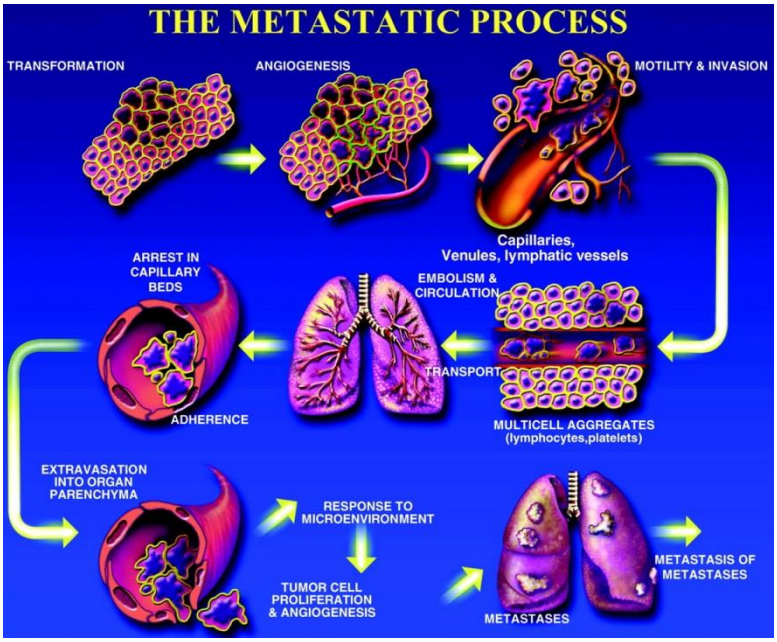
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Cancer of an Unknown Primary (CUP)

Introduction

Cancer can form in any tissue of the body. A primary cancer can spread to other parts of the body from the place in the body where it originally started. This process is called metastasis. Cancer cells usually look like the cells of the type of tissue in which the cancer originally began. For example, breast cancer cells may spread to the lung. Because the cancer began in the breast, the cancer cells in the lung will always look like breast cancer cells.



[Picture Credit: Metastasis]

Sometimes doctors find cancer which has spread to a particular part of the body but cannot find where in the body the cancer first began to grow. This type of cancer is called a cancer of unknown primary (CUP). It is also known as:

- occult (hidden) primary tumour
- carcinoma of unknown primary
- unknown primary cancer
- unknown primary tumour
- cancer of unknown origin

Cancer of unknown primary origin accounts for 2 to 9% of cancers diagnosed worldwide. Median survival ranges from 11 weeks to 11 months. The 5-year overall survival rate is about 11%. Most series reporting on, or reviewing cancer of unknown primary origin patient groups, give an approximate equal incidence for men and women. The median age on presentation for both men and women ranges from 59-66 years. 'Median age' refers to separating the higher half of a data sample or population from the lower half and is not the same as 'average age'.

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A variety of tests are done to try and find where the primary cancer started in the body and to get information about where the cancer has spread. When tests are able to find the primary cancer, the cancer is no longer a CUP and the treatment is then based on the type of primary cancer that was identified.
(National Cancer Institute; Cancer Research UK; E-Medicine; Medscape).

Incidence of Cancer of Unknown Primary in South Africa
According to the National Cancer Registry (2012) the following number of Cancer of Unknown Primary (CUP) cases were histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	1 703	1:83	4,63%
Asian males	50	1:101	5,92%
Black males	923	1:102	7,91%
Coloured males	257	1:46	5,93%
White males	477	1:66	2,38%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	1 847	1:106	4,91%
Asian females	76	1:81	7,03%
Black females	1 060	1:129	6,42%
Coloured females	221	1:73	5,29%
White females	490	1:79	3,09%

The frequency of histologically diagnosed cases of Cancer of Unknown Primary (CUP) in South Africa for 2012 were as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	9	16	67	173	449	518	313	96
Asian males	0	1	4	7	6	14	8	4
Black males	7	12	43	95	267	245	124	38
Coloured males	0	0	9	23	72	82	46	8
White males	1	3	7	38	88	151	112	43

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	8	22	100	201	409	485	373	167
Asian females	1	1	3	8	18	18	14	4
Black females	5	19	70	122	234	242	183	69
Coloured females	2	2	8	17	53	70	41	15
White females	0	0	11	44	81	133	118	74

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Causes of Cancer of Unknown Origin is Difficult to Find
The primary cancer (the cancer that first formed) may not be found for one of the following reasons:

- the primary cancer is very small and grows slowly
- the body's immune system killed the primary cancer
- the primary cancer was removed during surgery for another condition and doctors did not know cancer had formed. For example, a uterus with cancer may be removed during a hysterectomy to treat a serious infection

(National Cancer Institute).

