About Cancer of Unknown Primary

Overview and Types

If you have been diagnosed with a cancer of unknown primary or are worried about it, you likely have a lot of questions. Learning some basics is a good place to start.

- What Is a Cancer of Unknown Primary?

Research and Statistics

See the latest estimates for new cases of cancers of unknown primary in the US and what research is currently being done.

- Key Statistics for Cancers of Unknown Primary
- What's New in Cancer of Unknown Primary Research?

What Is a Cancer of Unknown Primary?

Cancer starts when cells begin to grow out of control. Cells in nearly any part of the body can become cancer, and can spread to other areas. Cancers often spread from their primary site (the part of the body where the cancer started) to one or more metastatic sites (other parts of the body). Cancers are named based on their primary site, regardless of where in the body they spread. For example, a lung cancer that spreads to the liver is still classified as lung cancer and not as liver cancer.
Sometimes it’s not clear where a cancer may have started. When cancer is found in one or more metastatic sites but the primary site cannot be determined, it is called a **cancer of unknown primary (CUP)** or an **occult primary cancer**. This happens in a small portion of cancers.

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

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

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

The main reason to look for the primary site of a CUP is to guide **treatment**. Since a cancer that starts in one place needs the same treatments when it spreads, knowing where a cancer started tells the doctor what types of treatments to use. This is especially important for certain cancers that respond well to specific chemotherapy or hormone drugs. When the types of cancer that respond best to treatment have been ruled out by tests, it usually becomes less important to find the exact origin or cancer type.

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

To learn more about how cancers start and spread, see [What Is Cancer?](#)

**General cancer types**

Cancers are classified by their primary site. They can also be grouped by the types of
cells in them, how the cancer cells look under the microscope, and on results of certain lab tests on the cells. Knowing the type of cell might give doctors a clue as to where the cancer started. When the cancer cells closely resemble normal cells of the organ where they start, the cancer is called **well differentiated**. When the cells do not look much like normal cells, the cancers are called **poorly differentiated**. Cancers of unknown primary are often poorly differentiated.

**Carcinomas**

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

**Squamous cell cancers**

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

**Adenocarcinomas**

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

**Other cancer types**

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

- **Lymphomas** develop from cells of the immune system found in lymph nodes and several other organs.
- **Melanomas** develop from cells that produce the skin’s tan or brown color.
- **Sarcomas** develop from connective tissue cells that usually are present in tendons, ligaments, muscle, fat, bones, cartilage, and related tissues.
- **Germ cell tumors** can develop in the testes (testicles) in men or the ovaries in women, or in the parts of the body where these organs developed in the fetus.
This list is not intended to include all types of cancers but merely to name the most common ones.

**Broad categories of cancers of unknown primary**

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

**Adenocarcinoma**

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

**Poorly differentiated carcinoma**

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

**Squamous cell cancer**

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

**Poorly differentiated malignant neoplasm**

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

**Neuroendocrine carcinoma**

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

Even when doctors don’t know where the cancer started, they do their best to classify the type of cancer. This can help them select the best treatment. Some cancers respond very well to specific treatments, so it is very important to classify the cancer as much as possible. This is best done by looking at the cancer under a microscope and doing special tests in the lab (see Tests for a Cancer of Unknown Primary⁴).

Other types

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

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

Hyperlinks

2. www.cancer.org/treatment/understanding-your-diagnosis/what-is-cancer.html

References


Key Statistics for Cancers of Unknown Primary

How common are cancers of unknown primary?

The exact number of cancers of unknown primary (CUP) diagnosed each year is unknown, because some cancers start out being diagnosed as unknown primary, but the primary site is found later. Still, the American Cancer Society estimates that about 32,590 cases of cancer of unknown primary will be diagnosed in 2023 in the United States. This number represents about 2% of all cancers. As more sophisticated lab tests become available to determine where a cancer started, the number of cancers of unknown primary may go down.

Visit the American Cancer Society’s Cancer Statistics Center for more key statistics.

Hyperlinks

1. cancerstatisticscenter.cancer.org/

References


What’s New in Cancer of Unknown Primary Research?

Research into the causes, diagnosis, and treatment of cancer is being done at many cancer research centers. Scientists are making progress in understanding how changes in a person’s DNA can cause normal cells to develop into cancer. A greater understanding of the gene changes that can occur in cancer is providing insight into why these cells become abnormal. Some of these advances may lead to better diagnosis\(^1\) and treatment\(^2\) of cancer of unknown primary (CUP).

**Diagnosis**

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

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

**Treatment**

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

As researchers have come to understand the genetic changes that cause these tumors,
they’ve been able to use newer treatments to target these changes. Some of these newer drugs are called targeted therapies\(^3\). These drugs have more selective effects than chemotherapy (chemo). Some of them, such as bevacizumab (Avastin\(^\circledR\)) and erlotinib (Tarceva\(^\circledR\)), are available to treat other cancers and have shown some activity in CUP.

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

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

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

Many patients with cancer of unknown primary face a serious prognosis, so the need for advances in treatment is obvious. Clinical trials\(^4\) of new treatments are essential if progress is to occur. Some of these trials are testing new chemo drugs, new drug combinations, and new ways to give these drugs. Other clinical trials are studying new approaches to treatment, such as biological therapy, immunotherapy\(^5\), and gene therapy. Because CUP is many types of cancers, progress against CUP is likely to depend on continued progress toward understanding the molecular basis of all cancers.

**Hyperlinks**

References


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