Cancer of Unknown Primary Early Detection, Diagnosis, and Staging

Detection and Diagnosis

Learn what tests are used to diagnose and stage cancers of unknown primary.

- Can a Cancer of Unknown Primary Be Found Early?
- Signs and Symptoms of a Cancer of Unknown Primary
- How Is a Cancer of Unknown Primary Diagnosed?
- Approaches to Testing for Cancer of Unknown Primary by Location

Stages and Outlook (Prognosis)

After a cancer diagnosis, staging provides important information about the extent of cancer in the body and anticipated response to treatment.

- How Is a Cancer of Unknown Primary Staged?
- Survival Statistics for Cancer of Unknown Primary

Questions to Ask About Cancer of Unknown Primary

Here are some questions you can ask your cancer care team to help you better understand your cancer diagnosis and treatment options.

- What Should You Ask Your Doctor About a Cancer of Unknown Primary?

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.

- References
  See all references for Cancer of Unknown Primary

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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.

References

See all references for Cancer of Unknown Primary

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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 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
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 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
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

References

See all references for Cancer of Unknown Primary

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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.

- References
See all references for Cancer of Unknown Primary

How Is a Cancer of Unknown Primary Staged?

After someone is diagnosed with a cancer, doctors will try to figure out if it has spread, and if so, how far. This process is called staging. A cancer's stage is determined by examining tissue removed during an operation and sometimes imaging tests and physical exam. The stage describes how much cancer is in the body. It helps determine how serious the cancer is and how best to treat it. Doctors also use a cancer's stage when talking about survival statistics.

How is the stage determined?

The staging system used for most cancers is the American Joint Committee on Cancer (AJCC) TNM system, which is based on 3 key pieces of information:

- The extent (size) of the tumor (T): How large is the cancer? Has it grown into nearby structures or tissues?
• The spread to nearby lymph nodes (N): Has the cancer spread to nearby lymph nodes?
• The spread (metastasis) to distant sites (M): Has the cancer spread to other parts of the body?

Numbers or letters after T, N, and M provide more details about each of these factors. Higher numbers mean the cancer is more advanced.

Once a person’s T, N, and M categories have been determined, this information is combined in a process called stage grouping to assign an overall stage. Most cancers have stages that range from I (1) through IV (4). As a rule, the lower the number, the less the cancer has spread. A higher number, such as stage IV, means cancer has spread more. Stage I is the least spread, and patients with this stage tend to have the best outlook. Stage IV cancers have the most spread and tend to have the poorest outlook.

For different types of cancer, each staging system is somewhat different. To determine a cancer’s stage, you first have to know where it started. Since the type of cancer is not known, it is difficult 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.

The most recent American Joint Committee on Cancer (AJCC) staging system, effective January 2018, applies to cancer that is found in the lymph nodes of the neck but the primary cancer has not been found. This is considered a cancer of unknown primary, but since most of these cancers are thought to start in the head and neck area they are treated as such. If your cancer fits this description, it is best to talk to your doctor about your specific stage.

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 well the cancer responds to treatment and a person’s overall health also play a role.

Cancer staging can be complex, so ask your doctor to explain it to you in a way you understand.

• References
See all references for Cancer of Unknown Primary
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.

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. (For more information, see Survival Rates for Ovarian Cancer, by Stage.)

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
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.

- References