Risk Factors for Cancer of Unknown Origin
Since CUP can be almost any type of primary cancer, the risk factors for all types of cancer can be risk factors for CUP. The following factors can raise a person's risk of developing CUP:

- age - the median age of being diagnosed with CUP is 60
- tobacco use, including cigarette smoking, chewing tobacco, and cigar smoking
- sun exposure
- exposure to large amounts of radiation
- exposure to chemicals in some manufacturing industries
- poor nutrition
- lack of exercise
- family history (specifically, if more than one brother, sister, parent, or grandparent has been diagnosed with breast, ovarian, or colorectal cancer, the risk of cancer increases.)

(Cancer.net).

How Cancer of Unknown Origin is Diagnosed
Cancers of unknown primary (CUP) are usually found as the result of the signs or symptoms a person is having.

The signs and symptoms of a cancer of unknown primary vary depending on which organs it has spread to. It is important to note that none of the symptoms listed below is caused only by CUP. In fact, it is more likely to be caused by something other than cancer. Still, if someone has symptoms that suggest that something abnormal may be going on, a doctor should be consulted 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 check-up.

A mass in the abdomen that can be felt or causes a feeling of 'fullness' - a mass is a swelling or firm area that can be caused by a tumour. 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 build-up of fluid inside the abdomen). The fluid build-up can swell the abdomen. It can sometimes lead to a feeling of fullness.

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 tumours pressing against internal organs.

Bone pain - cancer that has spread to the bones can sometimes cause severe pain. 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.

Skin tumours - 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.

Weakness, fatigue, poor appetite and weight loss - these symptoms are often seen with more advanced cancers. It 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.

Medical history and physical examination - if the patient has any signs or symptoms that suggest he/she might have cancer, the doctor will want to take a complete medical history to check for symptoms and risk factors, including a family history. This will be followed by a physical examination that will pay special attention to any parts of the body where there are symptoms.
(American Cancer Society).

Tests that May Assist in Diagnosing a Cancer of Unknown Origin
The following tests and procedures may be used:

Uirnalysis - a test to check the colour of urine and its contents such as sugar, protein, blood and bacteria.

Blood chemistry studies - a procedure in which a blood sample is checked to measure the amounts of certain substances released into the blood by organs and tissues in the body. An unusual (higher or lower than normal) amount of a substance can be a sign of disease in the organ or tissue that manufactures it.

Complete blood count - a procedure in which a sample of blood is drawn and checked for the following:

- The number of red blood cells, white blood cells, and platelets
- The amount of haemoglobin (the protein that carries oxygen) in the red blood cells
- The portion of the sample made up of red blood cells

Faecal occult (hidden) blood test - a test to check stool (solid waste) for blood that can only be seen with a microscope. Small samples of stool (faeces) are placed on special cards and returned to the doctor or laboratory for testing. As some cancers bleed, blood in the stool may be a sign of cancer in the colon or rectum.

If tests show there may be cancer, a biopsy is usually done. A biopsy is the removal of cells or tissues so they can be viewed under a microscope by a pathologist. The pathologist views the tissue under a microscope to look for cancer cells and to find out the type of cancer. The type of biopsy that is done depends on the part of the body being tested for cancer. One of the following types of biopsies may be used:

- excisional biopsy - the removal of an entire lump of tissue
- incisional biopsy - the removal of part of a lump or a sample of tissue
- core biopsy - the removal of tissue using a wide needle
- fine-needle aspiration (FNA) biopsy - the removal tissue or fluid using a thin needle

If cancer is found, one or more of the following laboratory tests may be used to study the tissue samples and find out the type of cancer:

Histologic study - a laboratory test in which stains are added to a sample of cancer cells or tissue and viewed under a microscope to look for certain changes in the cells. Certain changes in the cells are linked to certain types of cancer.

Immunohistochemistry study - a laboratory test in which dyes or enzymes are added to a sample of cancer cells or tissue to test for certain antigens (proteins that stimulate the body's immune response).

Reverse transcription–polymerase chain reaction (RT-PCR) test - a laboratory test in which cells in a sample of tissue are studied using chemicals to look for certain changes in the genes.

Cytogenetic analysis - a laboratory test in which cells in a sample of tissue are viewed under a microscope to look for certain changes in the chromosomes. Changes in certain chromosomes are linked to certain types of cancer.

