Cancer Association of South Africa (CANSA)

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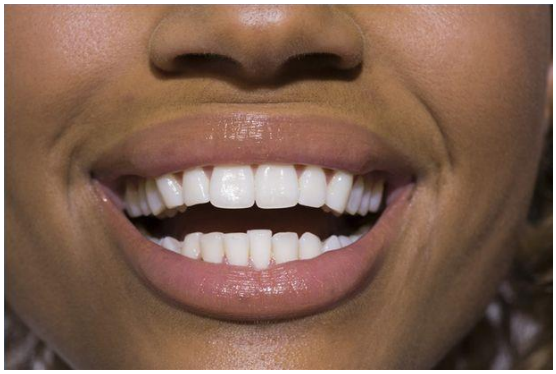
Fact Sheet
on
Cancer of the Mouth

Introduction

In human anatomy, the **mouth** is the first portion of the alimentary canal (digestive system). In addition to its primary role as the beginning of the digestive system, in humans the mouth also plays a significant role in communication. While primary aspects of the voice are produced in the throat, the tongue, lips, and jaw are also needed to produce the range of sounds included in human language.

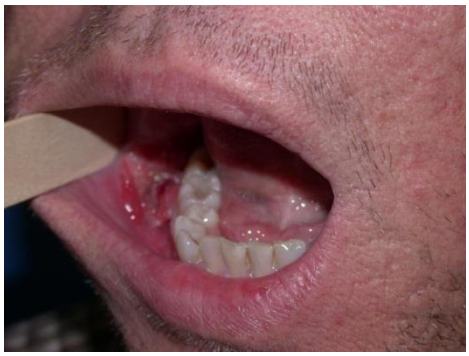


[Picture Credit: Mouth]

The mouth, consists of two regions, the vestibule and the oral cavity proper. The vestibule is the area between the teeth, lips and cheeks. The oral cavity is bounded at the sides and in front by the alveolar process (containing the teeth) and at the back by the isthmus of the fauces. Its roof is formed by the hard palate and soft palate and the floor is formed by the mylohyoid muscle and is occupied mainly by the tongue. Mucous membrane lines the sides and under surface of the tongue to the gum lining the inner aspect of the jaw mandible. It receives the secretions from the submaxillary and sublingual salivary glands.

Cancer of the Mouth

Mouth cancer, also known as oral cancer, is where a tumour develops on the surface of the tongue, mouth, lips or gums. Tumours can also occur in the salivary glands, tonsils and the pharynx (the part of the throat from the mouth to the windpipe) but these are less common.
(NHS Choices).



[Picture Credit: Mouth Cancer]

Mouth cancer occurs when cells on the lips or in the

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Diagnostic Radiographer; Dip Audiometry and Noise Measurement]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

mouth develop changes (mutations) in their DNA. These mutations allow cancer cells to grow and divide when healthy cells would die. The accumulating mouth cancer cells can form a tumour. With time they may spread to other areas of the mouth and on to other areas of the head and neck or other parts of the body.

Mouth cancers most commonly begin in the flat, thin cells (squamous cells) that line the lips and the inside of the mouth. Most oral cancers are squamous cell carcinomas.

It is not always clear what causes the mutations in squamous cells that lead to mouth cancer, but doctors have identified factors that may increase the risk of mouth cancer.
(Mayo Clinic).

Incidence of Cancer of the Mouth in South Africa

According to the National Cancer Registry (2013) the following number of cancer of the mouth cases was histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	342	1:403	0,95%
Asian males	10	1:516	1,16%
Black males	174	1:534	1,62%
Coloured males	45	1:364	1,07%
White males	114	1:241	0,57%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	191	1:1 109	0,52%
Asian females	12	1:563	1,12%
Black females	77	1:2 125	0,49%
Coloured females	30	1:688	0,73%
White females	73	1:492	0,46%

The frequency of histologically diagnosed cases of cancer of the mouth in South Africa for 2013 was as follows (National Cancer Registry, 2013):

Group - Males 2013	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	2	6	8	39	104	117	42	16
Asian males	0	0	1	0	2	2	1	0
Black males	2	4	4	21	52	57	11	7
Coloured males	0	1	1	6	16	11	4	1
White males	0	0	0	10	29	40	21	6

Group - Females 2013	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	1	4	9	15	31	51	35	22
Asian females	0	0	1	0	3	4	2	1
Black females	1	3	7	6	23	17	7	7
Coloured females	0	0	1	5	9	8	4	1
White females	0	1	0	4	14	19	21	10

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.

