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"Current Advances in Head and Neck Cancer Treatments: A Comprehensive Review of Therapeutic Strategies"

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ABSTRACT:
Head and neck cancers are the most common cancers in developing countries, especially in Southeast Asia. Head and neck cancers are more common in males compared to females. This is mainly attributed to tobacco, arecanut, alcohol, etc. Oral cancers are most common among all head and neck squamous cell cancers (HNSCC). HNSCCs in the developing world differ from those in the Western world in terms of age, site of disease, etiology, and molecular biology. Poverty, illiteracy, advanced-stage presentation, lack of access to health care, and poor treatment infrastructure pose a major challenge in the management of these cancers. The annual GDP (gross domestic product) spent on health care is very low in developing countries compared to developed countries. Cancer treatment leads to a significant financial burden on cancer patients and their families. Several health programs have been implemented to curb this rising burden of disease. The main aims of these health programs are to increase awareness among people regarding tobacco and to improve access to healthcare facilities, early diagnosis, treatment, and palliative care.

1. Introduction

The way a particular head and neck cancer behaves depends on the site in which it arises (the primary site). For example, cancers that begin in the vocal cords behave very differently than those that arise in the back of the tongue, which is only an inch or less from the vocal cords.

The most common type of cancer in the head and neck is squamous cell carcinoma which arises from the cells that line the inside of the nose, mouth, and throat. Squamous

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cell cancer is often associated with a history of smoking or exposure to the papillomavirus (HPV). Other less common types of head and neck cancers include salivary gland tumors, lymphomas, and sarcomas[1]

Methods of prevention include avoiding exposure to alcohol and tobacco products as well as vaccinating children and young adults against HPV.

- ✓ Cancers spread in four main ways. The first is a direct extension from the primary site to adjacent areas.
- ✓ Second is spread through the lymphatic channels to lymph nodes.
- ✓ Third is spread along nerves (perineural spread) to other areas of the head and neck.
- ✓ The fourth is spread through the blood vessels to distant sites in the body.

In head and neck cancer, a spread to the lymph nodes in the neck is relatively common. The lymph nodes most commonly involved depend on the location from which the primary tumor arises. Most lymph nodes are located along major blood vessels underneath the sternocleidomastoid muscles on each side of the neck. The risk of spreading to other parts of the body through the bloodstream is closely related to whether the cancer has spread to lymph nodesin the neck, how many nodes are involved, and their location in the neck. The risk is higher if cancer is in lymph nodes in the lower part of the neck rather thanonly in those located in the upper neck. Thediagnosis of cancer of the head and neck is often made by a dentist, oral surgeon, or physician after a patient notices symptoms such as a lump in the neck or a sore in the mouth that does not 2heal. [2-5] Even without symptoms, the diagnosis may be madeduring a routine examination.

2.Types of head and neck cancer

2.1 Laryngeal and hypopharyngeal cancer- [6-8]]

The larynx is commonly called the voice box. This tube-shaped organ in the neck is important for breathing, talking, and swallowing. It is located at the top of the windpipe, or trachea. The hypopharynx is also called a gullet. It is the lower part of the throat that surrounds the larynx.

A. Symptoms-

- ✓ Hoarseness or other voice changes that do not go awaywithin 2 weeks. This is often an early symptom.
- ✓ An enlarged lymph node or lump in the neck.
- ✓ Airway obstruction, difficulty breathing, and noisy breathing.
- ✓ Difficulty swallowing that does not go away.
- ✓ Ear pain.
- ✓ Chocking.
- ✓ Chronic bad breath, unexplained weight loss, fatigue.

B.Diagnosis

I. Indirect laryngoscopy: Before this procedure, the doctor often sprays the mouth and throat with a local anesthetic to numb the area and prevent gagging. The doctor then uses a small, long-handled mirror to see the vocal folds.

II. Fiber optic laryngoscopy:

During this procedure, the doctor inserts a flexible, lighted tube through the person's nose or mouth and down the throat to view the larynx and hypopharynx. The nose is often sprayed with a local anesthetic to make the procedure more comfortable.

III. Direct laryngoscopy:

- ✓ This procedure is done in an operating room, and the person receives a sedative general anesthetic to block the awareness of pain.
- ✓ The doctor then views the larynx and hypopharynx using an instrument called a laryngoscope.
- ✓ A sample of tissue for a biopsy is often taken during a direct laryngoscopy.
- ✓ Frequently, the doctor will recommend a triple endoscopy, a procedure done under general anesthesia to examine the ear, nose, and throat area, as well as the trachea and the bronchus, which are located next to the lung and the esophagus.

IV. Videostroboscopy:

- ✓ This fiber optic video technique is used so the doctor

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can better see the larynx. It is performed in the same wayas an indirect laryngoscopy (see above).

- ✓ It is used to view the vocal folds and detect motion abnormalities and other changes in vibration that are often important for finding a tumor.
- ✓ Videostroboscopy helps determine the location and size of a tumor, as well as how the tumor affects the function of the larynx and hypopharynx.

V. Biopsy:

- ✓ A biopsy is the removal of a small amount oftissue for examination under a microscope.
- ✓ The type of biopsy performed will depend on the location of the cancer.
- ✓ For instance, cells are taken using a thin needle inserted directly into the tumor.
- ✓ A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease.

VI. Computed tomography (CT or CAT)

- ✓ A CT scan takes a picture of the inside of the body using X-rays taken from different angles.
- ✓ A computer combines these pictures into a detailed, 3- 3-dimensional image that shows any abnormalities or tumors.
- ✓ A CT scan can be used to measure the tumor's size. Sometimes, a special dye called a contrast medium is given before the scan to provide betterdetail on the image.
- ✓ This dye can be injected into a patient's vein or given as a pill or liquid to swallow.

VII. Magnetic resonance imagining (MRI)

- ✓ An MRI uses magnetic fields, not X-rays, to produce detailed images of soft tissue, such asthe tonsils and the base of the tongue.
- ✓ MRI can be used to measure the tumor's size. A special dye called contrast medium is given before the scan to create a clearer picture.

VIII.Positron emission tomography (PET)

A PET scan is usually combined with a CT scan. A PET-CT scan creates pictures of organs and tissues in the body.

- ✓ First, a technician injects you with a small amount of radioactive substance. Your organs and tissues pick it up. The area that uses more energy picks up more.
- ✓ Cancer cells pick up a lot because they tend to use more energy than healthy cells. Then scan shows where the substance is in your body.

IX.Bone Scan:

- ✓ A bone scan uses a radioactive tracer to look at the inside of the bones. The tracer is injected into a patient's vein.
- ✓ It collects in areas of the bone and is detected by a special camera.
- ✓ Healthy bone appears gray to the camera, and areas of injury, such as those caused by cancer, appear dark.
- ✓ For people with head and neck cancer, a bone scan is recommended if there are signs that the cancer has spread to the bone.

