# Treating a Cancer of Unknown Primary

If you've been diagnosed with a cancer of unknown primary, your cancer care team will discuss your treatment options with you. It's important that you think carefully about each of your choices. Weigh the benefits of each treatment option against the possible risks and side effects.

**Types of treatment**

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

- Surgery for a Cancer of Unknown Primary
- Radiation Therapy for a Cancer of Unknown Primary
- Chemotherapy for a Cancer of Unknown Primary
- Hormone Therapy for a Cancer of Unknown Primary
- Targeted Therapy for a Cancer of Unknown Primary
- Other Drugs for a Cancer of Unknown Primary

**Common treatment approaches**

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

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

- Treatment of a Cancer of Unknown Primary by Location

- Palliative Care for a Cancer of Unknown Primary

### Who treats cancers of unknown primary?

Based on your treatment options, you might have different types of doctors on your treatment team. These doctors could include:

- A **surgical oncologist** (oncologic surgeon): a doctor who uses surgery to treat cancer
- A **radiation oncologist:** a doctor who treats cancer with radiation therapy
- A **medical oncologist:** a doctor who treats cancer with medicines such as chemotherapy or targeted therapy

You might have many other specialists on your treatment team as well, including physician assistants (PAs), nurse practitioners (NPs), nurses, psychologists, nutritionists, social workers, and other health professionals.

- Health Professionals Associated with Cancer Care

### Making treatment decisions

It's important to discuss all of your treatment options, including their goals and possible side effects, with your doctors to help make the decision that best fits your needs. It's also very important to ask questions if there's anything you're not sure about.

If time permits, it is often a good idea to seek a second opinion. A second opinion can give you more information and help you feel more confident about the treatment plan you choose.

- Questions to Ask About a Cancer of Unknown Primary
- Seeking a Second Opinion

### Thinking about taking part in a clinical trial

Clinical trials are carefully controlled research studies that are done to get a closer look at promising new treatments or procedures. Clinical trials are one way to get state-of-the art cancer treatment. In some cases they may be the only way to get access to newer treatments. They are also the best way for doctors to learn better methods to treat cancer.

helpline specialists. Or, if you prefer, you can use our chat feature on cancer.org to connect with one of our specialists.

- Palliative Care
- Programs & Services

**Choosing to stop treatment or choosing no treatment at all**

For some people, when treatments have been tried and are no longer controlling the cancer, it could be time to weigh the benefits and risks of continuing to try new treatments. Whether or not you continue treatment, there are still things you can do to help maintain or improve your quality of life.

Some people, especially if the cancer is advanced, might not want to be treated at all. There are many reasons you might decide not to get cancer treatment, but it's important to talk to your doctors as you make that decision. Remember that even if you choose not to treat the cancer, you can still get supportive care to help with pain or other symptoms.

- If Cancer Treatments Stop Working

*The treatment information given here is not official policy of the American Cancer Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your doctor. Your doctor may have reasons for suggesting a treatment plan different from these general treatment options. Don't hesitate to ask your cancer care team any questions you may have about your treatment options.*

# Surgery for a Cancer of Unknown Primary

- More information about Surgery

Surgery is used to treat many types of cancer, if they are found at an early stage. But because cancer of unknown primary (CUP) has already spread beyond the site where it

started, surgery is less likely to be helpful.

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

The type and extent of surgery will depend on where the cancer is and how extensive it

- External beam radiation therapy focuses a beam of radiation on the cancer from a machine.
- Internal radiation therapy (brachytherapy) places a radioactive material directly into or as close as possible to the cancer.

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

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

Depending on where the radiation is aimed or placed and what dose is given, side effects may include the following:

## Possible general side effects from radiation

- Fatigue (feeling tired)
- Loss of appetite
- Low blood counts
- Skin changes in areas getting radiation, ranging from redness to blistering and peeling

## Possible side effects from radiation to the chest

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

## Possible side effects from radiation to the abdomen

- Nausea
- Vomiting
- Diarrhea
- Poor appetite

## Possible side effects from radiation to the pelvis

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

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

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

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

## More information about radiation therapy

To learn more about how radiation is used to treat cancer, see Radiation Therapy[1].

To learn about some of the side effects listed here and how to manage them, see Managing Cancer-related Side Effects[2].

## Hyperlinks

1. www.cancer.org/cancer/managing-cancer/treatment-types/radiation.html
2. www.cancer.org/cancer/managing-cancer/side-effects.html

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Bochtler T, Löffler H, Krämer A. Diagnosis and management of metastatic neoplasms with unknown primary. *Semin Diagn Pathol*. 2018 May;35(3):199-206. doi: 10.1053/j.semdp.2017.11.013. Epub 2017 Nov 26. PMID: 29203116.

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# Chemotherapy for a Cancer of Unknown Primary

Chemo can be used in a number of situations for cancer of unknown primary (CUP). Because chemo reaches all parts of the body, it can sometimes be useful for cancers of unknown primary, as it may help kill cancer cells in areas where they haven't been detected. If your doctor recommends chemo, it's important that you understand what the goals of your treatment are.


