Cancer of Unknown Primary Early Detection, Diagnosis, and Staging

Find out how cancer of unknown primary is diagnosed, what tests may be done, and how it is often staged.

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?

- Screening tests

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 detectbreast,prostate[1,2]

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Last Revised: March 9, 2018

Signs and Symptoms of a Cancer of Unknown Primary

- Swollen, firm, non-tender lymph nodes
- A mass in the abdomen that can be felt or a feeling of "fullness"
- Shortness of breath
- Pain in the chest or abdomen
- Bone pain
- Skin tumors
- Low red blood cell counts (anemia)
- Weakness, fatigue, poor appetite, and weight loss

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 affectcers.i_c/F1 14 Tf 0 0 0 rg /GS138 gs (Weak weight loss)Tj 0 g t.eak weight loss

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Last Revised: March 9, 2018

Tests for a Cancer of Unknown Primary

Cancers of unknown primary (CUP) are usually found as the result of signs or symptoms a person is having. However, when the primary tumor cannot be located, specialized pathologic and molecular tests can be used to help find where the cancer started.

- Medical history and physical exam
- Approach to diagnosing a cancer of unknown primary
- Imaging tests
- Endoscopy
- Blood tests
- Biopsies
- Classifying cancers of unknown primary

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, 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. CT scans of the chest, abdomen, and pelvis are one of the most common imaging tests used to evaluate a patient for a CUP. If the patient is female, a mammography is usually done also. 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

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 a**colonoscope** and the procedure is called a **colonoscopy** .

Other 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)
- **Cystoscopy** to look at the bladder

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 (EUS): 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

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 esophageal, stomach, or intestinal bleeding caused by the cancer. This could point to those organs as the site of the cancer'sorigin.

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 to the liver 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[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:

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

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

5 main types:

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

Hyperlinks

1. www.cancer.org/cancer/types/cancer-unknown-primary/causes-risks-prevention/risk-factors.html
2. www.cancer.org/cancer/diagnosis-staging/tests/imaging-tests/imaging-radiology-tests-for-cancer.html
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Last Revised: May 27, 2024

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.

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

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/types/oral-cavity-and-oropharyngeal-cancer.html
2. www.cancer.org/cancer/types/laryngeal-and-hypopharyngeal-cancer.html
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Last Revised: March 9, 2018

Cancer of Unknown Primary Stages

- How is the stage determined?

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 **t**umor **(T):** How large is the cancer? Has it grown into

nearby structures or tissues?
- The spread to nearby lymph **n**odes **(N):** Has the cancer spread to nearby lymph nodes?
- The spread (**m**etastasis) 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.

Survival Rates for a Cancer of Unknown Primary

- 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 is familiar with your situation; ask how these numbers may apply to you.

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Last Revised:

Questions to Ask About a Cancer of Unknown Primary

- 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?

questions. To find more about speaking with your health care team, see The Doctor-Patient Relationship.[8]

Hyperlinks

1. www.cancer.org/cancer/types/cancer-unknown-primary.html
2. www.cancer.org/cancer/types/cancer-unknown-primary/treating.html
3. www.cancer.org/cancer/managing-cancer/finding-care/seeking-a-second-opinion.html
4. www.cancer.org/cancer/managing-cancer/making-treatment-decisions/clinical-trials.html
5. www.cancer.org/cancer/managing-cancer/side-effects.html
6. www.cancer.org/cancer/survivorship/coping/nutrition.html
7. www.cancer.org/cancer/survivorship/long-term-health-concerns/recurrence.html
8. www.cancer.org/cancer/managing-cancer/finding-care/the-doctor-patient-relationship.html

Last Revised: March 8, 2018

Written by

The American Cancer Society medical and editorial content team (https://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 editors and translators with extensive experience in medical writing.