



[cancer.org](https://www.cancer.org) | 1.800.227.2345

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](#)
- [Tests for a Cancer of Unknown Primary](#)
- [Testing for a 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.

- [Cancer of Unknown Primary Stages](#)
- [Survival Rates for a 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.

- [Questions to Ask 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](#)¹ about tests that may help detect breast, prostate,² cervical, and colorectal cancers early, before they cause any symptoms.

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.

Hyperlinks

1. www.cancer.org/healthy/find-cancer-early/cancer-screening-guidelines/screening-recommendations-by-age.html
2. www.cancer.org/healthy/find-cancer-early/cancer-screening-guidelines/screening-recommendations-by-age.html

References

Bochtler T, Löffler H, Krämer A. Diagnosis and management of metastatic neoplasms with unknown primary. *Semin Diagn Pathol*. 2017 Nov;26(pii). doi: 10.1053/j.semmp.2017.11.013. [Epub ahead of print].

Crawford SM, Skinner J, Coombes E, Jones AP. Cancer of unknown primary: A cancer registry Study of factors affecting access to diagnosis. *Clin Oncol (R Coll Radiol)*. 2017 Jan;29(1):e39-e46. doi: 10.1016/j.clon.2016.09.011.

Greco FA, Hainsworth JD. Carcinoma of Unknown Primary In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice*

of *Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2015: 1719-1736.

Søndergaard D, Nielsen S, Pedersen CNS, Besenbacher S. Prediction of primary tumors in cancers of unknown primary. *J Integr Bioinform*. 2017 Jul;14(2):pii. doi: 10.1515/jib-2017-0013.

Tomuleasa C, Zaharie F, Muresan MS, Pop L, Fekete Z, Dima D, Frinc I, Trifa A, Berce C, Jurj A, Berindan-Neagoe I, Zdrenghea M. How to diagnose and treat a cancer of unknown primary site. *J Gastrointest Liver Dis*. 2017 Mar;26(1):69-79. doi: 10.15403/jgld.2014.1121.261.haz.

Varadhachary GR, Lenzi R, Raber MN, Abbruzzese JL. Carcinoma of Unknown Primary In: Neiderhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 5th ed. Philadelphia, PA. Elsevier: 2014:1792-1803.

Last Medical Review: March 9, 2018 Last Revised: March 9, 2018

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, see 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

Greco FA, Hainsworth JD. Carcinoma of Unknown Primary In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2015: 1719-1736.

Søndergaard D, Nielsen S, Pedersen CNS, Besenbacher S. Prediction of primary tumors in cancers of unknown primary. *J Integr Bioinform*. 2017 Jul;14(2):pii. doi: 10.1515/jib-2017-0013.

National Cancer Institute. Physician Data Query (PDQ). *Cancer of Unknown Primary Treatment*. 07/25/2015. Accessed at: <https://www.cancer.gov/types/unknown-primary/hp/unknown-primary-treatment-pdq> on February 9, 2018.

Tomuleasa C, Zaharie F, Muresan MS, Pop L, Fekete Z, Dima D, Frinc I, Trifa A, Berce C, Jurj A, Berindan-Neagoe I, Zdrenghea M. How to diagnose and treat a cancer of unknown primary site. *J Gastrointestin Liver Dis*. 2017 Mar;26(1):69-79. doi: 10.15403/jgld.2014.1121.261.haz.

Varadhachary GR, Lenzi R, Raber MN, Abbruzzese JL. Carcinoma of Unknown Primary In: Neiderhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 5th ed. Philadelphia, PA. Elsevier: 2014:1792-1803.