X.Ultrasound:

- ✓ An ultrasound uses waves to createa picture of the internal organs
- ✓ This test can detect the spread of cancer to the liver or cervical lymph nodes in the neck.

XI.X-ray/ Barium swallow:

- ✓ An X-ray is a way to create a picture of the structures inside the body using a small amount of radiation.
- ✓ Sometimes, the patient will be asked to swallow barium, which coats the mouth and throat, to enhance the image on the x-ray. This is called a barium swallow.
- ✓ A barium swallow is used to identify abnormalities along the throat and esophagus.
- ✓ A special type of barium swallow, called a "modified barium swallow" may be needed to evaluate difficulties with swallowing and choking while

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eating.

- ✓ A dentist may take extensive x-rays of teeth, mandible (jawbone), and maxilla (upper jaw), including a panoramic radiograph, which is apanoramic view of the mouth, often called a panorex.

2.2 Nasal cavity and paranasal sinus cancer

The nasal cavity is the space just behind the nose where air passes on its way to the throat. The paranasal sinus is the air-filled areas that surround the nasal cavity.[9]

A.Symptoms:

People with nasal cavities or paranasal sinus cancer may experience the following symptoms or signs.

- ✓ Nasal obstruction or persistent nasal congestion and stuffiness, which is often called sinus congestion.
- ✓ Chronic sinus infections that do not go away with antibiotic treatment.
- ✓ Frequent headaches or pain in the sinus region.
- ✓ Pain or swelling in the face, eyes, or ears.
- ✓ Tearing of eyes.
- ✓ Bulging 1 of the eye or loss of vision.
- ✓ Decreased sense of smell.
- ✓ Pain and numbness in the teeth.

B.Diagnosis:

I.Physical examination: -

To make the diagnosis, a complete medical history and physical examination are necessary.

- ✓ During physical examinations, the doctor feelsfor any lumps on the neck, lips, gums, and cheeks.
- ✓ The doctor will also inspect the nose, mouth, throat, and tongue for abnormalities, often usinga light and/ or mirror for a clearer view.
- ✓ Signs of the nasal cavity and paranasal sinus cancer are often very similar to symptoms of chronic or allergic sinusitis.
- ✓ The physical examination is important, and doctors may perform 1 or more tests listed below to reach a diagnosis.

II.Endoscopy:

An endoscopy allows the doctor to see inside the body with a thin, lighted, flexible tube called an endoscope.

- ✓ The person may be sedated as the tube is inserted through the mouth or nose to examine the head and neck areas.
- ✓ Sedation is the use of medication to help a person become more relaxed, calm, or sleepy.
- ✓ This examination has different names depending on the areas of the body that are examined, such as laryngoscopy, which examines the larynx. pharyngoscopy, which examines the pharynx. or nasopharyngoscopy, which examines the nasal cavity and nasopharynx.

III.Biopsy:

- ✓ A biopsy is the removal of a small amount of tissue for examination under a microscope.
- ✓ Other tests can suggest that cancer is present, butonly a biopsy can make a definite diagnosis.
- ✓ A pathologist then analyzes the sample(s). A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease.

IV.X-ray:

An X-ray is a way to create a picture of the structures inside of the body, using a small amount of radiation.

- ✓ An x-ray can show if the sinuses are filled with something other than air. If they are, the issue is usually not cancer but, instead, a treatable infection. If that treatment doesn't work to clear the sinuses, then other specialized X-ray tests may be done to identify the blockage.
- ✓ Signs of cancer on an x-ray may be followed up with a computed tomography scan, also called a CT scan.

V.Computed tomography (CT or CAT) Scan:

- ✓ A CT scan takes pictures of the inside of the body using X-rays taken from different angles.

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- ✓ A computer combines these pictures into a detailed, 3-dimensional image that shows any abnormalities or tumors.
- ✓ A CT scan can be used to measure a tumor's size. Sometimes, a special dye called a contrast medium is given before the scan to create a clearer picture. This dye can be injected into a patient's vein or given as a pill or liquid to swallow.
- ✓ CT scans are very useful in identifying cancer of the nasal cavity or paranasal sinus.

VI.Bone Scan:

- ✓ A bone scan may be done to see if cancer has spread to the bones.
- ✓ A bone scan uses a radioactive tracer to look at the inside of the bones. The tracer is injected into a patient's vein. It collects in areas of the bone and is detected by a special camera.
- ✓ Healthy bone appears lighter to the camera, and areas of injury, such as those caused by cancer, stand out in the image.

VII.Positron emission tomography (PET) or PET-CT scan

- ✓ A PET scan is usually combined with a CT scan, called a PET-CT scan. A PET scan is a way to create pictures of organs and tissues inside the body.
- ✓ A small amount of a radioactive sugar substance is injected into the patient's body.
- ✓ This sugar substance is taken up by cells that use the most energy. Because cancer tends to use energy actively, it absorbs more of the radioactive substance.
- ✓ A scanner then detects this substance to produce images of the inside of the body.

After diagnostic tests are done, your doctor will review all of the results with you. If the diagnosis is cancer, these results also help the doctor describe the cancer. This is called staging.

2.3. Nasopharyngeal cancer:[10-14]

The nasopharynx is the air passageway at the upper part of the throat behind the nose.

A.Symptoms:

People with NPC may experience the following symptoms or signs.

A lump in the neck is the most common symptom.

- ✓ Nasal obstruction or stuffiness.
- ✓ Trouble hearing or hearing loss
- ✓ A sense of fullness or pain in the ear that is caused by a buildup of fluid in the middle ear, especially if it does not go away and occurs in just 1 ear
- ✓ Pain and ringing in the ear.
- ✓ A sore throat that doesn't seem to go away.
- ✓ Trouble breathing or speaking.
- ✓ Frequent nosebleeds.
- ✓ Pin, numbness, or paralysis in the face.
- ✓ Frequent headaches.
- ✓ Difficulty opening the mouth.
- ✓ Blurred or double vision.

B. Diagnosis

I.Physical examination and blood tests:

- ✓ During a physical examination, the doctor feels for any lumps on the neck, lips, gums, and cheeks. The doctor will look for any abnormalities in the nose, mouth, throat, and tongue, often using a light and/or mirror to get a clearer view.
- ✓ A blood test to check for antibodies against the EBV virus may be done at the same time.

II.Endoscopy:

- ✓ An endoscopy allows the doctor to see inside the body with a thin, lighted, flexible tube called an endoscope. The person may be sedated as the tube is inserted through the mouth or nose to examine the head and neck areas.
- ✓ Sedation is giving medication to become more relaxed, calm, or sleepy. When an endoscopy is done to look into the nasopharynx, it is called a nasopharyngoscopy.

