments such as surgery or radiation therapy. In some cases, such as with cancers that are likely to be germ cell tumors or certain types of lymphomas, it may be very effective in making tumors shrink or even go away altogether. In other cases, chemo may be used to try to relieve symptoms caused by the cancer and may be able to help people live longer.

For cancers that appear to have been removed completely with local therapies such as surgery or radiation, chemo may be added to try to kill any remaining cancer cells in the body.

Chemo drugs are often given in combinations, which are more likely to be effective than giving a single drug alone. Which chemo drugs are used depends on the type of cancer.

Adenocarcinoma and poorly differentiated carcinoma

For a CUP that is an adenocarcinoma or a poorly differentiated carcinoma, a number of chemo combinations may be used, including:

- Carboplatin plus paclitaxel (Taxol®), with or without etoposide (VP-16)
- Carboplatin plus docetaxel (Taxotere®)
- Cisplatin plus gemcitabine (Gemzar®)
- Gemcitabine plus docetaxel
- Oxaliplatin plus 5-fluorouracil and leucovorin (folinic acid)
- Oxaliplatin plus capecitabine (Xeloda)

Squamous cell cancer (carcinoma)

If chemotherapy is to be used for a CUP that is a squamous cell cancer, the options include:

- Cisplatin or carboplatin plus a taxane (paclitaxel or docetaxel)
- Cisplatin, docetaxel, and 5-fluorouracil (5-FU)
- Cisplatin plus gemcitabine

Neuroendocrine cancers (carcinomas)

Neuroendocrine carcinomas that are poorly differentiated are often treated with the same chemo as is used for small cell cancer of the lung: a platinum drug (cisplatin or carboplatin) and etoposide.

Well-differentiated neuroendocrine cancers are not often the cause of CUP, but may present with liver metastasis and an occult primary. These patients are treated like patients with well-differentiated carcinoid tumor, with drugs combinations such as:

- Doxorubicin (Adriamycin®) and streptozocin
- Temozolomide plus capecitabine

More information about the treatment of well-differentiated neuroendocrine cancers can be found in our documents *Gastrointestinal Carcinoid Tumors*, *Lung Carcinoid Tumor*, and *Pancreatic Cancer*.

Possible side effects of chemotherapy

Chemo drugs work by attacking cells that are dividing quickly, which is why they work against cancer cells. But other cells in the body, like those in the bone marrow, the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to side effects. Some people have many side effects, while others may have few.

The side effects of chemotherapy depend on the type of drugs, the amount taken, and the length of treatment. Some of the most common possible side effects include:

- Hair loss
- Mouth sores
- Loss of appetite
- Nausea and vomiting
- Low blood cell counts

Chemotherapy often affects the blood-forming cells of the bone marrow, leading to low blood cell counts. This can cause:

- Increased chance of infections (low white blood cell counts)
- Easy bruising or bleeding (low blood platelet counts)
- Fatigue (low red blood cell counts or other reasons)

These side effects are usually short-term and go away after treatment is finished. It's important to let your health care team know if you have any side effects, as there are often ways to lessen them. For example, drugs can be given to help prevent or reduce nausea and vomiting.

Several other side effects are also possible. Some of these are only seen with certain chemo drugs. Your cancer care team will give you information about the possible side effects of the specific drugs you are getting. It's important to know the specific side effects that can occur with your drugs so you know what to expect and when to call your doctor.

As with other types of treatment, the chance that the benefits of chemo will outweigh the downsides will depend on a number of factors, including the type and extent of the cancer and a person's general health before treatment. If you are considering chemo, it's important to talk to your doctor about the chances that it will be helpful versus the likely side effects you will have.

For more information on chemotherapy, see the "Chemotherapy" section of our website, or our document *A Guide to Chemotherapy*.

Hormone therapy for cancer of unknown primary

Some types of cancer grow in response to sex hormones in the body. For example, most breast cancers have proteins called *estrogen receptors* and/or *progesterone receptors* on the surface of their cells. These cancers grow faster when exposed to the hormone estrogen. Likewise, most prostate cancers grow in response to male hormones called *androgens*, such as testosterone.