Light and electron microscopy - a laboratory test in which cells in a sample of tissue are viewed under regular and high-powered microscopes to look for certain changes in the cells.

When the type of cancer cells or tissue removed is different from the type of cancer cells expected to be found, a diagnosis of CUP may be made.

The cells in the body have a certain look that depends on the type of tissue they come from. For example, a sample of cancer tissue taken from the breast is expected to be made up of breast cells. However, if the sample of tissue is a different type of cell (not made up of breast cells), it is likely that the cells have spread to the breast from another part of the body. In order to plan treatment, doctors first try to find the primary cancer (the cancer that first formed).

Tests and procedures used to find the primary cancer depend on where the cancer has spread. In some cases, the part of the body where cancer cells are first found helps the doctor decide which diagnostic tests will be most helpful.

- When cancer is found above the diaphragm (the thin muscle under the lungs that helps with breathing), the primary cancer site is likely to be in the upper part of the body, such as in the lung or breast.
- When cancer is found below the diaphragm, the primary cancer site is likely to be in the lower part of the body, such as the pancreas, liver, or other organ in the abdomen.
- Some cancers commonly spread to certain areas of the body. If cancer is found in the lymph nodes in the neck, the primary cancer site is likely to be in the head or neck, because head and neck cancers often spread to the lymph nodes in the neck.

The following tests and procedures may be done to find where the cancer first began:

Computerised Tomography (CT) scan (CAT scan): a procedure that makes a series of detailed pictures of areas inside the body, such as the chest or abdomen, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerised tomography, or computerised axial tomography.

Magnetic Resonance Imaging (MRI): a procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body. This procedure is also called nuclear magnetic resonance imaging (NMRI).

Positron Emission Tomography (PET) scan): a procedure to find malignant tumour cells in the body. A small amount of radioactive glucose (sugar) is injected into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumour cells show up brighter in the picture because they are more active and take up more glucose than normal cells do.

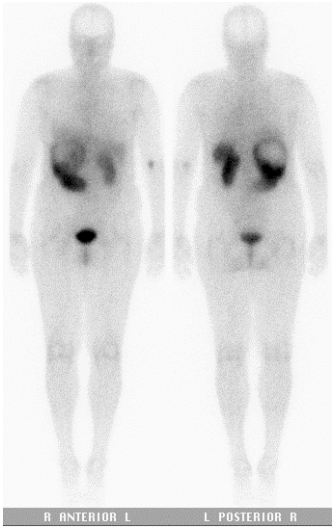
Mammogram: an x-ray of the breast.

Endoscopy: a procedure to look at organs and tissues inside the body to check for abnormal areas. An endoscope is inserted through an incision (cut) in the skin or opening in the body, such as the mouth. An endoscope is a thin, tube-like instrument with a light and a lens at its tip for viewing. It may also have a tool to remove tissue or lymph node samples, which are checked under a microscope for signs of disease.

Tumour marker test: a procedure in which a sample of blood, urine, or tissue is checked to measure the amounts of certain substances made by organs, tissues, or tumour cells in the body. Certain substances are linked to specific types of cancer when found in increased levels in the body. These are called tumour markers. The blood may be checked for the levels of CA-125, CgA, alpha-fetoprotein (AFP), beta human chorionic gonadotropin (β-hCG), or prostate-specific antigen (PSA).

Sometimes, none of the tests can find the primary cancer site. In these cases, treatment may be based on what the doctor thinks is the most likely type of cancer.
(National Cancer Institute; Cancer.Net).

Octreoscan: an octreoscan is a scinitigraphic study that uses a ^{111}In labelled octreotide which is a somatostatin analog (Indium In-111 Pentetreotide). It is particularly useful for assessment of neuroendocrine tumours (Neuroendocrine tumours (NETs) are neoplasms that arise from cells of the endocrine (hormonal) and nervous systems).



[Picture Credit: OctreoScan]

An OctreoScan is fairly straightforward, while it cannot give an indication as to tumour size, it can indicate the extent of disease metastasis and how possible loci for tumours which may or may not have been suspected. Essentially what happens is: about 40 to 24 hours prior to scanning, a nuclear tag (about 6 milliCuries) piggybacked onto a somatostatin analog (like Sandostatin) is injected.