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III.Biopsy:

- ✓ A biopsy is the removal of a small amount of tissue for examination under a microscope. Other tests can suggest that cancer is present, but only a biopsy can make a definite diagnosis.
- ✓ A pathologist then analyzes the sample(s). A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease. The type of biopsy performed will depend on the location of the cancer

IV.X-ray:

- ✓ An X-ray is a way to create a picture of the structures inside of the body, using a small amount of radiation. Sometimes, a barium swallow may be required before having an x-ray.
- ✓ The barium coats the mouth and throat to enhance the image on the x-ray. An x-ray of the skull and chest may be needed to learn more about the extent of NPC.

V.Computed tomography (CT or CAT) scan:

- ✓ A CT scan takes pictures of the inside of the body using X-rays taken from different angles. A computer combines these pictures into a detailed, 3-dimensional image that shows any abnormalities or tumors.
- ✓ A CT scan can be used to measure the tumor's size. Sometimes, a special dye called a contrast medium is given before the scan to provide better detail on the image. This dye can be injected into a patient's vein or given as a pill or liquid to swallow.

VI.Bone Scan:

- ✓ A bone scan uses a radioactive tracer to look at the inside of the bones. The tracer is injected into a patient's vein. It collects in areas of the bone and is detected by a special camera. Healthy bone appears lighter to the camera, and areas of injury, such as those caused by cancer, stand out in the image.

VII.Magnetic resonance imaging (MRI):

- ✓ An MRI uses magnetic fields, not X-rays, to produce detailed images of the body, especially images of soft tissue such as the tonsils and base of the tongue.
- ✓ An MRI is more sensitive than a CT scan in detecting a tumor of the nasopharynx and any possible spread to nearby tissues or lymph nodes.
- ✓ MRI can be used to measure a tumor's size. A special dye called a contrast medium is given before the scan to create a clearer picture. This dye can be injected into a patient's vein or given as a pill or liquid to swallow.

VIII.Neurological tests:

- ✓ During these examinations, the doctor tests a person's nerve function, especially the sense of touch in their face and the motor function of certain nerves in the head and neck area.

IX.Hearing test:

- ✓ The doctor may perform a hearing test if it seems that fluid could be in the middle ear

X.Positron emission tomography (PET) or PET-CT scan:

- ✓ A PET scan is usually combined with a CT scan, called a PET-CT scan. A PET scan is a way to create pictures of organs and tissues inside the body.
- ✓ A small amount of a radioactive sugar substance is injected into the patient's body. This sugar substance is taken up by cells that use the most energy. Because cancer tends to use energy actively, it absorbs more of the radioactive substance.
- ✓ A scanner then detects this substance to produce images of the inside of the body.

2.4. Oral and oropharyngeal cancer:[15-17]

The oral cavity includes the mouth and tongue. The oropharynx includes the middle of the throat, from the tonsils to the tip of the voice box.

A.Symptoms:

- ✓ Sore in the mouth or on the lip that does not heal; this is the most common symptom
- ✓ Red or white patch on the gums, tongue, tonsil, or lining of the mouth
- ✓ Lump on the lip, mouth, neck, or throat or a feeling of thickening in the cheek

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- ✓ Persistent sore throat or feeling that something is caught in the throat
- ✓ Hoarseness or change in voice
- ✓ Numbness of the mouth or tongue
- ✓ Pain or bleeding in the mouth
- ✓ Difficulty chewing, swallowing, or moving the jaws or tongue
- ✓ Ear and/or jaw pain
- ✓ Chronic bad breath
- ✓ Changes in speech
- ✓ Loosening of teeth or toothache
- ✓ Dentures that no longer fit
- ✓ Unexplained weight loss
- ✓ Fatigue

B.Diagnosis:

I.Physical examination: -

- ✓ Dentists and doctors often find lip and oral cavity cancers during routine checkups. If a person shows signs of oral or oropharyngeal cancer, the doctor will take a complete medical history, asking about the patient's symptoms and risk factors.
- ✓ The doctor will feel for any lumps on the neck, lips, gums, and cheeks. Because people with oral or oropharyngeal cancer have a higher risk of other cancers elsewhere in the head and neck region, the doctor will examine the area behind the nose, the larynx (voice box), and the lymph nodes of the neck.

II.Endoscopy: -

An endoscopy allows the doctor tosee inside the mouth and throat.

- ✓ Typically, a thin, flexible tube with an attached light and view lens, called an endoscope, is inserted through the nose to examine the head and neck areas.
- ✓ Sometimes, a rigid endoscope, which is a hollow tube with a light and view lens, is placed into the back of the mouth to see the back of the throat in more detail.

III.Biopsy: -

- ✓ A biopsy is the removal of a small amount of tissue for examination under a microscope. Other tests can suggest that cancer ispresent, but only a biopsy can make a definite diagnosis.
- ✓ The type of biopsy performed will depend on the location of the cancer.
- ✓ During a fine needle aspiration biopsy, cells are removed using a thin needle inserted directly into the suspicious area.
- ✓ A pathologist then analyzes the cells. A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease.

IV.Oral brush biopsy: -

- ✓ During routine dental examinations, some dentists are using a newer, simple technique to detect oral cancer in which the dentist uses a small brush to gather cell samples of a suspicious area.
- ✓ The specimen is then sent to a laboratory for analysis. This procedure can be done in the dentist's chair with very little or no pain. If cancer is found using this method, a traditional biopsy is recommended to confirm the results.

V.HPV Testing

- ✓ HPV testing may be done on a sample of the tumor removed during the biopsy. HPV has been linked to a higher risk of oropharyngeal cancer. Knowing if a person has HPV can help determine the cancer's stage and the treatment options that are likely to be most effective.
- ✓ HPV testing is done for all patients newly diagnosed with oropharyngeal squamous cell carcinoma.
- ✓ This is a type of oropharyngeal cancer that starts in flat, scale-like cells called squamous cells. Testing is not usually recommended for oropharyngeal cancer that starts in other types of cells or for other types of head and neck cancer

VI.X-ray: -

- ✓ An X-ray is a way to create a picture of the structures

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inside of the body, using a small amount of radiation. X-rays may be recommended by your dentist or doctor to look for abnormal findings in the mouth or neck.

VII.Barium swallow/modified barium swallow:

- ✓ There are 2 barium swallow tests that are generally used to look at the oropharynx and to check a patient's swallowing.
- ✓ The first is a traditional barium swallow. During an x-ray exam, the patient is asked to swallow liquid barium.
- ✓ This lets the doctor look for any changes in the structure of the oral cavity and throat and see whether the liquid passes easily to the stomach.
- ✓ A modified barium swallow, or video fluoroscopy, may be used to evaluatedifficulties with swallowing

VIII.Computed tomography (CT or CAT) scan: -

- ✓ A CT scan takes pictures of the inside of the body using X-rays taken from different angles. A computer combines these pictures intoa detailed, 3-dimensional image that shows any abnormalities or tumors.
- ✓ A CT scan can be used to measure the tumor'ssize, help the doctor decide whether the tumor can be surgically removed, and show whether the cancer has spread to lymph nodes in the neck or lower jawbone.
- ✓ Sometimes, a special dye called a contrast medium is given before the scan to provide better detail on the image. This dye can be injected into a patient‟ 's vein or given as a pill or liquid to swallow.