In cases where a cancer of unknown primary (CUP) is likely to be a breast or prostate cancer, hormone therapy may be an effective way to slow the growth of the cancer, or perhaps even shrink it, and may help you live longer.

For breast cancer, types of hormone therapy include drugs like tamoxifen, LHRH agonists like leuprolide (Lupron®) and goserelin (Zoladex®), and the aromatase inhibitors anastrozole (Arimidex®), letrozole (Femara®), and exemestane (Aromasin®). These drugs either lower estrogen levels or prevent cancer cells from being able to use it. For more information on how these drugs are used and their potential side effects, see our document *Breast Cancer*.

Hormone therapy can also be used to treat prostate cancer. Some commonly used drugs include LHRH agonists such as leuprolide and goserelin, and anti-androgens such as flutamide (Eulexin®) and bicalutamide (Casodex®). These drugs either lower the testosterone level or prevent cancer cells from being able to use it. Surgery to remove the testicles (orchiectomy) is another option. For more information, see our document *Prostate Cancer*.

Targeted therapy for cancer of unknown primary

Targeted therapy is a newer type of cancer treatment that uses drugs or other substances to identify and attack cancer cells while doing little damage to normal cells. These therapies attack the cancer cells' inner workings – the programming that makes them different from normal, healthy cells. Each type of targeted therapy works differently, but all alter the way a cancer cell grows, divides, repairs itself, or interacts with other cells.

One target on squamous cell cancers of the head and neck is called *epidermal growth factor receptor (EGFR)*. Cells from many of these cancers have too many copies of EGFR, which helps them grow faster and become more resistant to radiation or chemotherapy (chemo). A drug called cetuximab (Erbitux®) blocks EGFR, and can help patients with squamous cell cancers of the head and neck area. It's often used along with radiation or chemotherapy (chemo), but it can also be used by itself to treat people whose cancers no longer respond to chemo and who can't take radiation.

A number of targeted therapy drugs are used to treat breast cancer, including trastuzumab (Herceptin®), pertuzumab (Perjeta®), lapatinib (Tykerb®), and everolimus (Affinitor®). For more information, see the section "Targeted therapy for breast cancer" in our *Breast Cancer* document.

Other targeted therapy drugs are used for cancers that start in other areas, and may be helpful in some cases of cancer of unknown primary. For example, sunitinib (Sutent®) and everolimus (Afinitor®) are helpful in treating pancreatic neuroendocrine cancer, and may be used to treat well differentiated neuroendocrine cancers of unknown primary.

Other drugs for cancer of unknown primary

Bisphosphonates

Bisphosphonates are drugs that are used to help strengthen and reduce the risk of fractures in bones that have been weakened by metastatic cancer. Examples include pamidronate (Aredia®) and zoledronic acid (Zometa®). They are given intravenously (IV). To treat cancer that has spread to bone, they are given once a month.

Bisphosphonates can have side effects, including flu-like symptoms and bone pain. They can also cause kidney problems, so people with kidney problems can't use them. A rare but very distressing side effect of intravenous bisphosphonates is damage (osteonecrosis) in the jaw bones (ONJ). It can be triggered by having a tooth extraction (removal) while getting treated with the bisphosphonate. ONJ often appears as an open sore in the jaw that won't heal. It can lead to loss of teeth or infections of the jaw bone. Doctors don't know why this happens or how to treat it, other than to stop the bisphosphonates. Maintaining good oral hygiene by flossing, brushing, making sure that dentures fit properly, and having regular dental check-ups may help prevent this. Most doctors recommend that patients have a dental check-up and have any tooth or jaw problems treated before they start taking a bisphosphonate.

Denosumab

Like bisphosphonates, denosumab (Prolia®, Xgeva®) is a drug that can be used to strengthen bones and lower the risk of fractures in bones weakened by cancer spread. To treat cancer that has spread to bone, this drug is given as an injection under the skin, once a month.

Side effects include low levels of calcium and phosphate and ONJ. This drug does not cause kidney damage, so it is safe to give to people with kidney problems.