Risks and Causes of Cancer of the Mouth
The following risks and causes of mouth cancer has been identified.

Smoking and alcohol use - smoking tobacco (cigarettes, cigars and pipes) and consuming alcohol are the main risk factors for mouth and oropharyngeal cancers in the western world. If a person smokes, he/she is at a higher than average risk of developing these types of cancers. People exposed to secondhand smoke at home or in the environment have a small increase in their risk of mouth or oropharyngeal cancer.

Drinking alcohol increases the risk of oropharyngeal cancer and may increase mouth cancer risk when combined with smoking. A large Cancer Research UK study looking at lifestyle factors that cause cancer found that around a third of cancers of the mouth and throat (30%) were caused by drinking alcohol.

Cigarettes and alcohol contain nitrosamines and other chemicals that are known to cause cancer. The nitrosamines in alcohol pass over the mouth, throat and top of the epiglottis as one swallows. When smoking, the smoke passes through the mouth, throat and the larynx on its way to the lungs. The risk increases the longer one smokes.

Individuals who smoke are more likely to develop cancer of the mouth or oropharynx. If one smokes and regularly drinks more than the recommended amounts of alcohol, the risk is especially high. Cancers of the mouth or oropharynx do sometimes occur in people who do not smoke or drink much, but this is less common.

Chewing tobacco or betel quid - chewing tobacco (smokeless tobacco) or betel quid (gutkha; areca nut) is known to cause mouth cancer and oropharyngeal cancer. It is not a safe alternative to cigarettes. It is very common in parts of Asia. It is also popular in some immigrant groups in Europe, North America and Australia.

The term ‘quid’ means a substance or mixture of substances put in the mouth and chewed, usually for long periods. It usually contains tobacco, either on its own or mixed with areca nut (from the Areca catechu tree) and slaked lime and sometimes spices. The mixture is wrapped in a leaf called a betel leaf, which is where the name betel quid (also called ‘paan’) comes from. The harmful substances in tobacco and betel quid can cause cancer if they are in contact with the gums and tongue over long periods.

Mouth cancer is more common in parts of the world where people chew betel quid. Of the estimated 400 000 cases of oral cancer worldwide each year, around two thirds occur in developing countries. In some parts of India, it is the most common type of cancer.

Diet - a poor diet may increase one’s risk of certain types of mouth and oropharyngeal cancer. This may be due to a lack of vitamins and minerals, such as iron or folic acid. Poor diet can lead to a breakdown in the oral mucosa and this can make it more prone to developing cancer. If one eats a well balanced diet with plenty of protein, one is unlikely to be short of vitamins and minerals.

A diet high in fresh fruit (in season) and vegetables seems to reduce the risk of developing cancer of the mouth. This may be because these foods contain a lot of antioxidant vitamins and other substances that help prevent damage to body cells.

Human papilloma virus (HPV) - viruses can help to cause some cancers. But this does not mean that one can catch these cancers like an infection. The virus can cause genetic changes in cells that make them more likely to become cancerous in the future.

Mouth and oropharyngeal cancers have been linked to the human papilloma virus (HPV), especially type 16. There are more than 100 different types of (HPV). Some types are called the wart virus, because they cause warts on the genital area or skin. Other types of HPV are known to increase the risk of some types of cancer. These include cancer of the cervix, vaginal cancer, vulval cancer and anal cancer.

HPV can be passed on during sexual contact. Most sexually active adults will be infected with at least one type of HPV at some time during their life. For many people, the virus causes no harm and goes away without treatment. Only a very small percentage of people with HPV develop oropharyngeal cancer. The risk of HPV infection in the mouth and throat is linked to certain sexual behaviours, such as oral sex. The risk increases with the number of sexual partners a person has. Smoking also increases the risk of HPV infection in the mouth.