IX.Magnetic resonance imaging (MRI):-

- ✓ An MRI uses magnetic fields, not X-rays, to produce detailed images of the body, especially images of soft tissue, such as the tonsils and the base of the tongue.
- ✓ MRI can be used to measure the tumor‟ 's size.A special dye called a contrast medium isgiven before the scan to create a clearer picture. This dye can be injected into a patient‟ 's vein or given as a pill or liquid to swallow.

X.Ultrasound: -

- ✓ An ultrasound uses sound wavesto create a picture of the internal organs. This testcan detect the spread of cancer to the lymph nodes in the neck, which doctors also call the "cervical lymph nodes."

XI.Positron emission tomography (PET) orPET-CT scan: -

- ✓ A PET scan is usually combined with a CT scan, called a PET-CT scan. A PET scan is a way to create pictures of organs and tissues inside the body.
- ✓ A small amount of a radioactive sugarsubstance is injected into the patient's body.
- ✓ This sugar substance is taken up by cells that use the most energy. Because cancer tends to use energy actively, it absorbs more of the radioactive substance. However, the amount of radiation in the substance is too low to be harmful.
- ✓ A scanner then detects this substance to produce images of the inside of the body.

2.5. Salivary gland cancer: -

The salivary gland produces saliva. Saliva is the fluid that is releasedinto the mouth to keep it moist and contains enzymesthat begin breaking down.

A.Symptoms:

- ✓ People with salivary gland cancer mayexperience the following symptoms or signs.
- ✓ A lump on the face, neck, or mouth that isusually painless
- ✓ Numbness in the face
- ✓ Inability to move some facial muscles, especiallyif the muscle on 1 side of the face stops moving and the affected area slowly expands. This is known as progressive facial muscle paralysis.
- ✓ Pain or swelling in the face, chin, jawbone area,or neck
- ✓ A difference between the size and/or shape of theleft and right sides of the face or neck

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B. Diagnosis

I.Ultrasound-guided needle biopsy:

- ✓ During this type of biopsy, the doctor uses the images produced by an ultrasound to guide a needle into the tumor.
- ✓ An ultrasound uses sound waves to create apicture of the internal organs. A pathologistthen analyzes the sample(s).
- ✓ A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease.

II.Panoramic radiograph:

- ✓ Also called a Panorex, this is a rotating, or panoramic, x-ray of the upper and lower jawbones to find cancer or evaluate teeth before cancer treatment.
- ✓ This x-ray is not generally used to evaluate salivary gland tumors because it mostly evaluates only bone and teeth structures.

III.Biopsy

- ✓ A biopsy is the removal of a small amount of tissue for examination under a microscope. Other tests can suggest that cancer ispresent, but only a biopsy can make a definite diagnosis.
- ✓ A pathologist then analyzes the sample(s). A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease.
- ✓ The pathologist will also look at the tissue and may perform lab tests on the sample to learn more about it. The results will be part of the pathology report.

IV.Endoscopy: -

- ✓ An endoscopy allows the doctor to see inside the body with a thin, lighted, flexible tube called an endoscope. The personmay be sedated while the tube is inserted throughthe mouth, down the esophagus, and into the stomach and small bowel.
- ✓ The examination has different names depending on the area of the body that is examined, such as laryngoscopy (larynx), pharyngoscopy (pharynx), or nasopharyngoscopy (nasopharynx). Sedation is giving medication to become more relaxed, calm, or sleepy.

V.Computed tomography (CT or CAT) scan: -

- ✓ A CT scan creates a 3-dimensional picture of the inside of the body using X-rays taken from different angles.
- ✓ A computer combines these pictures into a detailed, cross-sectional image that shows any abnormalities or tumors.
- ✓ A CT scan can be used to measure the tumor's size or to see if a tumor involvesnearby bone.
- ✓ Sometimes, a special dye called a contrastmedium is given before the scan to provide better detail on the image.
- ✓ This dye can be injected into a person's vein or given as a liquid to swallow.

VI.Magnetic resonance imaging (MRI):

- ✓ An MRI uses magnetic fields, not X-rays, to produce detailed images of the body, especially images of soft tissue, such as the tonsils and base of the tongue.
- ✓ MRI can be used to measure the tumor's size. A special dye called a contrast medium is given before the scan to create a clearer picture. This dye can be injected into a patient's vein or given as a pill or liquid to swallow.

VII.Positron emission tomography (PET) orPET-CT scan:

- ✓ A PET scan is usually combined with a CT scan, called a PET-CT scan. A PET scan is a way to create pictures of organs and tissues inside the body.
- ✓ A small amount of a radioactive sugar substance is injected into a person's body. This sugar substance is taken up by cells that use the most energy.
- ✓ Because cancer tends to use energy actively, it absorbs more of the radioactive substance. A scanner then detects this substance to produce images of the inside of the body.

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C.Treatment

Many cancers of the head and neck can be cured, especially if they are found early. Although eliminating the cancer is the primary goal of treatment, preserving the function of the nearby nerves, organs, and tissues is also very important. When planning treatment, doctors consider how treatment might affect a person's quality of life, such as how a person feels, looks, talks, eats, and breathes.

Overall, the main treatment options are surgery, radiation therapy, chemotherapy, and targeted therapy. Surgery or radiation therapy by themselves or a combination of these treatments may be part of the treatment plan.[18-19]

I. Surgery

During surgery, the goal is to remove the cancerous tumor and some surrounding healthy tissue during an operation. Types of surgery for head and neck cancer include.

i. **Laser technology:** This may be used to treat an early-stage tumor, especially if it was found in the larynx.

ii. **Excision.** This is an operation to remove the cancerous tumor and some surrounding healthy tissue, known as a margin.

iii. **Lymph node dissection or neck dissection.** If the doctor suspects the cancer has spread, the doctor may remove lymph nodes in the neck. This may be done at the same time as an excision.

iv. **Reconstructive (plastic) surgery**. If cancer surgery requires major tissue removal, such as removing the jaw, skin, pharynx, or tongue, reconstructive or plastic surgery may be done to replace the missing tissue. This type of operation helps restore a person's appearance and the function of the affected area. For example, a prosthodontist may be able to make an artificial dental or facial part to help restore the ability to swallow and speak. A speech pathologist may then be needed to help the patient relearn how to swallow and communicate using new techniques or special equipment.[20]

II.How does reconstructive surgery work? [21-23]

Reconstructive surgery often uses tissue from 1 area of your body to repair another area. For example, head and neck surgery might change the shape of your jawbone. So your surgeon may take some bone from your leg to repair your jaw. This can restore the shape of your jaw and help it work normally.