This tag is then taken up by any tissue exhibiting a type two receptor. Usually one finds type two receptors in carcinoid cancers, lymphomas, some breast cancers and so on. The body of the person is then scanned at intervals of 24, 48 and even 72 hours or whenever the oncologist and radiologist deem it beneficial. The tag being tumour-specific will cause any tissue with the requisite receptors to light up on the scan film. The test is sort of a 'go or no-go'.

Most carcinoid tumours have the receptors and light up the film; about 2 percent of tumours do not have the receptors and thus do not show up. If the patient is on a somatostatin (growth hormone-inhibiting hormone (GHIH)) such as Sandostatin, the receptors will be blocked and the tumours will not show up. Medications like Sandostatin has to be stopped about 3 days prior to scanning for an accurate test to be performed.
(Carcinoid.org).

Different Types of Unknown Primary Tumours

Even when a primary tumour cannot be found, better diagnostic tests may now give much more information about it. Gender, the position of the secondary cancer in the body, as well as detailed laboratory information about the tumour cells, are important clues in the diagnosis. The type of cancer depends on the types of cells it has developed from. To determine this the doctor will take a tissue sample (biopsy) and send it to a laboratory where a pathologist will examine it closely.

The tumour cells may look very abnormal under a microscope. The term for this is poorly differentiated or undifferentiated. This means that it may not be possible to tell what type of cancer it is just by looking at the shape and structure of the cells.

The pathologist may also test the tissue sample using antibodies to find tumour markers. Tumour markers are chemicals produced by cancer cells. Some tumour markers are produced by one type of cancer, while others can be made by several different types of cancer. The study of tumour markers is called immunohistochemistry (IHC) and tumour markers are often called IHC markers.

Melanoma – in 5% of all melanoma cases the primary tumour cannot be found. When a biopsy of the secondary tumour shows that it is melanoma it is called a melanoma of unknown primary (MUP). It is then treated as stage 3 or 4 melanoma.

Lymphoma - some lymphoma cells can look like other types of cancer. Lymphoma can sometimes be mistaken for secondary cancer in the lymph nodes and is classed as CUP. Tumour markers can help to make a diagnosis of lymphoma. This means that lymphoma is the primary cancer and it is treated as any other lymphoma of a similar type and stage. Very rarely a mass of leukaemia cells can also look similar to other cancers.

Carcinoma - most cancers of unknown primary (CUP) are carcinomas subdivided into:

- germ cell tumours
- squamous cell tumours
- neuroendocrine tumours
- adenocarcinoma
- carcinoma of solid tumours

Germ cell tumours - germ cell tumours develop from cells that become sperm or eggs. Almost all of them are either seminoma or teratoma of the testicle. Germ cell tumours occur very rarely in women. 1 or 2% of ovarian tumours are germ cell and are usually found in young women. Rarely, these tumours occur in other parts of the body, which can make the primary tumour very hard to find. Immunohistochemistry tests (IHC) can identify this type of tumour. The secondary tumour often occurs in lymph nodes in the middle area of the abdomen or chest.

Squamous cell tumours - squamous cell tumours make up 5 to 10% of CUP. Squamous cells are found in the skin and in the membranes that line the airways close to the outside of the body, such as the nose, throat, cervix and anus. The secondary tumours are usually noticed as enlarged lymph nodes in the neck or groin. Local treatments such as surgery and radiotherapy can work well for these tumours.

Neuroendocrine tumours - neuroendocrine tumours (NETs) make up about 5% of CUP. The most common of these are carcinoid tumours which occur mainly in the small bowel or other parts of the digestive system. NETs may also occur in the lung, pancreas, kidney, ovary and testicle. If this type of CUP can be identified, it can respond very well to treatment.

Adenocarcinoma - adenocarcinoma makes up at least 3 out of 5 (60%) of all unknown primary cancers. A more realistic figure may be closer to 90%. Adenocarcinoma is cancer of glandular tissue. The primary tumour occurs in the tubes or ducts of body organs. Studies suggest that in unknown primary adenocarcinoma the secondary cancers are found in the;

- lung – in 27% of cases
- pancreas – 19%
- bowel – 11%
- kidney or adrenal gland – 6%
- liver or bile duct – 6%
- stomach – 5%
- ovary or uterus – 3%
- prostate – 2%

Of the remaining 20% of unknown primary adenocarcinomas, less than 1% occur in the breast.

Carcinoma of solid tumours - The primary site of carcinoma of solid tumours is usually the liver, kidney or endocrine glands. They are often grouped with adenocarcinomas.
(Cancer Research UK).