Last Medical Review: March 9, 2018 Last Revised: March 9, 2018

Tests for Cancer of Unknown Primary

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](#)¹, 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, the doctor may use the following different types of tests to look for cancer, see what kind it is, and find out where it is located (and where it might have started):

- Imaging tests such as x-rays, ultrasound, or CT (computed tomography) or MRI (magnetic resonance imaging) scans
- Endoscopy exams to look at organs through a lighted tube placed into a body opening such as the mouth, nose, or anus
- Blood tests
- Biopsies to remove samples of tissues or cells and look at them with a microscope or test them in the lab

Imaging tests

[Imaging tests](#)² 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
- To help determine if treatment has been effective

Somatostatin receptor scintigraphy

Somatostatin receptor scintigraphy (SRS) an imaging test also known as **OctreoScan**, can be very helpful in diagnosing neuroendocrine tumors (NETs), including neuroendocrine carcinomas that may be suspected if you have a CUP. SRS uses a hormone-like substance called **octreotide** that has been bound to radioactive indium-111. A small amount of octreotide is injected into a vein and attaches to proteins on the tumor cells of many NETs. A special camera is then 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

For endoscopy, the doctor puts a flexible lighted tube (endoscope) with a tiny video camera on the end into the body.

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 **acolonoscope**.

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

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 looked at 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. 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). 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.

More information about these tests can be found in [Endoscopy](#)³.

Blood tests

If signs and symptoms suggest you might 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) can tell if you have a [low blood count](#)⁴ (red blood cells, white blood cells, or 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 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](#)⁵.
- **Human chorionic gonadotropin (HCG):** High levels of HCG suggest a germ cell tumor, a type of cancer that can begin in the [testicles](#)⁶, 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](#)⁷.
- **Chromogranin A (CgA):** CgA levels can go up with neuroendocrine cancers.

Other tumor markers that may be helpful include:

- **CA-125:** A high CA-125 level in a woman suggests [ovarian](#)⁸, fallopian tube, or primary peritoneal cancer may be the cause.
- **CA 19-9:** High levels of this tumor marker suggest that the cancer started in the [pancreas](#)⁹ or [bile ducts](#)¹⁰.

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](#)¹¹, lung, ovaries, pancreas, [stomach](#)¹² 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.

- Needle biopsy
- Core needle biopsy
- Surgical biopsy
- Endoscopic biopsy

For more detailed information about biopsies see [Types of Biopsies Used to Look for Cancer](#).¹³

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. Ultrasound often 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 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, a thin, hollow needle is inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow. A bone marrow biopsy is usually done just after the aspiration. A small piece of bone and marrow (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. 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 with a microscope by a pathologist, a doctor who has special training in laboratory diagnosis of cancers. How the cancer cells look will often provide clues to where it started. If the diagnosis isn't clear, then further testing might help.

Immunohistochemistry

For this lab test, a part of the biopsy sample is treated with man-made 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](#)¹⁴ 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 may help identify some types of cancer. Several types of chromosome changes can be found in cancer cells. With this type of testing, the doctor needs to know what

abnormalities to look for. Cytogenetic tests are not being used much in people with CUP since immunohistochemistry tests are becoming more advanced in identifying cell changes that may be related to certain cancers.

Molecular genetic testing

Sometimes, 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 if a cytogenetic test is used. PCR testing also requires that the doctors know what they are looking for. It can also be used to look for certain viruses. For example, it can be used to find the Epstein-Barr virus. Finding this virus in cancer cells from an enlarged neck lymph node can mean that it's a [nasopharyngeal cancer](#)¹⁵.

This type of 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

An electron microscope uses beams of electrons that may help find very tiny details of cancer cell structure that can provide clues to the tumor type or origin.

This technique is not used often for CUP due to the more sophisticated tests already discussed, but it might help find the source of the cancer or 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

Hyperlinks

1. www.cancer.org/cancer/cancer-unknown-primary/causes-risks-prevention/risk-factors.html
2. www.cancer.org/treatment/understanding-your-diagnosis/tests/imaging-radiology-tests-for-cancer.html
3. www.cancer.org/treatment/understanding-your-diagnosis/tests/endoscopy.html
4. www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts.html
5. www.cancer.org/cancer/prostate-cancer.html
6. www.cancer.org/cancer/testicular-cancer.html
7. www.cancer.org/cancer/liver-cancer.html
8. www.cancer.org/cancer/ovarian-cancer.html
9. www.cancer.org/cancer/pancreatic-cancer.html
10. www.cancer.org/cancer/bile-duct-cancer.html
11. www.cancer.org/cancer/colon-rectal-cancer.html
12. www.cancer.org/cancer/stomach-cancer.html
13. www.cancer.org/treatment/understanding-your-diagnosis/tests/testing-biopsy-and-cytology-specimens-for-cancer/biopsy-types.html
14. www.cancer.org/cancer/lymphoma.html
15. www.cancer.org/cancer/nasopharyngeal-cancer.html