The medical term for this type of surgery is "autologous reconstruction." This means that the tissue used in the surgery comes from your own body. It is a common type of reconstructive surgery.

In the new area, your surgeon will use tiny stitches to connect the tissue and blood vessels so that the tissue gets a good blood supply. The stitches are so small, you would need a microscope to see them. This is also called "microvascular" surgery.

Other types of reconstructive surgeries include:

i. **Skin, tendon, and bone grafts.**

Your surgeon will move, or transplant, healthy tissue from another part of your body to the area that needs repair.

ii. **Local flap surgery.**

Your doctor uses tissue from a nearby area to cover the damaged area. The tissue stays attached to your body's blood supply. This can speed up healing and also reduce scarring.

iii. **Artificial implants.**

You might receive an artificial body part or implant. For example, implants are available for a breast, testicle, or penis that has been removed as part of cancer treatment.

Depending on the location, stage, and type of cancer, some people may need more than 1 operation. Sometimes, it is not possible to completely remove the cancer, and additional treatments may be necessary. For example, surgery may be followed by radiation therapy, chemotherapy, or both to destroy cancer cells that cannot be removed during surgery.

iv. **Side effects of surgery**.

- ✓ Side effects of surgery depend on the type and location of the surgery. Every patient is encouraged to talk with their doctor about the side effects expected from a specific surgery and how long the side effects are likely to last.

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- ✓ Common side effects from head and neck surgery include temporary or permanent loss of normal voice, impaired speech, and hearing loss.
- ✓ People often have difficulty chewing or swallowing after cancer surgery, which may require a tube inserted in the stomach for feeding purposes.
- ✓ If lymph nodes were removed, there may be stiffness in the shoulders afterward. In addition, lymphedema can occur.
- ✓ After a total laryngectomy, which is the removal of the larynx, people may have decreased thyroid gland function that will need to be managed, such as by taking thyroid hormone medication.

Another potential side effect is swelling of the mouth and throat area, making it difficult to breathe. If this side effect develops, patients may receive a temporary tracheostomy, which creates a hole in the windpipe to make breathing easier.

Some people experience facial disfigurement from surgery. Reconstructive surgery may be recommended to help appearance or maintain important functions, such as chewing, swallowing, and breathing.[24]

III. Radiation therapy:

Radiation therapy is the use of high-energy X-rays or other particles to destroy cancer cells. A radiation therapy regimen, or schedule, usually consists of a specific number of treatments given over a set period. It can be the main treatment for head and neck cancer, or it can be used after surgery to destroy small areas of cancer that cannot be removed surgically.

The most common type of radiation therapy is called external-beam radiation therapy, which is radiation given from a machine outside the body. A specific type of external beam radiation therapy is called intensity-modulated radiation therapy (IMRT). IMRT uses advanced technology to accurately direct the beams of radiation at the tumor. This helps reduce damage to nearby healthy cells, potentially causing fewer side effects.[25-27]

IV.Proton therapy:[28-30]

Is another type of external-beam radiation therapy that uses protons rather than X-rays. At this time, proton therapy is not a standard treatment option for most types of head and neck cancer.

Proton therapy can be added to a treatment plan to reduce the damage done to healthy tissue. This radiation therapy technique may help protect important structures in the head, such as the brain stem and the optic nerves that run to the eyes, when used to treat nasopharyngeal cancer, chordoma, or chondrosarcoma. A chordoma is a rare tumor that usually occurs in the spine or the base of the skull. Chondrosarcoma is a tumor that develops in cartilage. They are both types of bone cancer.

Before beginning radiation therapy for any type of head and neck cancer, patients should be examined by an oncologic dentist or oral oncologist. Because radiation therapy can cause tooth decay, damaged teeth may need to be removed. Often, tooth decay can be prevented with proper treatment from a dentist before beginning treatment. People should also receive an evaluation from a speech-language pathologist who has experience treating people with head and neck cancer.

Patients may experience short- and long-term pain or difficulty swallowing, changes in voice because of swelling and scarring, and loss of appetite due to a change in their sense of taste. It is important that patients begin speech and swallowing therapy early, before radiation therapy begins to help prevent long-term problems with speaking or eating.[28]

V. Side Effect: [28]

In addition, radiation therapy to the head and neck may cause redness or skin irritation in the treated area, swelling, dry mouth or thickened saliva from damage to salivary glands, bone pain, nausea, fatigue, mouth sores, and sore throat. Many of these side effects go away soon after treatment has finished. Other side effects may include hearing loss due to a buildup of fluid in the middle ear, a buildup of earwax that dries out because of the radiation therapy's effect on the ear canal, and scarring (fibrosis). If the treatment damaged lymph nodes, there may be a risk for lymphedema.

Radiation therapy also may cause a condition called hypothyroidism in which the thyroid gland (located in the neck) slows down and causes the patient to feel tired and sluggish. This may be treated with thyroid hormone replacement medication. Every patient who receives

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radiation therapy to the neck area should have their thyroid function checked regularly. Patients are encouraged to talk with their healthcare team about what side effects of radiation therapy to expect before treatment begins, including how these side effects can be prevented or managed.[29]

VI.Therapies using medication:

Systemic therapy is the use of medication to destroy cancer cells. This type of medication is given through the bloodstream to reach cancer cells throughout the body. Systemic therapies are generally prescribed by a medical oncologist.

Common ways to give systemic therapies include an intravenous (IV) tube placed into a vein using a needle or in a pill or capsule that is swallowed (orally).

The types of systemic therapies used for head and neck cancer include:

- ✓ **Chemotherapy**
- ✓ **Targeted therapy**
- ✓ **Immunotherapy**

Each of these types of therapies is discussed below in more detail. A person may receive 1 type of systemic therapy at a time or a combination of systemic therapies given at the same time. They can also be given as part of a treatment plan that includes surgery and/or radiation therapy[33].

VII. Chemotherapy:

Chemotherapy is the use of drugs to destroy cancer cells, usually by keeping the cancer cells from growing, dividing, and making more cells.

A chemotherapy regimen, or schedule, usually consists of a specific number of cycles given over a set period of time. A patient may receive 1 drug at a time or a combination of different drugs given at the same time.

Doctors use chemotherapy in different ways at different times. These include:

- ✓ Before surgery or radiation therapy to shrink tumors. This is called neoadjuvant chemotherapy.
- ✓ After surgery or radiation therapy to destroy any remaining cancer cells. This is called adjuvant chemotherapy.
- ✓ As the only treatment. For example, to treat cancers of the blood or lymphatic system, such as leukemia and lymphoma.
- ✓ For cancer that comes back after treatment, called recurrent cancer.
- ✓ For cancer that has spread to other parts of the body, called metastatic cancer.

i.How is chemotherapy given?