Staging of Cancer of Unknown Primary (CUP)
There is no staging system for carcinoma of unknown primary (CUP); instead, the staging depends on the histology (the study of tissues or micro anatomy) of the cancer. In addition, patients with cancer of unknown primary origin are defined as patients with histologically proven metastatic malignant tumours in which the primary site cannot be identified during pre-treatment evaluation.

The pathologist, familiar with cancer of unknown primary origin, has an indispensable and essential role in the evaluation of the cancer. Tumours provided for pathologic review should come from tissue that has, whenever possible, been excised, if such tissue is available and accessible. Needle biopsy specimens may provide insufficient tissue for diagnosis or provide tissue that has been too damaged or distorted by the biopsy procedure for accurate diagnosis.

Studies used to evaluate cancer of unknown primary include light microscopy, immunohistochemical stains, electron microscopy and chromosomal analysis including cytogenetics.

Classification of occult (hidden) primary tumours
Major subtypes after microscopic evaluation include the following:
- well or moderately differentiated adenocarcinoma (cancer that develops in the glandular tissues of the body)
- poorly differentiated adenocarcinoma
- undifferentiated adenocarcinoma
- squamous cell carcinoma
- poorly differentiated malignant neoplasm
- neuroendocrine tumours

(E-Medicine.Medscape)

Treatment of Cancer of Unknown Primary (CUP)
Treatment for cancer of unknown primary (CUP) may include:

Surgery - surgery is a common treatment for 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 is still a chance that the cancer may be elsewhere in the body. If one is considering surgery as a treatment option, it is important to understand how likely it is to help the patient.

The type and extent of surgery will depend on where the cancer is and how extensive it is. If surgery is used, it may be followed by radiation therapy and possibly chemotherapy to try to kill any remaining cancer cells in the body.

Radiation therapy - radiation therapy uses high-energy rays or particles to destroy cancer cells or slow their rate of growth. The goal of radiation therapy may change based on the situation.

For some cancers that have not spread too far from where it started, radiation can be used alone or with other treatments such as surgery with the goal of trying to cure the cancer.

If cancer has spread extensively, radiation can be used to relieve symptoms such as pain, bleeding, trouble swallowing, intestinal blockage, compression of blood vessels or nerves by tumors, and problems caused by metastases to bones.

> *External beam radiation therapy* - the most common way to deliver radiation to a cancer is to carefully focus a beam of radiation from a machine outside the body. This is known as external beam radiation. To reduce the risk of side effects, doctors carefully figure out the exact dose and aim the beam as accurately as they can to hit the target. The radiation is usually divided into many treatments over several days or weeks.
>
> *Internal radiation therapy (brachytherapy)* - another method of delivering radiation is called *internal radiation*, *interstitial radiation*, or *brachytherapy*. Instead of using radiation beams aimed from a large machine, a radioactive material is placed directly into, or as close as possible to, the cancer. This type of radiation travels a very short distance in the body. The material itself may be left in the body for only a short time, or it may be left there permanently. Sometimes, both internal and external beam radiation therapies are used together.

Chemotherapy - chemotherapy uses anti-cancer drugs that are usually injected into a vein or taken by mouth. These drugs enter the bloodstream and can reach cancer that has spread. Because chemotherapy 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 have not been detected.

Chemotherapy can be used in a number of situations for cancer of unknown primary (CUP). If the doctor recommends chemotherapy, it is important that one understands what the goals of the treatment are.

Chemotherapy may be the main treatment for cancers that are clearly advanced and are unlikely to be helped by local treatments such as surgery or radiation therapy. In some cases, such as with cancers that are likely to be germ cell tumours or certain types of lymphomas, it may be very effective in making tumours shrink or even go away altogether. In other cases, chemotherapy 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 local therapies such as surgery or radiation, chemotherapy may be added to try to kill any remaining cancer cells in the body.

Chemotherapy drugs are often given in combinations, which are more likely to be effective than giving a single drug alone.

- For adenocarcinomas and poorly differentiated cancers where the site of origin is not clear, doctors usually recommend a combination that includes a platinum drug

(cisplatin or carboplatin) and a taxane drug (paclitaxel [Taxol®] or docetaxel [Taxotere®]). Other drugs such as gemcitabine (Gemzar®) and etoposide (VP-16) may also be used.

- If chemotherapy is to be used for a squamous cell cancer, the most commonly used drugs are cisplatin, 5-fluorouracil (5-FU), and a taxane (paclitaxel or docetaxel).
- For neuro-endocrine carcinomas that are poorly differentiated, treatment usually includes a platinum drug (cisplatin or carboplatin) and etoposide.
- Well-differentiated neuro-endocrine cancers are not often the cause of CUP, but may present with liver metastasis and an occult primary. These patients are treated like patients with well-differentiated carcinoid tumour.