Octreotide

Octreotide (Sandostatin®) is an agent chemically related to a natural hormone, somatostatin. It's very helpful for some patients with neuroendocrine tumors. If the tumor releases hormones into the bloodstream (which is rare in the poorly differentiated tumors that cause cancer of unknown primary), this drug can stop the hormone release. It can also cause tumors to stop growing or (rarely) to shrink. This drug is available as a short-acting version given as injection 2 to 4 times a day. It's also available as a long-acting injection that needs to be given only once a month. A similar drug, lanreotide (Somatuline®), is also available. It's also

given as an injection once a month. These drugs are most likely to help treat cancers that show up on somatostatin receptor scintigraphy (OctreoScan).

Clinical trials for cancer of unknown primary

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

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

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

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

Clinical trials are one way to get state-of-the art cancer treatment. In some cases they may be the only way to get access to newer treatments. They are also the only way for doctors to learn better methods to treat cancer. Still, they are not right for everyone.

You can get a lot more information on clinical trials in our document called *Clinical Trials: What You Need to Know*.

Complementary and alternative therapies for cancer of unknown primary

When you have cancer you are likely to hear about ways to treat your cancer or relieve symptoms that your doctor hasn't mentioned. Everyone from friends and family to Internet groups and websites may offer ideas for what might help you. 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 you feel better. Some methods that are used along with regular treatment are meditation 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 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 you may lose the chance to be helped by standard medical treatment. Delays or interruptions in your medical treatments may give the cancer more time to grow and make it less likely that treatment will help.

Finding out more

It's easy to see why people with cancer think about alternative methods. You want to do all you can to 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 of these alternative methods have not been tested and proven to work in treating cancer.

As you consider your 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 have regular medical treatments? Is the treatment a "secret" that requires you to visit certain providers or travel to another country?
- Talk to your doctor or nurse about any method you are thinking about using.
- Contact us at 1-800-227-2345 or see the "Complementary and Alternative Medicine" section of our website to learn more about complementary and alternative methods in general and to find out about the specific methods you are looking at.

The choice is yours

Decisions about how to treat or manage your cancer are always yours to make. If you want to use a non-standard treatment, learn all you can about the method and talk to your doctor about it. With good information and the support of your health care team, you may be able to safely use the methods that can help you while avoiding those that could be harmful.

Treatment of specific instances of a cancer of unknown primary

The types of treatment used for a cancer of unknown primary depend on several factors, including the size and location of the cancer, the results of lab tests, and how likely it is to be a certain type of cancer. Your overall health and ability to tolerate treatment matter also. Of course, if the origin of the cancer can be determined during testing, the cancer would no longer be an unknown primary and would be treated according to where it started.

Squamous cell carcinoma in lymph nodes in the neck

Often these cancers began somewhere in the mouth, throat, or larynx. They are often treated with surgery and/or radiation therapy.

Surgical treatment removes lymph nodes and other tissue from the neck. This operation is called a *neck dissection*. There are several types that differ in the amount of tissue removed from the neck:

- A *partial* or *selective* neck dissection removes only a few lymph nodes.
- A *modified radical* neck dissection removes most lymph nodes on one side of the neck between the jawbone and collarbone, as well as some muscle and nerve tissue.
- A *radical* neck dissection removes nearly all the nodes on one side, as well as even more muscles, nerves, and veins.

The most common side effects of any neck dissection are numbness of the ear, weakness in raising the arm above the head, and weakness of the lower lip. These side effects are caused by injury during the operation to the nerves that supply these areas. After a selective neck dissection, the weakness of the arm and lower lip usually go away after a few months. But if a nerve is removed as part of surgery, the weakness will be permanent. After any neck dissection, physical therapists can show the patient exercises to improve neck and shoulder movement.

Radiation therapy might be used instead of surgery. One potential advantage is that the area treated would include both the nodes with metastatic cancer and several of the areas of the neck likely to contain a primary tumor.

Some patients are treated with both surgery and radiation therapy. This is considered when large and/or many tumors are present. The radiation may be given before or after surgery.

When tumors are very large or present on both sides of the neck, chemotherapy (chemo) and radiation therapy are often used together. Cisplatin and 5-FU with a taxane [docetaxel (Taxotere) or paclitaxel (Taxol)] are the usual chemotherapy drugs used. Cetuximab (Erbitux) may also be used with radiation (instead of chemo).