Chemotherapy may be given in several different ways, which are discussed below.

ii.Intravenous (IV) chemotherapy:

Many drugs require injection directly into a vein. This is called intravenous or IV chemotherapy. Treatment takes a few minutes to a few hours. Some IV drugs work better if you get them over a few days or weeks.

iii.**Oral chemotherapy**:

You can take some drugs by mouth. They can be in a pill, capsule, or liquid. This means that you may be able to pick up your medication at the pharmacy and take it at home. Oral treatments for cancer are now more common. Some of these drugs are given daily, and others are given less often. For example, a drug may be given daily for 4 weeks followed by a 2-week break.

iv.Injected chemotherapy:

The shot may be given in a muscle or injected under the skin. You may receive these shots in the arm, leg, or abdomen. Abdomen is the medical word for your belly.

v.Chemotherapy into an artery:

An artery is a blood vessel that carries blood from your heart to another part of your body. Sometimes chemotherapy is injected into an artery that goes directly to the cancer. This is called intra-arterial or IA chemotherapy.

vi.Chemotherapy into the peritoneum or abdomen:

vii. For some cancers, medication might be placed directly in your abdomen. This type of treatment works for cancers involving the peritoneum. The peritoneum covers the

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surface of the inside of the abdomen and surrounds the intestines, liver, and stomach. Ovarian cancer is one type of cancer that frequently spreads to the peritoneum.[30-32]]

D.Target for head and neck cancer:

Targeted therapy is a treatment that targets the cancer's specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This type of treatment blocks the growth and spread of cancer cells while limiting damage to healthy cells.

Not all tumors have the same targets. To find the most effective treatment, your doctor may run tests to identify the genes, proteins, and other factors in your tumor. This helps doctors better match each patient with the most effective treatment whenever possible [33-34]]

E. EGFR inhibitors:

For head and neck cancers, treatments that target a tumor protein called epidermal growth factor receptor (EGFR) may be recommended. Researchers have found that drugs that block EGFR help stop or slow the growth of certain types of head and neck cancer.[34]

3.EGFR DESCRIPTION, WT, AND MUTANTS

3.1. Structural Analysis of EGFR Kinase Domain:

As in many kinases, the tyrosine kinase domain of EGFR consists of two lobes connected by a sequence of ten amino acids called "hinge" (in green, Fig. 1 and 2). The NH2-terminal lobe (N-lobe) is formed from mostly - strands and one --helix, whereas the larger COOH-terminal lobe (C-lobe) is mostly -helical. The juxtaposition of lobes and the hinge forms a hole-binding domain of ATP, ATP analogs, and ATP-competitive inhibitors (the activesite in Fig. 1)

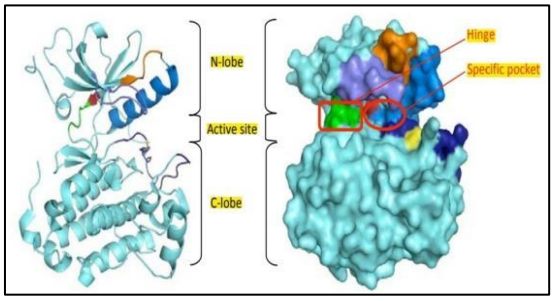

Fig 1. Crystallographic structure of EGFR

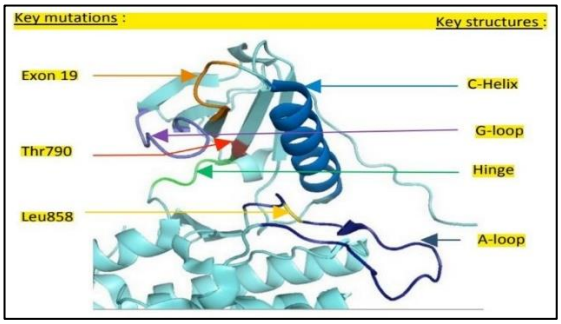

Fig. 2. Active site of EGFR with the position ofdifferent key mutations.

The relative orientation of these two lobes influences the shape of the active site by creating a pocket beside the hinge (specific pocket or hydrophobic pocket, Fig. 1). This pocket is linked to the hinge by one amino acid called «gatekeeper» which plays an essential role for the docking of inhibitors (in red,Fig. 1 and 2)

The hole is bordered by important catalytic machinery on the N-lobe including the glycine-rich loop (G-loop, in purple on Fig. 2) (Gly743- Gly748) and C-helix (in blue on Fig. 2) (Pro753- Ser768), whereas the C-lobe contributes to the DFG motif (Asp855-Gly857), the presumptive catalytic (general base) Asp837, the catalytic loop (Arg836- Asn842), and the activation loop (A-loop, in darkblue on Fig. 2)) (Asp855-Val876). Forty residues of the COOH-terminal tail of EGFR contain sites of auto-phosphorylation and play a key role in signal transduction by serving as a docking site for signaling molecules that bind to the phosphorylated tyrosine.[43]

3.2.Active vs. Inactive Conformation:

EGFR appears in two different conformations: the active and the inactive. In the active conformation: the A-loop is open and the C-Helix is close to the binding site of ATP forming a very small hydrophobic pocket. In the inactive conformation:the N-terminal portion of the A-loop forms a helical turn, which displaces the C-helix to form a bigger hydrophobic pocket. Leu858 can thus slide into and stabilize the inactive conformation. The G-loop comes down on the active site and reduces moves (Fig. 3) [35]

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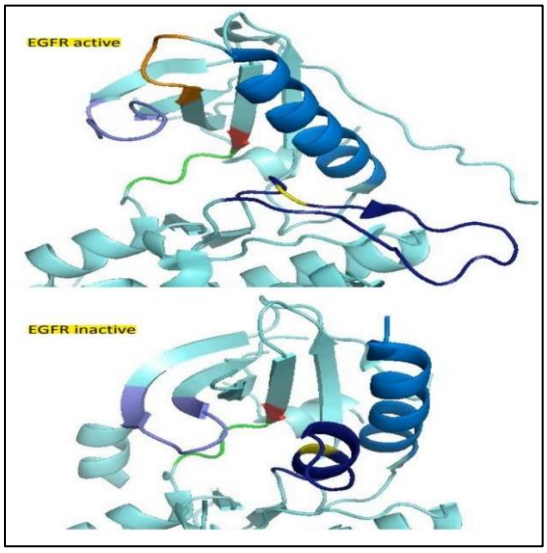

Fig. (3). The two conformations of EGFR. We can see the C-helix mismatch and the formation of the short-helix in the A-loop. (PDB code: 2GS2 (active) and 1XKK (inactive)).

3.3. EGFR L858R and EGFR Del19:

Specific changes reported in the EGFR gene are very dependent on the patient's characteristics. These mutations were more frequent in adenocarcinomas (21%) than in other NSCLCs (2%), in women (20%) than in men (9%), and in the patients from Japan (26%) than in those from the United States (2%). Moreover, these specific somatic mutations in theEGFR gene are present in 10-15% of Western patients with NSCLC, and even in NSCLC no-smoker patients. Importantly, these activating mutations of EGFR were among the first markers found to be associated with response to treatment with EGFR TKI.