Hormone therapy - some types of cancer grow in response to sex hormones in the body. For example, most breast cancers have proteins called *estrogen receptors* and/or *progesterone receptors* on the surface of their cells. These cancers grow faster when exposed to the hormone estrogen. Likewise, most prostate cancers grow in response to male hormones called *androgens*, such as testosterone.

In cases where a cancer of unknown primary (CUP) is likely to be a breast or prostate cancer, hormone therapy may be an effective way to slow the growth of the cancer, or perhaps even shrink it and may help the patient to live longer.

For breast cancer, types of hormone therapy include drugs like tamoxifen, LHRH agonists like leuprolide (Lupron®) and goserelin (Zoladex®), and the aromatase inhibitors anastrozole (Arimidex®), letrozole (Femara®), and exemestane (Aromasin®). These drugs either lower estrogen levels or prevent cancer cells from being able to use it.

Some commonly used drugs include LHRH agonists such as leuprolide and goserelin and anti-androgens such as flutamide (Eulexin®), as well as bicalutamide (Casodex®). These drugs either lower the testosterone level or prevent cancer cells from being able to use it. Surgery to remove the testicles (orchiectomy) is another option. For more information, see our Fact Sheet on *Prostate Cancer*.

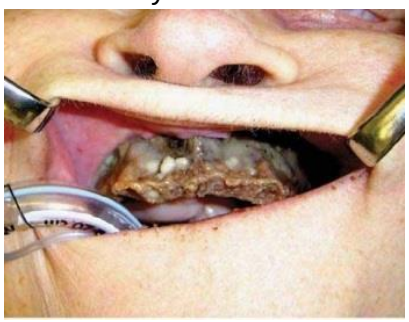
Targeted therapy - targeted therapy is a newer type of cancer treatment that uses drugs or other substances to identify and attack cancer cells while doing little damage to normal cells. These therapies attack the cancer cells' inner workings – the programming that makes it different from normal, healthy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

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 it grow faster and become more resistant to radiation or chemotherapy. A drug called cetuximab (Erbitux®) blocks EGFR and can help patients with squamous cell cancers of the head and neck area. It is often used along with radiation or chemotherapy, but it can also be used by itself to treat patients whose cancers no longer respond to chemotherapy and who cannot take radiation therapy.

A number of targeted therapy drugs are used to treat breast cancer, including trastuzumab (Herceptin®), pertuzumab (Perjeta®), lapatinib (Tykerb®), as well as everolimus (Affinitor®). 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.

Other drugs – other drugs used in the treatment of Cancer of Unknown Origin include:

Bisphosphonates **-** bisphosphonates are drugs that are used to help strengthen and reduce the risk of fractures in bones that have been weakened by metastatic cancer. Examples include pamidronate (Aredia®) and zoledronic acid (Zometa®). It is given intravenously (IV). To treat cancer that has spread to bone, it is given monthly.



[Picture Credit: ONJ]

Bisphosphonates can have side effects, including flu-like symptoms and bone pain. It can also cause kidney problems, so people with kidney problems cannot use it. A rare but very distressing side effect of intravenous bisphosphonates is damage (osteonecrosis) in the jaw bones (ONJ – osteonecrosis of the jaw). It can be triggered by having a tooth extraction (removal) 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 usually only stop the bisphosphonates. Maintaining good oral hygiene by flossing, brushing, making sure that dentures fit properly, whilst 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 lower the risk of fractures in bones weakened by cancer spread. To treat cancer that has spread to bone, this drug is given as an injection under the skin, once a month.

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

Octreotide **-** octreotide (Sandostatin®) is an agent chemically related to a natural hormone, somatostatin. It is very helpful for some patients with neuro-endocrine tumours. If the tumour releases hormones into the bloodstream (which is rare in the poorly differentiated tumours that cause cancer of unknown primary), this drug can stop the hormone release. It can also cause tumours to stop growing or (rarely) to shrink. This drug is available as a short-acting version given as injection 2 to 4 times a day. It is also available as a long-acting injection that needs to be given only once a month. A similar drug, lanreotide (Somatuline®), is also available. It is also given as an injection once a month. These drugs are most likely to help treat cancers that show up on somatostatin receptor scintigraphy (OctreoScan).

(American Cancer Society; Cancer Research UK).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may

also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

Medical Disclaimer

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