References

Bochtler T, Löffler H, Krämer A. Diagnosis and management of metastatic neoplasms with unknown primary. *Semin Diagn Pathol*. 2017 Nov;26(pii). doi: 10.1053/j.semmp.2017.11.013. [Epub ahead of print].

Crawford SM, Skinner J, Coombes E, Jones AP. Cancer of unknown primary: A cancer registry Study of factors affecting access to diagnosis. *Clin Oncol (R Coll Radiol)*. 2017 Jan;29(1):e39-e46. doi: 10.1016/j.clon.2016.09.011.

Economopoulou P, Pentheroudakis G. Cancer of unknown primary: Time to put the pieces of the puzzle together? *Lancet Oncol*. 2016 Oct;17(10):1339-1340. doi: 10.1016/S1470-2045(16)30377-1.

Greco FA, Hainsworth JD. Carcinoma of Unknown Primary In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2015: 1719-1736.

Hainsworth JD, Rubin MS, Spigel DR, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: A prospective trial of the Sarah Cannon Research Institute. *J Clin Oncol*. 2013;31:217–223. Retrieved from http://jco.ascopubs.org/content/31/2/217.abstract?ijkey=3338ed6f72b64f237f88cf763553cbeb708e3f1d&keytype=tf_ipsecsha

Löffler H, Puthenparambil J, Hielscher T, Neben K, Krämer A. Patients with cancer of unknown primary: A retrospective analysis of 223 patients with adenocarcinoma or undifferentiated carcinoma. *Dtsch Arztebl Int*. 2014 Jul 7;111(27-28):481-7. doi: 10.3238/arztebl.2014.0481.

National Cancer Institute. Physician Data Query (PDQ). *Cancer of Unknown Primary Treatment*. 07/25/2015. Accessed at: <https://www.cancer.gov/types/unknown-primary/hp/unknown-primary-treatment-pdq> on February 9, 2018.

National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Occult Primary*. v.1.2018. Accessed at https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf on February 9, 2018.

Raghav K, Mhadgut H, McQuade JL, Lei X, Ross A, Matamoros A, Wang H, Overman MJ, Varadhachary GR. Cancer of unknown primary in adolescents and young adults: Clinicopathological features, prognostic factors and survival outcomes. *PLoS One*. 2016 May 12;11(5):e0154985. doi: 10.1371/journal.pone.0154985.

Santos MTD, Souza BF, Cárcano FM, Vidal RO, Scapulatempo-Neto C, Viana CR, Carvalho AL. An integrated tool for determining the primary origin site of metastatic tumours. *J Clin Pathol*. 2017 Dec;16(pii). doi: 10.1136/jclinpath-2017-204887. [Epub ahead of print]

Søndergaard D, Nielsen S, Pedersen CNS, Besenbacher S. Prediction of primary tumors in cancers of unknown primary. *J Integr Bioinform*. 2017 Jul;14(2):pii. doi: 10.1515/jib-2017-0013.

Tomuleasa C, Zaharie F, Muresan MS, Pop L, Fekete Z, Dima D, Frinc I, Trifa A, Berce C, Jurj A, Berindan-Neagoe I, Zdrenghea M. How to diagnose and treat a cancer of unknown primary site. *J Gastrointest Liver Dis*. 2017 Mar;26(1):69-79. doi: 10.15403/jgld.2014.1121.261.haz.

Varadhachary GR, Lenzi R, Raber MN, Abbruzzese JL. Carcinoma of Unknown Primary In: Neiderhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 5th ed. Philadelphia, PA. Elsevier: 2014:1792-1803.