The most frequent mutation is a point substitution L858R, the leucine 858 is substituted by an arginine in approximately 40% of all EGFR mutations found in NSCLC. Leucine 858 is found in the activation loop (A loop), just before the “DFG” motif. Unlike the leucine residue, arginine cannot be favorably accommodated in the hydrophobic pocket; moreover, an H-bond is formed between Arg858 and Arg836 as demonstrated by the structure shown in (fig 4).

These effects stabilize the active conformation of EGFR and increase its activity.

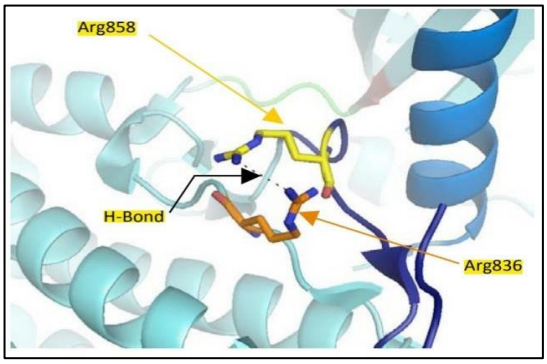

Fig. 4. EGFR mutation L858R and the H-bondwhich link it with Arg836. (PDB code: 2ITV).

Another frequent mutation is the exon 19 deletionthat removes residues 746–750 of the expressed protein. The position of exon 19 is between one end of the C-Helix and the active site as shown in Fig.2. Consequently, its deletion blocks the C-Helix closeto the active site as shown in (Fig. 5) and could induce the active position of EGFR. However,structural studies of this mutation will be required toconfirm this hypothesis.

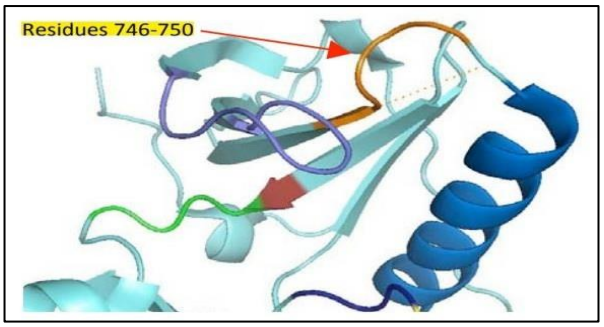

Fig. (5). The exon 19, dots represent the deletion, which brings the C-Helix close to the active site. (PDB code: 2GS2)

These two mutations are a common mechanism of tumorigenesis as they are activating of EGFR function by increasing the affinity with ATP. Therefore, these two EGFR mutants are good targets for ATP competitive inhibitors.[36-38]

3.4.EGFR T790M:

A secondary mutation substitutes the threonine 790 with a methionine (T790M). It has been found in 50% of lung adenocarcinomas from patients with acquired resistance to gefitinib and erlotinib. Thismutation appears only after treatment and is frequently found with another mutation

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L858R.

The threonine 790 corresponds to the gatekeeper of EGFR and takes part in the binding of some inhibitors by forming an H-Bond between alcohol and another H-Bond donor (often a nitrogen atom) ofthe ligands either directly or via a water molecule (described later for erlotinib and gefitinib with Fig 8 and 9). When it is substituted by a methionine, this residue is not able to form H-Bonds, moreover, the methionine has a side chain longer and bulkier than the threonine, which induces a steric hindrance between the hinge and the specificity pocket. Therefore, inhibitors cannot bind inside the activesite and that is responsible for resistance to the drug (Fig. 6).

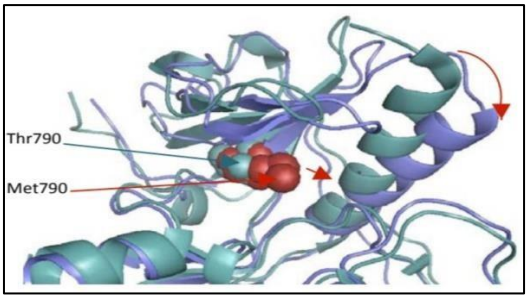

Fig. (6). Influence of T790M mutation on the active site of EGFR: superimposition of EGFR WT (in green-blue) and EGFR T790M (in purple), we can seein red the Met790. (PDB code: 2GS2 (WT) and 2JIT (T790M).

Nevertheless, the presence of the T790M mutation does not influence the affinity for ATP and does not substantially alter the production, degradation, or conformation active/inactive of the EGFR. Thus, the T790M mutation has no influence on the time to progression of the tumor but only prevents the inhibition of the tyrosine kinase activity by the TKI of the first generation. That's why the double mutation L858R/T790M that activates EGFR and prevents the inhibition remains a major hindrance in the fight against [39-41]

3.5. EGFR-dependent cancers:

The TKI strategy aimed to bypass these mutations. Several ways were envisaged to reach this purpose according to the inhibitor's specificity, which are described below.

3.5.1.Reversible Inhibitor:

The reversible inhibitors, or first-generation inhibitors, are small molecules that can bind to the active site of EGFR. They are ATP competitive and do not stay bound for a long time.

I. Gefitinib (Iressa):

Gefitinib (Iressa) was the first epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)approved for the treatment of advanced non-small cell lung cancer. A phase I clinical study showed that the maximum tolerated dose (MTD) for oral administration was 800 mg per day.

The common adverse events were diarrhea and rash. Several studies showed that a 250 mg/day dose is efficient for antitumor activity.

FDA (Food and Drug Administration) approved gefitinib for NSCLC in 2003 but in 2005, the FDA withdrew approval for the use in new patients due toa lack of evidence that it extended life.

Tumor regressions have particularly been found in some patients with NSCLC, more frequently in Japan, females, never-smokers, and patients withadenocarcinomas.

In Europe, gefitinib has been indicated since 2009 in advanced NSCLC in all lines.