The outlook for these patients depends on the size, number, and location of the lymph nodes containing metastatic cancer. For more information about the usual treatments for these

cancers see our documents *Nasal Cavity and Paranasal Sinus Cancers*, *Oral Cavity and Oropharyngeal Cancer* and *Laryngeal and Hypopharyngeal Cancer*.

Adenocarcinoma in lymph nodes under the arm

Because most cancers that have spread to the axillary nodes (lymph nodes under the arm) in women are breast cancers, the recommended treatment is similar to that for women diagnosed with breast cancer that has spread to these nodes.

Surgery to remove axillary nodes (called an *axillary lymph node dissection*) is done, and the breast on the same side may be treated with mastectomy (surgery to remove the breast) or radiation therapy.

Depending on the woman's age and whether the cancer cells contain estrogen and/or progesterone receptors, additional (adjuvant) treatment may include hormonal therapy (with tamoxifen or an aromatase inhibitor), chemo, or both. The cancer can also be tested for a protein called *HER2*. If positive, a drug that targets the HER2 protein such as trastuzumab (Herceptin) may be used. For more information about prognosis and treatment of breast cancer that has spread to the lymph nodes, see our document *Breast Cancer*.

Although cancer in axillary lymph nodes in men may represent spread from a breast cancer, spread from a lung cancer is much more likely. An axillary lymph node dissection and/or radiation therapy to the underarm area may be considered in some cases, but many doctors would recommend chemo first and waiting to see how the enlarged lymph nodes respond. The combination of drugs would probably be the same as that given for adenocarcinomas or poorly differentiated carcinomas found in other parts of the body.

Cancer in groin lymph nodes

It's important to search carefully for the origin of these cancers, as many of them can be treated effectively if it is found. If the primary tumor can't be found, surgery is usually the main treatment.

If the cancer appears to be confined to a single lymph node, removing it may be the only treatment. In other cases, more extensive surgery (a lymph node dissection) may be needed. If more than one lymph node is found to contain cancer, radiation therapy and/or chemotherapy may be recommended as well.

Women with cancer throughout the pelvic cavity

Unless tests have found a primary cancer outside the ovaries (in which case the diagnosis of cancer of unknown primary would no longer apply), these cancers are most likely to be spread from either ovarian cancer, fallopian tube cancer, or primary peritoneal carcinoma (PPC). Fallopian tube cancer and PPC are diseases similar to ovarian cancer and they are all treated the same way.

Treatment is typically surgery to remove the uterus, both ovaries, both fallopian tubes, and as much of the cancer as possible. After surgery, 6 to 8 months of chemo is recommended, usually with a taxane (paclitaxel or docetaxel) and platinum drug (cisplatin or carboplatin). For more information, see our document *Ovarian Cancer*.

Cancer in the retroperitoneum (back of the abdomen) or mediastinum (middle of the chest)

If lab tests of the tumor sample have ruled out lymphoma, the most likely diagnosis (particularly in younger men) is a germ cell tumor. Even cancers in these areas that do not have lab results typical of germ cell tumors often respond to chemotherapy combinations for treating testicular germ cell tumors. Chemo drugs used include cisplatin and etoposide, sometimes with bleomycin or ifosfamide. More information about the treatment of germ cell tumors can be found in our documents *Testicular Cancer* and *Ovarian Cancer*.

If a carcinoma is in the mediastinum in an older patient it may be treated as a non-small cell lung cancer.

Melanoma in lymph nodes only

Once a cancer of unknown primary (CUP) has been diagnosed as a melanoma, it’s no longer a true CUP. This situation is mentioned, nonetheless, because some tests to identify melanomas may take several days. Until they are complete, these patients are considered to have CUP.

The recommended initial treatment of melanoma of unknown primary with only lymph node spread is surgery to remove the lymph nodes in the affected area. If spread to other nodes becomes apparent at a later time and all of the cancer can be removed, these nodes are also removed. For more information see our document *Melanoma Skin Cancer*.

Cancer in other locations such as bone or liver

This group represents the majority of people with CUP. Usually the cancer is in the bones, lung, or liver. Once lab testing of the biopsy specimen has excluded cancers of the breast, prostate, thyroid, and lymphoma (all of which often respond well to specific treatments), many of the remaining patients are treated with chemo to try to shrink the tumor and reduce symptoms.