Last Medical Review: March 9, 2018 Last Revised: March 9, 2018

Testing for a Cancer of Unknown Primary by Location

Based on the classification and the location of the metastatic cancer of unknown primary, 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](#)¹, [larynx](#)², [esophagus](#)³ (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](#)⁴ 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](#)⁵ 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](#)⁶.

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](#)⁷, 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 \(PR\)](#)⁸. 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](#)⁹, [vagina](#)¹⁰, [cervix](#)¹¹, [penis](#)¹², [skin of the legs](#)¹³, [anus](#)¹⁴, [rectum](#)¹⁵, or [bladder](#)¹⁶, 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](#)¹⁷.
- 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 CA-125 levels 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 [Ovarian Cancer](#)¹⁸.

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](#)¹⁹ or [ovaries](#)²⁰), 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](#)²¹). In women, tests may be done to see if the cancer started in the [breast](#)²² 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](#)²³ 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](#)²⁴, which are often effectively treated with radioactive iodine injections.
- Tests of the cancer cells can help identify [breast cancers](#)²⁵ 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](#)²⁶, 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.

- Information about neuroendocrine cancers that start in the pancreas may be found in [Pancreatic Cancer](#)²⁷.
- Information about neuroendocrine cancers that start in the GI tract can be found in [Gastrointestinal Carcinoid Tumors](#)²⁸.
- Information about neuroendocrine tumors that start in the lungs can be found in [Lung Carcinoid Tumors](#)²⁹.

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.

Hyperlinks

1. www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer.html
2. www.cancer.org/cancer/laryngeal-and-hypopharyngeal-cancer.html
3. www.cancer.org/cancer/esophagus-cancer.html
4. www.cancer.org/treatment/understanding-your-diagnosis/tests/imaging-radiology-tests-for-cancer.html
5. www.cancer.org/cancer/lung-cancer.html
6. www.cancer.org/cancer/thyroid-cancer.html
7. www.cancer.org/cancer/breast-cancer.html
8. www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-hormone-receptor-status.html
9. www.cancer.org/cancer/vulvar-cancer.html
10. www.cancer.org/cancer/vaginal-cancer.html
11. www.cancer.org/cancer/cervical-cancer.html
12. www.cancer.org/cancer/penile-cancer.html

13. www.cancer.org/cancer/skin-cancer.html
14. www.cancer.org/cancer/anal-cancer.html
15. www.cancer.org/cancer/colon-rectal-cancer.html
16. www.cancer.org/cancer/bladder-cancer.html
17. www.cancer.org/cancer/prostate-cancer.html
18. www.cancer.org/cancer/ovarian-cancer.html
19. www.cancer.org/cancer/testicular-cancer.html
20. www.cancer.org/cancer/ovarian-cancer.html
21. www.cancer.org/cancer/lung-cancer.html
22. www.cancer.org/cancer/breast-cancer.html
23. www.cancer.org/cancer/melanoma-skin-cancer/treating.html
24. www.cancer.org/cancer/thyroid-cancer.html
25. www.cancer.org/cancer/breast-cancer.html
26. www.cancer.org/cancer/prostate-cancer.html
27. www.cancer.org/cancer/pancreatic-cancer.html
28. www.cancer.org/cancer/gastrointestinal-carcinoid-tumor.html
29. www.cancer.org/cancer/lung-carcinoid-tumor.html

References

Economopoulou P, Pentheroudakis G. Cancer of unknown primary: Time to put the pieces of the puzzle together? *Lancet Oncol*. 2016 Oct;17(10):1339-1340. doi: 10.1016/S1470-2045(16)30377-1.

Greco FA, Hainsworth JD. Carcinoma of Unknown Primary In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2015: 1719-1736.

Löffler H, Puthenparambil J, Hielscher T, Neben K, Krämer A. Patients with cancer of unknown primary: A retrospective analysis of 223 patients with adenocarcinoma or undifferentiated carcinoma. *Dtsch Arztebl Int*. 2014 Jul 7;111(27-28):481-7. doi: 10.3238/arztebl.2014.0481.