Low immunity - research has found that people have an increased risk of mouth cancer if they have a reduced immunity due to HIV or AIDS. Taking medicines to suppress immunity after organ transplants also gives a higher risk of mouth cancer than in the general population.

Sunlight and sunbeds - skin cancers are relatively common on the face and neck, as these areas are often exposed to ultraviolet light (UV). Both the sun and tanning beds give off UV rays. These rays can cause skin cancers in unprotected skin. Some studies have shown an increase of skin cancer in people who regularly use sunbeds. Melanoma is the most serious type of skin cancer and can occur on the lip.

Previous cancer - people who have had mouth or oropharyngeal cancer have an increased risk of getting a second one. People who have had some other types of cancer also have an increased risk of mouth cancer. These include

- Cancer of the food pipe (oesophagus)
- Squamous cell skin cancer
- Cervical, anal or genital cancer in women
- Cancer of the anus or penis in men

Family history - people often worry that they are at a higher risk of cancer because someone in their family has it. There does seem to be a slightly higher risk of getting mouth cancer if one has a close relative (a parent, brother, sister or child) who has had mouth cancer. The reason for this is no known.

Mouth conditions - sometimes changes can happen in the cells of the lining of the mouth and they cause red or white patches to appear. Doctors call these red patches erythroplakia and white patches leukoplakia.

In some people these changes may develop into cancer over some years. Dentists can see these patches during dental checks so it is important to have regular dental appointments to find these changes early.

Genetic conditions - people with certain syndromes caused by inherited changes (mutations) in particular genes have a high risk of mouth and throat cancer.

These include:

- Fanconi anaemia – a genetic disorder that can affect children and adults from any ethnic background. It is also called Fanconi's syndrome. People with Fanconi anaemia are short, have bone changes, and are at risk of developing cancers, leukaemia, and bone marrow failure (aplastic anaemia)
- Dyskeratosis congenita – a genetic syndrome that can cause aplastic anaemia, skin rashes, and abnormally shaped fingernails and toenails. People with this syndrome have a high risk of developing cancer of the mouth and throat when they are young.

Hydrochlorothiazide - hydrochlorothiazide is a drug used to treat high blood pressure (hypertension). One of its possible side effects is photosensitivity (increased sensitivity to sunlight). A small study showed hydrochlorothiazide may increase the risk of developing lip cancer.
(Cancer Research UK).

Types of Mouth Cancers
The following types of mouth cancer have been identified:

- Squamous cell carcinoma - more than 90% of cancers that occur in the oral cavity and oropharynx are squamous cell carcinoma. Normally, the throat and mouth are lined with so-called squamous cells, which are flat and arranged in a scale-like way. Squamous cell carcinoma means that some squamous cells are abnormal.

- Verrucous carcinoma - about 5% of all oral cavity tumours are verrucous carcinoma, which is a type of very slow-growing cancer made up of squamous cells. This type of oral cancer rarely spreads to other parts of the body, but can invade the tissue surrounding the site of origin.

- Minor salivary gland carcinomas - this category includes several kinds of oral cancer that can develop on the minor salivary glands, which are found throughout the lining of the mouth and throat. These types include adenoid cystic carcinoma, mucoepidermoid carcinoma, and polymorphous low-grade adenocarcinoma.

- Lymphomas - oral cancers that develop in lymph tissue, which is part of the immune system, are known as lymphomas. The tonsils and base of the tongue both contain lymphoid tissue.

- Benign oral cavity and oropharyngeal tumours - several types of non-cancerous tumours and tumour-like conditions can arise in the oral cavity and oropharynx.

Sometimes, these conditions may develop into cancer. For this reason, benign tumours, which usually do not recur, are often surgically removed.

The types of benign (non-cancerous) lesions include:

- Eosinophilic granuloma
- Fibroma
- Granular cell tumour
- Karatoacanthoma
- Leiomyoma
- Osteochondroma
- Lipoma
- Schwannoma
- Neurofibroma
- Papilloma
- Condyloma acuminatum
- Verruciform xanthoma
- Pyogenic granuloma
- Rhabdomyoma
- Odontogenic tumors (lesions that begin in tooth-forming tissues)

- Leukoplakia and erythroplakia - these non-cancerous conditions mean that there are certain types of abnormal cells in the mouth or throat. With leukoplakia, a white area can be seen, and with erythroplakia, there is a red area, flat or slightly raised, that often bleeds when scraped. Both conditions may be precancerous; that is, they can develop into different types of cancer. When these conditions occur, a biopsy or other test is done to determine whether the cells are cancerous.