Most doctors use a standard chemotherapy regimen. It consists of either cisplatin or carboplatin, combined with a taxane drug such as paclitaxel or docetaxel. Other drugs like gemcitabine may be used as well. It’s important to stop chemo if it’s not working to relieve symptoms or shrink the cancer, as the side effects of these drugs can be severe and impair quality of life.

Sometimes chemo can be quite helpful. About 15% of patients treated with aggressive chemo will have a complete response (with no visible cancer left after treatment), and in some of these the cancer stays away for years.

Patients in poor health who would not be able to tolerate the side effects of aggressive chemo are sometimes treated with lower doses or with drugs that cause fewer side effects. But the benefit of this approach is not clearly proven. Another option is to focus on relieving symptoms as they occur. Many patients with cancer spread to bones benefit from treatment with bisphosphonates (discussed in the section "Other drugs for cancer of unknown primary"). These drugs can help strengthen bones weakened by cancer, preventing fractures (breaks), and reducing pain.

Some poorly differentiated small cell cancers of unknown origin can shrink dramatically using chemo combinations originally developed to treat small cell lung cancer. The benefit usually lasts for several months, but these cancers almost always return.

Some neuroendocrine cancers may respond to treatment with octreotide (Sandostatin) or lanreotide (Somatuline). These drugs may be able to slow or stop growth for some time. The tumors most likely to respond are the ones able to be seen on somatostatin receptor scintigraphy (imaging). Some other drugs known as targeted therapy that are helpful in treating pancreatic neuroendocrine cancers may be used as well. More information about these can be found in the section "Chemotherapy for pancreatic cancer" in our document *Pancreatic Cancer*.

More information about treatments for cancers that have spread can be found in our document *Advanced Cancer*.

Palliative care for cancer of unknown primary

Some cancers of unknown primary can be treated effectively or even cured, but most are advanced cancers for which treatments are unlikely to provide long-term benefits. It's very important that people with advanced cancer of unknown primary (CUP) are aware that even if the cancer can't be cured, there are treatments available to help prevent or relieve pain and other symptoms. More information about these can be found in our document *Advanced Cancer*.

Pain is a significant concern for patients with cancer of unknown primary. There are proven ways to relieve pain due to cancer of unknown primary using a combination of medicines and, in some cases, surgical procedures. Patients should not hesitate to take advantage of these treatments, which means they must tell their doctors if they have pain. Otherwise the doctor can't help. For most patients, treatment with morphine or drugs related to it (called *opioids* because they are related to opium) can reduce pain considerably while still allowing them to function well. For the treatment to be effective, the pain medicines must be given regularly on a schedule, not just when the pain becomes severe. Several long-acting forms of

morphine and other long-acting opioid drugs have been developed that need only be given once or twice a day.

For more information on pain, what can be done about it, and how to keep track of it, see the "Cancer-related Pain" section of our website, or our document "*Guide to Controlling Cancer Pain*."

More treatment information

For more details on treatment options – including some that may not be addressed in this document – the National Cancer Institute (NCI) and the National Comprehensive Cancer Network (NCCN) are good sources of information.

The NCI provides treatment information via phone (1-800-4-CANCER) and its website (www.cancer.gov). Information for patients as well as more detailed information intended for use by cancer care professionals is also available on www.cancer.gov.

The NCCN, made up of experts from many of the nation's leading cancer centers, develops cancer treatment guidelines for doctors to use when treating patients. These are available on the NCCN website (www.nccn.org).

What should you ask your doctor about a cancer of unknown primary?

It's important to have frank, open, and honest communication with your doctor about your condition. Don't be afraid to ask questions, no matter how minor you think they are. For instance, consider these questions:

- Should I have extensive testing to find out what kind of cancer of unknown primary (CUP) I have?
- What kind of CUP do I have? How extensive is it?
- Have you done all the appropriate tests on my biopsy specimen?
- What are my treatment choices?
- Are there any clinical trials I should think about taking part in?
- Which treatment do you recommend, and why?
- How long will treatment last? What will it involve? Where will it be done?
- What are the likely side effects to the treatment(s) that you recommend?
- What can I do to help reduce the side effects I may have from treatment?