National Cancer Institute. Physician Data Query (PDQ). *Cancer of Unknown Primary Treatment*. 07/25/2015. Accessed at: <https://www.cancer.gov/types/unknown-primary/hp/unknown-primary-treatment-pdq> on February 9, 2018.

National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Occult Primary*. v.1.2018. Accessed at

https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf on February 9, 2018.

Raghav K, Mhadgut H, McQuade JL, Lei X, Ross A, Matamoros A, Wang H, Overman MJ, Varadhachary GR. Cancer of unknown primary in adolescents and young adults: Clinicopathological features, prognostic factors and survival outcomes. *PLoS One*. 2016 May 12;11(5):e0154985. doi: 10.1371/journal.pone.0154985.

Santos MTD, Souza BF, Cárcano FM, Vidal RO, Scapulatempo-Neto C, Viana CR, Carvalho AL. An integrated tool for determining the primary origin site of metastatic tumours. *J Clin Pathol*. 2017 Dec;16(pii). doi: 10.1136/jclinpath-2017-204887. [Epub ahead of print]

Søndergaard D, Nielsen S, Pedersen CNS, Besenbacher S. Prediction of primary tumors in cancers of unknown primary. *J Integr Bioinform*. 2017 Jul;14(2):pii. doi: 10.1515/jib-2017-0013.

Tomuleasa C, Zaharie F, Muresan MS, Pop L, Fekete Z, Dima D, Frinc I, Trifa A, Berce C, Jurj A, Berindan-Neagoe I, Zdrenghea M. How to diagnose and treat a cancer of unknown primary site. *J Gastrointest Liver Dis*. 2017 Mar;26(1):69-79. doi: 10.15403/jgld.2014.1121.261.haz.

Varadhachary GR, Lenzi R, Raber MN, Abbruzzese JL. Carcinoma of Unknown Primary In: Neiderhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 5th ed. Philadelphia, PA. Elsevier: 2014:1792-1803.

Last Medical Review: March 9, 2018 Last Revised: March 9, 2018

Cancer of Unknown Primary Stages

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](#)¹ 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](#)² can be complex, so ask your doctor to explain it to you in a way you understand.

Hyperlinks

1. www.cancer.org/cancer/cancer-unknown-primary/treating.html
2. www.cancer.org/treatment/understanding-your-diagnosis/staging.html

References

Greco FA, Hainsworth JD. Carcinoma of Unknown Primary In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2015: 1719-1736.

National Cancer Institute. Physician Data Query (PDQ). *Cancer of Unknown Primary Treatment*. 07/25/2015. Accessed at: <https://www.cancer.gov/types/unknown-primary/hp/unknown-primary-treatment-pdq> on February 9, 2018.

National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Occult Primary*. v.1.2018. Accessed at https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf on February 9, 2018.

Last Medical Review: March 9, 2018 Last Revised: March 9, 2018

Survival Rates for Cancer of Unknown Primary

Survival rates tell you what portion of people with the same type and stage of cancer are still alive a certain amount of time (usually 5 years) after they were diagnosed. They can't tell you how long you will live, but they may help give you a better understanding about how likely it is that your treatment will be successful.

Cancer of unknown primary (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

difficult 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 successful, 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 CUPs 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.

Survival statistics can sometimes be useful as a general guide, but they may not accurately represent any one person's prognosis (outlook). This is because survival rates are often based on previous outcomes of large numbers of people who had the disease, but they can't predict what will happen in any particular person's case. Your doctor can tell you how these numbers may apply to you, as he or she is familiar with your particular situation.

References

Greco FA, Hainsworth JD. Carcinoma of Unknown Primary In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2015: 1719-1736.

Howlander N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). *SEER Cancer Statistics Review, 1975-2014*, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

National Cancer Institute. Physician Data Query (PDQ). *Cancer of Unknown Primary Treatment*. 07/25/2015. Accessed at: <https://www.cancer.gov/types/unknown-primary/hp/unknown-primary-treatment-pdq> on February 9, 2018.