  Most leukoplakia is benign. About 25% of cases of leukoplakia are either cancerous when first discovered or become precancerous. Erythroplakia is usually more serious, with about 70% of cases cancerous either at the time of diagnosis or later.

(Cancer Treatment Centers of America).

Diagnosis of Mouth Cancers

Any discussion of diagnosis must be prefaced with the issue of discovery. While an annual screening for oral cancer is important, it is possible that you will notice some change in your mouth or throat that needs examination between your annual screenings. You are the most important factor in an early diagnosis. You should always contact your doctor or dentist immediately if you notice the following symptoms in yourself or a loved one:

- A sore or lesion in the mouth that does not heal within two weeks.
- A lump or thickening in the cheek.
- A white or red patch on the gums, tongue, tonsil, or lining of the mouth.
- A sore throat or a feeling that something is caught in the throat.
- Difficulty chewing or swallowing.
- Difficulty moving the jaw or tongue.
- Numbness of the tongue or other area of the mouth.
- Swelling of the jaw that causes dentures to fit poorly or become uncomfortable.
- Chronic hoarseness.

These symptoms may be caused by other, less serious problems, but they also indicate the possible presence of oral cancer. Only a professional will be able to tell. Some think that a visit to their medical doctor is the appropriate course of action. But remember that dentists are trained in this simple, quick screening, which involves the examination of the oral cavity as a whole and not just the teeth. Besides a visual examination of all the tissues in one's mouth, a doctor will feel the floor of the mouth and portions of the back of the throat with his/her fingers, in the search for abnormalities. A thorough oral screening also includes indirect examination of the nasopharynx and larynx, and involves manually feeling the neck for swollen lymph nodes, and other abnormalities such as hardened masses.

The doctor will also check the mouth for white patches, red patches, ulcerations, lumps, loose teeth, and review dental X-rays for abnormalities. Be sure to tell the doctor if you have been a tobacco user in any form. Tobacco use is implicated in many cases of oral cancer. After the physical examination of the mouth, if the doctor finds any areas that are suspicious, he/she may recommend a biopsy. This is simply taking a small portion of the suspicious tissue for examination under a microscope.

The most traditional type of biopsy is incisional. It may be done by the doctor who examines the patient, or the patient may be referred to another doctor for the procedure. In an incisional biopsy, the doctor will remove part or all of the lesion depending on its size and his/her ability to define the extent of it at this early stage. The sample of tissue is then sent to a pathologist who examines the tissue under a microscope to check for abnormal, or malignant cells. When dealing with an area of significant mass, such as an enlarged lymph node, fine needle aspiration cytology (fine needle biopsy or FNB) has found an increasing role in diagnosis. The technique is reliable and relatively inexpensive. In it, a small needle attached to a syringe is inserted into the questionable mass, and cells are aspirated, or pulled out into the syringe as the doctor draws back the piston of the syringe. The success of this method depends on how accurately the needle is placed, and, as with all biopsies, on the skill and experience of the tissue pathologist who will be examining the cells. It is likely that the doctor will insert the needle and draw out cellular material from several different locations in the mass to ensure that a thorough and representative sample has been taken.

Another form of incisional biopsy is referred to as a punch biopsy. In this case, a very small circular blade is pressed down into the suspect area cutting a round border. The doctor then pulls on the centre of this area, and with a scalpel or a pair of small tissue scissors snips it free of the surrounding tissue, removing a perfect plug of cells from the sampled area. As before this is sent to a pathologist for examination. The area where the plug was removed will not bleed much, and heals normally without the need for any stitches since it is so small.

Some dental offices are doing a "brush biopsy" where a sampling of cells is collected by aggressively rubbing a brush against the suspect area. While this has some usefulness in preliminary evaluation of a suspect area, it is not a stand-alone procedure, and if a positive find returns, this must be confirmed by a conventional incisional biopsy.