- What are the chances that my CUP will come back if initial treatment seems to be successful? What would we do if that happens?

Be sure to write down any questions that occur to you that are not on this list. For instance, you might want specific information about treatment recovery times. Or you may want to ask about second opinions.

Other things to consider

How about your emotional health?

During cancer treatment, you may find yourself overwhelmed by emotions. This happens to a lot of people. You may find that you think about the potential of your own death, or the effect of your cancer on your family, friends, and career.

This is an ideal time to seek out emotional and social support. You need people you can turn to for strength and comfort. Support can come in many forms: family, friends, cancer support groups, church or spiritual groups, online support communities, or individual counselors.

Almost everyone who is going through through cancer can benefit from getting some type of support. What's best for you depends on your situation and personality. Some people feel safe in peer-support groups or education groups. Others would rather talk in an informal setting, such as church. Others may feel more at ease talking one-on-one with a trusted friend or counselor. Whatever your source of strength or comfort, make sure you have a place to go with your concerns.

The cancer journey can feel very lonely. It's not necessary or realistic to go it all by yourself. And your friends and family may feel shut out if you decide not include them. Let them in – and let in anyone else who you feel may help. If you aren't sure who can help, call your American Cancer Society at 1-800-227-2345 and we can put you in touch with an appropriate group or resource.

You can't change the fact that you have cancer. What you can change is how you live the rest of your life – making healthy choices and feeling as well as possible, physically and emotionally.

If treatment for cancer of unknown primary stops working

If cancer keeps growing or comes back after one kind of treatment, it's possible that another treatment plan might still cure the cancer, or at least shrink it enough to help you live longer and feel better. But when a person has tried many different treatments and the cancer has not gotten any better, the cancer tends to become resistant to all treatment. If this happens, it's

important to weigh the possible limited benefits of a new treatment against the possible downsides. Everyone has their own way of looking at this.

This is likely to be the hardest part of your battle with cancer – when you have been through many medical treatments and nothing's working anymore. Your doctor may offer you new options, but at some point you may need to consider that treatment is not likely to improve your health or change your outcome or survival.

If you want to continue to get treatment for as long as you can, you need to think about the odds of treatment having any benefit and how this compares to the possible risks and side effects. In many cases, your doctor can estimate how likely it is the cancer will respond to treatment you are considering. For instance, the doctor may say that more chemo or radiation might have about a 1% chance of working. Some people are still tempted to try this. But it's important to think about and understand your reasons for choosing this plan.

No matter what you decide to do, you need to feel as good as you can. Make sure you are asking for and getting treatment for any symptoms you might have, such as nausea or pain. This type of treatment is called *palliative care*.

Palliative care helps relieve symptoms, but is not expected to cure the disease. It can be given along with cancer treatment, or can even be cancer treatment. The difference is its purpose - the main purpose of palliative care is to improve the quality of your life, or help you feel as good as you can for as long as you can. Sometimes this means using drugs to help with symptoms like pain or nausea. Sometimes, though, the treatments used to control your symptoms are the same as those used to treat cancer. For instance, radiation might be used to help relieve bone pain caused by cancer that has spread to the bones. Or chemo might be used to help shrink a tumor and keep it from blocking the bowels. But this is not the same as treatment to try to cure the cancer.

At some point, you may benefit from hospice care. This is special care that treats the person rather than the disease; it focuses on quality rather than length of life. Most of the time, it's given at home. Your cancer may be causing problems that need to be managed, and hospice focuses on your comfort. You should know that while getting hospice care often means the end of treatments such as chemo and radiation, it doesn't mean you can't have treatment for the problems caused by your cancer or other health conditions. In hospice the focus of your care is on living life as fully as possible and feeling as well as you can at this difficult time. You can learn more about hospice in our documents called *Hospice Care* and *Nearing the End of Life*.

Staying hopeful is important, too. Your hope for a cure may not be as bright, but there's still hope for good times with family and friends – times that are filled with happiness and meaning. Pausing at this time in your cancer treatment gives you a chance to refocus on the most important things in your life. Now is the time to do some things you've always wanted to do and to stop doing the things you no longer want to do. Though the cancer may be beyond your control, there are still choices you can make.

What’s new in research and treatment for cancer of unknown primary?