- Adenocarcinoma and poorly differentiated carcinoma
- Squamous cell cancer (carcinoma)
- Neuroendocrine cancers (carcinomas)
- Possible side effects of chemotherapy
- More information about chemotherapy


Chemotherapy (chemo) is the use of drugs to treat cancer. Often, these drugs are injected into a vein (IV) or taken by mouth. They enter the bloodstream and reach throughout the body, making this treatment potentially useful for cancers that have spread beyond the organ they started in.

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

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

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

## Adenocarcinoma and poorly differentiated carcinoma

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

- Carboplatin plus paclitaxel (Taxol®)

- Carboplatin plus docetaxel (Taxotere®)
- Cisplatin plus gemcitabine (Gemzar®)
- Cisplatin plus docetaxel
- Gemcitabine plus docetaxel
- ®Irinotecan (Camptosar®) plus carboplatin
- Irinotecan plus gemcitabine

  Oxaliplatin (E1alipxn®

2. www.cancer.org/cancer/types/lung-carcinoid-tumor.html
3. www.cancer.org/cancer/types/pancreatic-cancer.html
4. www.cancer.org/cancer/managing-cancer/side-effects/fatigue.html
5. www.cancer.org/cancer/managing-cancer/treatment-types/chemotherapy.html
6. www.cancer.org/cancer/managing-cancer/side-effects.html

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# Hormone Therapy for a Cancer of Unknown Primary

To learn more about how hormone therapy is used to treat cancer, see Hormone

*Clinical Oncology*. 5th ed. Philadelphia, PA. Elsevier: 2014:1792-1803.

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# Targeted Therapy for a Cancer of Unknown Primary

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


- Genetic testing for cancer of unknown primary (CUP) samples
- Targeted therapy drugs for cancer of unknown primary (CUP)
- More information about targeted therapy


## Genetic testing for cancer of unknown primary (CUP) samples

The tumor sample removed from a patient with CUP is typically tested for "targetable mutations". This means that the tumor undergoes genetic testing, also known as **next generation sequencing** or genomic profiling[1]. The results may show if the tumor has DNA mutations that would respond to current targeted therapy. Examples of tumor mutations which may respond to specific targeted therapy include EGFR, ALK, ROS1, BRAF, NTRK, HER2, KRAS and others.

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

## Targeted therapy drugs for cancer of unknown primary (CUP)

A number of targeted therapy drugs are used to treat breast cancer, including trastuzumab (Herceptin®), pertuzumab (Perjeta®), lapatinib (Tykerb®), everolimus (Afinitor®), ado-trastuzumab emtansine (Kadcyla®, also known as TDM-1), and neratinib (Nerlynx®). For more information, see Targeted Therapy for Breast Cancer[2].

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

## More information about targeted therapy

To learn more about how targeted drugs are used to treat cancer, see Targeted Cancer Therapy[3].

To learn about some of the side effects listed here and how to manage them, see Managing Cancer-related Side Effects[4].

## Hyperlinks

1. www.cancer.org/cancer/managing-cancer/treatment-types/precision-medicine.html
2. www.cancer.org/cancer/types/breast-cancer/treatment/targeted-therapy-for-breast-cancer.html
3. www.cancer.org/cancer/managing-cancer/treatment-types/targeted-therapy.html
4. www.cancer.org/cancer/managing-cancer/side-effects.html

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Bochtler T, Löffler H, Krämer A. Diagnosis and management of metastatic neoplasms with unknown primary. Semin Diagn Pathol. 2018 May;35(3):199-206. doi: 10.1053/j.semdp.2017.11.013. Epub 2017 Nov 26. PMID: 29203116.

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.

# Other Drugs for a Cancer of Unknown Primary

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

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

## Denosumab

Like bisphosphonates, denosumab (Prolia®, Xgeva®) is a drug that can be used to strengthen bones and reduce the risk of fractures in those that have been weakened by metastatic cancer. This drug is injected under the skin, once a month to treat cancer that has spread to bone.

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

## Somatostatin analogs

Octreotide(Sandostatin®) and lanreotide (Samatuline) are drugs that are chemically related to a natural hormone, somatostatin. They are called Somatostatin analogs. This type of drug is very helpful for some patients with well-differentiated neuroendocrine tumors. If the tumor releases hormones into the bloodstream (which is rare in the poorly differentiated tumors that cause cancer of unknown primary), this drug can stop the hormone release. It can also cause tumors to stop growing or to shrink. This drug is available as a short-acting version injected 2 to 4 times a day, or as a long-acting injection that needs to be given only once a month.These drugs are most likely to help treat cancers that show up on somatostatin receptor scintigraphy (OctreoScan).

### Peptide receptor radiation therapy (PRRT)

Lutetium Lu-177 dotatate (Lutathera) is a type of radiotherapy, that is made up of two parts: somatostatin analog plus radiation. This drug finds and attaches to cancer cells that has the somotastatin receptor. Once attached, the drug enters the cell, releases

# Treatment of a Cancer of Unknown Primary by Location

likely it is to be a certain type of cancer. Your overall health and ability to tolerate treatment matter also. If the origin of the cancer can be determined during testing, the cancer would no longer be an unknown primary and would be treated according to where it started.