The entire point of course, is that no treatment decisions should be made before there is confirmation of malignancy. Even in the case of what would seem to be an obvious malignancy, appearances can occasionally be misleading, hence the need for a proper biopsy. Also, the degree of differentiation between healthy and malignant tissues, along with the stage of the disease will influence treatment strategy and prognosis.

Other ways to determine the presence or extent of oral cancer exist. For instance, radiographs, also referred to as X-rays, can assist in determining the potential growth of a

tumour into bone. While oral cancers unlike many other malignancies can usually be seen with the naked eye, some cancers are located internally in the body, making their detection difficult. Different scanning options, some of which assist in determining the presence of tumours or growths, and some of which can even detect malignancy, are necessary in these instances.

CT, or CAT (co-axial tomography) scan technology has developed rapidly over the last few decades, and these scans can provide images of great diagnostic quality and usefulness. A CT scan could be described as a series of X-rays, each one a view of a 3mm section of the area being scanned, which are then manipulated by a computer, allowing doctors a dynamic view of the affected soft tissue areas of the body with much greater detail than a simple X-ray. However, CT is only able to detect the actual presence of masses, and only a biopsy can verify that the mass is malignant. Another recent technology, Magnetic Resonance Imaging (MRI), is helpful in providing accurate views of the affected area. MRI is a procedure in which pictures are created using magnets and radio frequencies linked to a computer imaging system. The hydrogen atoms in the patient's body react to the magnetic field and emit signals that are analysed by a computer to produce detailed images of organs and structures in the body. Occasionally a dye is injected into the bloodstream during scanning to bring greater detail to the soft tissue areas of the scan. Again, this procedure is only able to detect the actual presence of masses, and it still requires a biopsy for confirmation.

PET, or Positron Emission Tomography, provides another kind of image of the body's interior. Instead of taking a picture of the bones, like an X-ray, or the internal organs and soft tissue, like a MRI, PET scanning lets doctors display the body's actual metabolism. Since cells use a simple sugar, glucose, as a source of energy, PET can track down how much glucose is being metabolized in different areas of the body.

Because cancer cells are dividing rapidly, they break down glucose much faster than normal cells. The increased activity will show up on a PET scan, and can indicate both primary and metastatic tumours.

Although less frequently used for oral cancer detection, ultrasonography is another way to produce pictures of areas in the body. In it, high-frequency sound waves (ultrasound) are bounced off organs and tissue. The pattern of echoes produced by these waves creates a picture called a sonogram. It is useful in finding masses with in an area, if palpation discloses something of questionable nature.

Radionuclide scanning can show whether cancer has spread to other organs elsewhere in the body. In it, the patient swallows or receives an injection of a mildly radioactive substance, and a scanner measures and records the level of radioactivity in certain organs to reveal abnormal areas.

All these types of scans are still used largely for confirmation or measuring extent. The best indicator of tumour involvement is still the clinical assessment, relying on both direct

examination of the area as well as biopsy. The ability to detect cancer at the earliest stages, as well as its precise location in the body, can improve the survival rate of this disease, and allow for less disfiguring ways to address the tumours and lesions associated with oral cancer.

If the pathologist examining the cells from a patient finds oral cancer, the patient's doctor needs to know the stage, or extent, of the disease in order to plan the best treatment. Staging a cancer involves trying to carefully establish the degree to which the cancer has spread, and to what extent it involves other areas of the mouth and neck, or even distant locations elsewhere in the body. After determining how much the cancer has spread, doctors also use this point of diagnosis to grade a cancer, which is a way of expressing how rapidly the cancer is spreading, if at all. The aggressiveness of this spreading is described using the terms well differentiated, moderately differentiated, or poorly differentiated. A well-differentiated cancer is not overly aggressive in the rate it is spreading; a moderately differentiated cancer is intermediately aggressive; and a poorly differentiated is much more aggressive in the speed with which it is spreading.

These staging tests and examinations almost always include incisional biopsy, and often one or more of the types of scans listed above. Most oral lesions allow for a small incisional biopsy, one that can be performed while the patient is conscious. Local anaesthesia is adequate in most cases. For lesions or tumours in deeper tissues or less accessible areas, a general anaesthetic can provide a better opportunity to perform the biopsy and also to make a full clinical assessment of the lesion.