Research into the causes, diagnosis, and treatment of cancer is being done at many cancer research centers. Scientists are making progress in understanding how changes in a person’s DNA can cause normal cells to develop into cancer. A greater understanding of the gene changes that can occur in cancer is providing insight into why these cells become abnormal. Some of these advances may lead to better diagnosis and treatment of cancer of unknown primary (CUP).

Diagnosis

It’s important that doctors are able to identify the origin of cancers of unknown primary so that the most effective treatments can be used. Immunohistochemistry and other lab tests can be very helpful in this regard, but they are not yet able to tell where all CUPs have started. Newer lab tests now becoming available will help classify CUP more precisely and predict a patient’s prognosis and response to treatment.

Hopefully at some point in the future, the number of cancers of unknown primary will drop dramatically, as doctors will be able to test tumor samples and determine what types of cancer they are.

Treatment

Because CUP represents a number of different types of cancer, it’s unlikely that a single treatment breakthrough will benefit all people with CUP. Still, progress in treating some of the more common types of cancer is likely to benefit people with CUP as well, especially if the cancers can be classified more accurately.

Some newer drugs called *targeted therapies* are being studied. These drugs have more selective effects than chemotherapy (chemo). Some of these, such as bevacizumab (Avastin®) and erlotinib (Tarceva®), are available to treat other cancers and have shown some activity in CUP.

Recent studies have found that cancers starting in each organ are not all the same. They can have different changes in their most important molecules and respond differently to treatments.

As targeted treatments are found for more of the specific molecular changes in cancer cells, knowing the origin of a cancer may become less important. Instead, detailed information about changes in the cancer cells’ DNA and RNA may become more important in choosing the treatments most likely to help individual patients.

Cancer cells from CUP are sometimes tested in a lab to try to see which chemo drugs will be likely to work. Unfortunately, these tests don't always do a good job of predicting the right chemo drugs. Many doctors don't find them very helpful.

Many patients with cancer of unknown primary face a serious prognosis, so the need for advances in treatment is obvious. Clinical trials of new treatments are essential if progress is to occur. Some of these trials are testing new chemo drugs, new drug combinations, and new ways to give these drugs. Other clinical trials are studying new approaches to treatment, such as biological therapy, immunotherapy, and gene therapy. Because CUP is a very diverse category of many types of cancers, progress against CUP is likely to depend on continued progress toward understanding the molecular basis of all cancers.

Additional resources for cancer of unknown primary

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.

Dealing with cancer and treatment

Health Professionals Associated With Cancer Care

Talking With Your Doctor (also in Spanish)

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

Coping With Cancer in Everyday Life (also in Spanish)

Advanced Cancer (also in Spanish)

When Cancer Doesn't Go Away

Family and caregiver concerns

Talking With Friends and Relatives About Your Cancer (also in Spanish)

Helping Children When A Family Member Has Cancer: Dealing With Diagnosis (also in Spanish)

What It Takes to Be a Caregiver

Insurance and financial issues

In Treatment: Financial Guidance for Cancer Survivors and Their Families (also in Spanish)

Health Insurance and Financial Assistance for the Cancer Patient (also in Spanish)

More on cancer treatments

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

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)

Targeted Therapy

Cancer treatment side effects

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

Distress in People With Cancer

Anxiety, Fear, and Depression

Nausea and Vomiting

Guide to Controlling Cancer Pain (also in Spanish)

Get Relief From Cancer Pain

Pain Diary

Anemia in People With Cancer

Fatigue in People With Cancer

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.

National organizations and web sites*

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

National Cancer Institute (NCI)
Toll-free number: 1-800-422-6237 (1-800-4-CANCER)

TTY: 1-800-332-8615
Website: www.cancer.gov

Their "Cancer Information Service" offers a wide variety of free, accurate, up-to-date information about cancer to patients, their families, and the general public; also can help people find clinical trials in their area

National Coalition for Cancer Survivorship (NCCS)
Toll-free-number: 1-888-650-9127
Website: www.canceradvocacy.org

Has publications on many cancer-related topics; also offers the Cancer Survival Toolbox – a free program that teaches skills that can help people with cancer meet the challenges of their illness

**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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1-800-227-2345 or www.cancer.org