Raghav K, Mhadgut H, McQuade JL, Lei X, Ross A, Matamoros A, Wang H, Overman

MJ, Varadhachary GR. Cancer of unknown primary in adolescents and young adults: Clinicopathological features, prognostic factors and survival outcomes. *PLoS One*. 2016 May 12;11(5):e0154985. doi: 10.1371/journal.pone.0154985.

Varadhachary GR, Lenzi R, Raber MN, Abbruzzese JL. Carcinoma of Unknown Primary In: Neiderhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 5th ed. Philadelphia, PA. Elsevier: 2014:1792-1803.

Last Medical Review: March 9, 2018 Last Revised: March 9, 2018

Questions to Ask About Cancer of Unknown Primary

It's important to have open, honest communication with your doctor about your condition. Don't be afraid to ask questions, no matter how small it might seem. Some questions to consider:

When you're told you have a cancer of unknown primary (CUP)

- Should I have extensive testing to find out what kind of cancer of unknown primary (CUP) I have?
- What [kind of CUP](#)¹ do I have? How extensive is it?
- Have you done all the appropriate [tests](#) on my biopsy specimen?

When deciding on a treatment plan

- How much experience do you have treating these tumors?
- What are my [treatment](#)² choices?
- Which treatment do you recommend, and why?
- What's the goal of treatment?
- Should I get a [second opinion](#)³? How do I do that? Can you recommend someone?
- How quickly do we need to decide on treatment?
- What should I do to get ready for treatment?

- Are there any [clinical trials](#)⁴ I should think about taking part in?
- How long will treatment last? What will it be like? Where will it be done?
- What risks or side effects should I expect? How long are they likely to last?
- Will treatment affect my daily activities?
- What are the chances that my CUP will come back if initial treatment seems to be successful? What would we do if that happens?

During treatment

- How will we know if the treatment is working?
- Is there anything I can do to help [manage side effects](#)⁵?
- What symptoms or side effects should I tell you about right away?
- How can I reach you on nights, holidays, or weekends?
- Do I need to change what I [eat during treatment](#)⁶?
- Are there any limits on what I can do?
- Should I exercise? What should I do, and how often?
- Can you suggest a mental health professional I can see if I start to feel overwhelmed, depressed, or distressed?

After treatment

- Are there any limits on what I can do?
- What symptoms should I watch for?
- What kind of exercise should I do now?
- What type of follow-up will I need after treatment?
- How often will I need to have follow-up exams and tests?
- How will we know if the cancer has [come back](#)⁷? What should I watch for?
- What will my options be if the cancer comes back?

Along with these examples, be sure to write down some of your own questions. For instance, you might want more information about clinical trials or working during treatment.

Keep in mind that doctors aren't the only ones who can give you information. Other health care professionals, such as nurses and social workers, can answer some of your questions. To find more about speaking with your health care team, see [The Doctor-](#)

Patient Relationship.⁸

Hyperlinks

1. www.cancer.org/cancer/cancer-unknown-primary.html
2. www.cancer.org/cancer/cancer-unknown-primary/treating.html
3. www.cancer.org/treatment/finding-and-paying-for-treatment/choosing-your-treatment-team/seeking-a-second-opinion.html
4. www.cancer.org/treatment/treatments-and-side-effects/clinical-trials.html
5. www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects.html
6. www.cancer.org/treatment/survivorship-during-and-after-treatment/staying-active/nutrition/nutrition-during-treatment.html
7. www.cancer.org/treatment/survivorship-during-and-after-treatment/understanding-recurrence.html
8. www.cancer.org/treatment/understanding-your-diagnosis/talking-about-cancer/the-doctor-patient-relationship.html

Last Medical Review: March 8, 2018 Last Revised: March 8, 2018

Written by

The American Cancer Society medical and editorial content team
(www.cancer.org/cancer/acs-medical-content-and-news-staff.html)

Our team is made up of doctors and oncology certified nurses with deep knowledge of cancer care as well as journalists, editors, and translators with extensive experience in medical writing.

American Cancer Society medical information is copyrighted material. For reprint requests, please see our Content Usage Policy (www.cancer.org/about-us/policies/content-usage.html).

cancer.org | 1.800.227.2345