Following biopsy confirmation of the presence of an oral cancer, a patient undergoes a thorough assessment of their overall health, and the state of their disease. The patient's overall fitness in anticipation of treatment is determined. Many patients afflicted by oral cancer, though certainly not all, are elderly. Older patients may be suffering from other illnesses, and they are also at risk of having other cancers in the respiratory or digestive tract. These "synchronous carcinomas" of the head and neck, lungs, or oesophagus occur as frequently as 10 percent of the time with elderly oral cancer patients. Therefore, checking for cancer in these areas as well, can be part of the diagnostic process.

In many ways, the diagnostic stage of treatment affects everything that follows, and so care should be taken to both accurately and effectively determine the malignancy and stage of the cancer. This detailed diagnosis gives those prescribing treatment specific knowledge, which in turn allows for specific, more successful treatment.
(The Oral Cancer Foundation).

Staging of Mouth Cancer
One tool that doctors use to describe the stage is the TNM system. TNM is an abbreviation for tumour (**T**), node (**N**), and metastasis (**M**). Doctors look at these three factors to determine the stage of cancer:

- How large is the primary tumour and where is it located? **(Tumour, T)**
- Has the tumour spread to the lymph nodes? **(Node, N)**
- Has the cancer metastasised to other parts of the body? **(Metastasis, M)**

The results are combined to determine the stage of cancer for each person. There are five stages: stage 0 (zero) and stages I through IV (one through four). The stage provides a

common way of describing the cancer, so doctors can work together to plan the best treatments.

Here are more details on each part of the TNM system for oral and oropharyngeal cancer.

Tumour. Using the TNM system, the "T" plus a letter or number (0 to 4) is used to describe the size and location of the tumour. Some stages are also divided into smaller groups that help describe the tumour in even more detail.
Specific tumour stage information is listed below.

TX: The primary tumour cannot be evaluated.
T0: No evidence of a tumour is found.
Tis: Describes a stage called carcinoma (cancer) in situ. This is a very early cancer where cancer cells are found only in one layer of tissue.
T1: The tumour is 2 centimetres (cm) at its greatest dimension.
T2: The tumour is larger than 2 cm, but not larger than 4 cm.
T3: The tumour is larger than 4 cm.
T4: Describes any of the following conditions:
T4a (lip): The tumour began on the lip but has invaded adjacent tissue, such as the bone or floor of the mouth or the skin of the face.
T4a (oral cavity): The tumour has invaded through the cortical bone deep into structures in the mouth, such as the muscle of the tongue or into the sinuses.
T4a (oropharynx): The tumour has spread to the larynx, tongue, or jawbone.
T4b (oral cavity): The tumour has invaded the base of the skull and/or encases the internal arteries.
T4b (oropharynx): The tumour has spread into the nasopharynx, skull base, or nearby arteries and muscles.

Node. The “N” in the TNM staging system is for lymph nodes, the tiny, bean-shaped organs that help fight infection. Lymph nodes near where the cancer started are called regional lymph nodes. Lymph nodes in other parts of the body are called distant lymph nodes. There are many lymph nodes in the head and neck area, and careful assessment of lymph nodes is an important part of staging.

NX: The regional lymph nodes cannot be evaluated.
N0: There is no evidence of cancer in the regional lymph nodes.
N1: The cancer has spread to a single lymph node on the same side as the primary tumour, and the cancer found in the node is 3 cm or smaller.
N2: Describes any of these conditions:
N2a: Cancer has spread to a single lymph node on the same side as the primary tumour and is larger than 3 cm, but not larger than 6 cm.
N2b: Cancer has spread to more than one lymph node on the same side as the primary tumour, and none measure larger than 6 cm.
N2c: Cancer has spread to more than one lymph node on either side of the body, and none measure larger than 6 cm.
N3: The cancer found in the lymph nodes is larger than 6 cm.

Distant metastasis. The "M" in the TNM system describes cancer that has spread to other parts of the body.
MX: Distant metastasis cannot be evaluated.
M0: Cancer has not spread to other parts of the body.
M1: Cancer has spread to other parts of the body.

Cancer Stage Grouping

Doctors assign the stage of the cancer by combining the T, N, and M classifications.