- Squamous cell carcinoma in lymph nodes in the neck
- Adenocarcinoma in lymph nodes under the arm
- Cancer in groin lymph nodes
- Cancer throughout the pelvic cavity
- Cancer in the retroperitoneum (back of the abdomen) or mediastinum (middle of the chest)
- Melanoma in lymph nodes only
- Cancer in other locations such as bone or liver

## Squamous cell carcinoma in lymph nodes in the neck

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

Surgical treatment removes lymph nodes and other tissue from the neck. This operation is called a **neck dissection**.

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

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

Radiation therapy might be used instead of surgery. One potential advantage is that the area treated would include both the nodes with metastatic cancer and several of the

areas of the neck likely to contain a primary tumor.

When large and/or many tumors are present, some patients will be treated with both surgery and radiation therapy. The radiation may be given before or after surgery.

When tumors are very large or present on both sides of the neck, chemotherapy (chemo) and radiation therapy are often used together.

The outlook for these patients depends on the size, number, and location of the lymph nodes containing metastatic cancer. For more information about the usual treatments for these cancers see Nasal Cavity and Paranasal Sinus Cancers[1], Oral Cavity and Oropharyngeal Cancer[2] and Laryngeal and Hypopharyngeal Cancer[3].

## Adenocarcinoma in lymph nodes under the arm

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

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

Depending on the woman's age and whether the cancer cells contain estrogen and/or progesterone receptors, additional (adjuvant) treatment may include hormonal therapy, chemo, or both. The cancer can also be tested for a protein called HER2. If positive, a drug that targets the HER2 protein may be used. For more information about prognosis and treatment of breast cancer that has spread to the lymph nodes, see Breast Cancer[4].

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

## Cancer in groin lymph nodes

It's important to search carefully for the origin of these cancers, as many of them can be

treated effectively if it is found. If the primary tumor can't be found, surgery is usually the main treatment.

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

## Cancer throughout the pelvic cavity

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

Treatment is typically surgery to remove the uterus, both ovaries, both fallopian tubes, and as much of the cancer as possible. After surgery, 6 to 8 months of chemo may be recommended. For more information, see Ovarian Cancer[5].

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

If lab tests of the tumor sample have ruled out lymphoma, the most likely diagnosis (particularly in younger men) is a germ cell tumor. Even cancers in these areas that do not have lab results typical of germ cell tumors often respond to chemotherapy combinations for treating testicular germ cell tumors. More information about the treatment of germ cell tumors can be found in Testicular Cancer[6]and Ovarian Cancer[7].

If a carcinoma is found in the mediastinum in an older patient it may be treated as a non-small cell lung cancer[8].

## Melanoma in lymph nodes only

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

The recommended initial treatment of melanoma of unknown primary with only lymph

node spread is surgery to remove the lymph nodes in the affected area. If spread to other nodes becomes apparent at a later time and all of the cancer can be removed, these nodes are also removed. For more information see Melanoma Skin Cancer[9].

## Cancer in other locations such as bone or liver

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

Most doctors use a standard chemotherapy regimen. It's important to stop chemo if it's not working to relieve symptoms or shrink the cancer, as the side effects of these drugs can be severe and impair quality of life.

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

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

Some poorly differentiated small cell cancers of unknown origin can shrink dramatically when chemo combinations originally developed to treat small cell lung cancer[10] are used. The benefit usually lasts for several months, but these cancers almost always return.

Some neuroendocrine cancers may respond to treatment with octreotide (Sandostatin) or lanreotide (Somatuline). These drugs may be able to slow or stop growth for some time. The tumors most likely to respond are the ones able to be seen on somatostatin receptor scintigraphy (imaging). Some other drugs known as targeted therapy that are helpful in treating pancreatic neuroendocrine cancers may be used as well.

More information about treatments for cancers that have spread can be found in Advanced Cancer[11].

## Hyperlinks

1. www.cancer.org/cancer/types/nasal-cavity-and-paranasal-sinus-cancer.html
2. www.cancer.org/cancer/types/oral-cavity-and-oropharyngeal-cancer.html
3. www.cancer.org/cancer/types/laryngeal-and-hypopharyngeal-cancer.html
4. www.cancer.org/cancer/types/breast-cancer.html
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10. www.cancer.org/cancer/types/lung-cancer/treating-small-cell.html
11. www.cancer.org/cancer/managing-cancer/advanced-cancer.html

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# Palliative Care for a Cancer of Unknown Primary

- More information about palliative care

Some cancers of unknown primary can be treated effectively or even cured, but most are advanced cancers for which treatments are unlikely to provide long-term benefits. It's very important that people with advanced cancer of unknown primary (CUP) are aware that even if the cancer can't be cured, there are treatments available to help prevent or relieve pain and other symptoms. Many patients with CUP may benefit from palliative care as part of their treatment plan. Palliative care includes **supportive care** managed by your care team, such as relief from symptoms, pain, and stress. It's meant to improve quality of life for patients and their families. Treatment to control the cancer may also be included in a supportive care plan. More information can be found in Advanced Cancer.[1]

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

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.

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