Stage 0:
Describes a carcinoma in situ (Tis) with no spread to lymph nodes (N0) or distant metastasis (M0).

Stage I:
Describes a small tumour (T1) with no spread to lymph nodes (N0) and no distant metastasis (M0).

Stage II:
Describes a tumour that is smaller than 4 cm (T2) and has not spread to lymph nodes (N0) or to distant parts of the body (M0).

Stage III:
Describes a larger tumour (T3) with no spread to lymph nodes (N0) or metastasis (M0), as well as smaller tumours (T1, T2) that have spread to regional lymph nodes (N1) but have no sign of metastasis (M0).

Stage IVA:
Describes any invasive tumour (T4a) with either no lymph node involvement (N0) or spread to only a single, same-sided lymph node (N1) but no metastasis (M0). It is also used for any tumour (any T) with more significant nodal involvement (N2) but no metastasis (M0).

Stage IVB:
Describes any tumour (any T) with extensive nodal involvement (N3) but no metastasis (M0).

Stage IVC:
Indicates there is evidence of distant spread (any T, any N, M1).

Recurrent:
Recurrent cancer is cancer that has come back after treatment. If there is a recurrence, the cancer may need to be staged again (called re-staging) using the system above.

Tumour Grade (G)

Doctors also describe this type of cancer by its grade (G), which describes how much cancer cells look like healthy cells when viewed under a microscope. The doctor compares the cancerous tissue with healthy tissue. Healthy tissue usually contains many different types of cells grouped together. If the cancer looks similar to healthy tissue and contains different cell groupings, it is called differentiated or a low-grade tumour. If the cancerous tissue looks very different from healthy tissue, it is called poorly differentiated or a high-grade tumour. The cancer's grade can help the doctor predict how quickly the cancer will spread. In general, the lower the tumour's grade, the better the prognosis.

GX: The grade cannot be evaluated.
G1: The cells look more like normal tissue and are well differentiated.
G2: The cells are only moderately differentiated.
G3 and G4: The cells don't resemble normal tissue and are poorly differentiated.
(Cancer.Net).

Treatment of Mouth Cancer
Oral cancer treatment may include surgery, radiation therapy, or chemotherapy. Some patients have a combination of treatments.

At any stage of disease, people with mouth (oral) cancer may have treatment to control pain and other symptoms, to relieve the side effects of therapy, and to ease emotional and practical problems. This kind of treatment is called supportive care, symptom management, or palliative care.

A patient may want to talk to the doctor about taking part in a clinical trial, a research study of new treatment methods.

Surgery - surgery to remove the tumour in the mouth or throat is a common treatment for oral cancer. Sometimes the surgeon also removes lymph nodes in the neck. Other tissues in the mouth and neck may be removed as well. Patients may have surgery alone or in combination with radiation therapy.

Radiation therapy - radiation therapy (also called radiotherapy) is a type of local therapy. It affects cells only in the treated area. Radiation therapy is used alone for small tumours or for patients who cannot have surgery. It may be used before surgery to kill cancer cells and shrink the tumour. It also may be used after surgery to destroy cancer cells that may remain in the area. Radiation therapy uses high-energy rays to kill cancer cells. Doctors use two types of radiation therapy to treat oral cancer:

- External radiation: The radiation comes from a machine. Patients go to the hospital or clinic once or twice a day, generally 5 days a week for several weeks.
- Internal radiation (implant radiation**)**: The radiation comes from radioactive material placed in seeds, needles, or thin plastic tubes put directly in the tissue. The patient stays in the hospital. The implants remain in place for several days. Usually they are removed before the patient goes home.

Some people with oral cancer have both kinds of radiation therapy.

Chemotherapy - chemotherapy uses anticancer drugs to kill cancer cells. It is called systemic therapy because it enters the bloodstream and can affect cancer cells throughout the body. A new targeted therapy called cetuximab, which blocks a growth factor upon which cancer cells may depend, is being used today, either alone or in combination with radiation and older chemotherapy drugs.

Chemotherapy is usually given by injection. It may be given in an outpatient part of the hospital, at the doctor's office, or at home. Rarely, a hospital stay may be needed.
(Medicine.Net).

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).

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