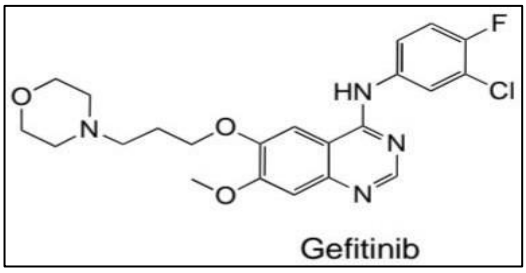

Fig no .7. Structure of Gefitinib

Gefitinib is built with a 4-anilinoquinazoline scaffold, a hydrophobic 3-chloro-4-fluroaniline moiety that can fit within the specific pocket of EGFR, and a hydrophilic morpholino moiety. The interactions of gefitinib in the active site of the wild-type EGFR are shown in (Fig 8). The quinazoline ring is oriented with the 1-N and C8-containing edge in the back of the ATP-binding pocket, where its hydrogen bonds with the main chain amide of Met793. Met793 lies in the so-called hinge‟ regionof the

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kinase, which connects the N and C lobes. Gefitinib forms only a single hydrogen bond to the hinge. The 3-chloro-4-fluoro aniline substituent extends into the hydrophobic pocket beside of the ATP-binding cleft. The aniline ring forms approximately a 45° angle with the plane of the quinazoline, and the chloro group orients „up" and is surrounded by the side chains of residues Lys745, Leu788, and Thr790. The fluorine substituent in the para position extends toward the side chains of Leu788, Met766, and Glu762. The 6- 6-propylmorpholino group extends into the solvent, and the weak electron density for this portion of the inhibitor indicates that this group is poorly ordered. The methoxy group in the 7 positions of the quinazoline is engaged in a Van der Waals contact with Gly796. Still, the orientation of the methyl group is not well defined in the density.[41-42]

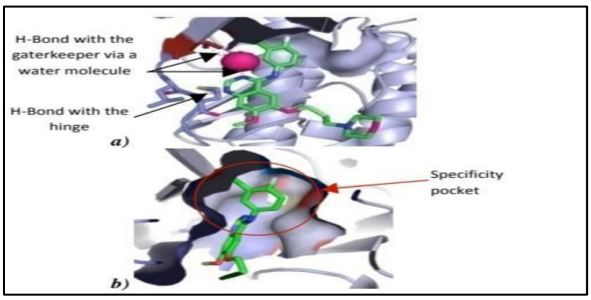

Fig. (8). Docking of gefitinib (green) in EGFR active site (purple). a) We can see the H-Bonds between gefitinib and the Thr790 via a water molecule. (pink). b) The specificity pocket of EGFR. (PDB code: 2ITY).

II. Erlotinib (Tarceva)

Erlotinib was FDA-approved in 2005 for treatinglocally advanced or metastatic NSCLC that has failed at least one prior chemotherapy regimen.

It is a potent and selective ATP site-directed inhibitor of EGFR. Its in vitro IC50 is 2 nm. on purified receptors and the selectivity against other tyrosine kinases can reach a ratio of 1000-fold. It reduces EGFR auto-phosphorylation in intact tumor cells with an IC50 of 20 nm.

The MTD is 150 mg/day orally administrated and the adverse events include diarrhea and clinically intolerable acneiform rash.

III. Structural Docking to EGFR:

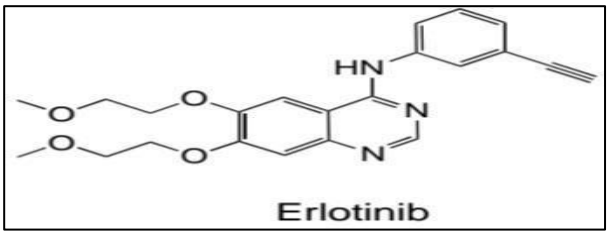

Fig No. 9. Structure of Erlotinib

Erlotinib is built with a 4-anilinoquinazoline scaffold, a hydrophobic 3-aminophenylacetylene moiety, which can fit within the specific pocket of EGFR, and two hydrophilic methoxy-ethyl moieties. (Fig. 10) shows the interaction between erlotinib and the active site of EGFR. The quinazoline ring is oriented with the 1-N and C8-containing edge in the back of the ATP-binding pocket, where it forms a single hydrogen bond with the main chain amide of Met793, which lies in the "hinge".

The 3- 3-aminophenylacetylene substituent is sequestered in a hydrophobic pocket and the methoxyethyl extended on the opposite end guiding therefore the connectingsegment into the solvent.

The aromatic rings form approximately a 42° angle which orientates the acetylenemoiety into a pocket shared by many kinase domains. [43]

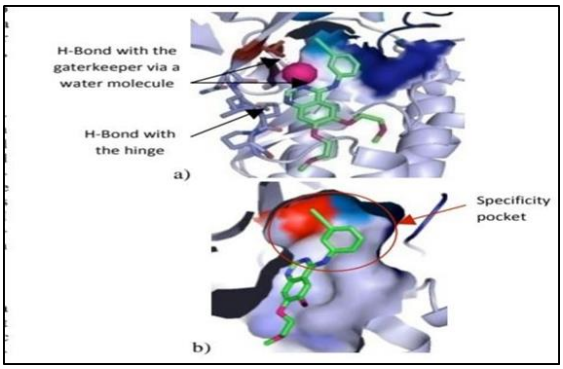

Fig. (10). Docking of erlotinib (green) in EGFR active site (purple).

a) We can see the H-Bonds betweenerlotinib and the Thr790 via a water molecule (pink).

b) The specificity pocket of EGFR. (PDB code: 1M17)

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IV.Lapatinib (Tyverb):

Lapatinib was FDA-approved in 2007 for the treatment of Metastatic Breast Cancer (MBC) and it is currently in phase II of clinical trials for lung cancer treatment.

It is orally administered and targets both EGFR and HER2 with in vitro IC50 of 3 nm. and 15 nm., respectively. In humans, lapatinib is administered as the monohydrate tosylate salt. The MTD is 1.25 g per day as recommended by the FDA and it is reduced to 750 mg/day in patients with liver disease.

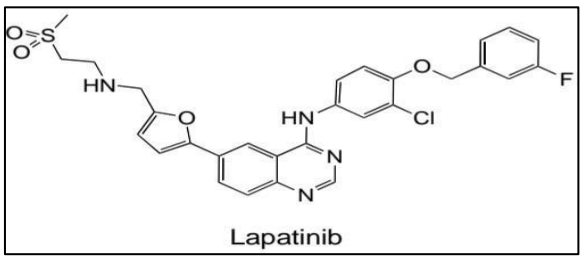

Fig no.11. Structure of Lapatinib

V. Structural Docking to EGFR:

Lapatinib has a quinazoline core as other efficient EGFR TKIs (gefitinib and erlotinib), it is substituted by a hydrophobic 3-chloro-4-(3-fluoro benzyloxy)-aniline group which can fit within the specificity pocket of EGFR, and a hydrophilic methyl-sulfonyl-ethyl-amino-methyl phenyl group. The crystal structure of lapatinib bound with EGFR is shown in Fig.

The quinazoline ring is hydrogen-bonded to the hinge region. N1 of the quinazoline is hydrogen bonded to the main chain NH of Met793, whereas N3 makes a water-mediated hydrogen bond to the side chain of Thr830. The quinazoline ring is surrounded from the top andbottom by the side chains of Ala743 and Leu844, respectively. The 3-chloro-4- (3-fluoro benzyloxy)- aniline group is oriented deep in the back of the ATP binding site and makes predominantly hydrophobic interactions with the protein

The 3-chloro-aniline group is positioned in a pocket formed by the side chains of Val726, Lys745, Leu788, Thr790, Thr854, and Asp855. The 3-fluorobenzyloxy group occupies a pocket formed by the side chains of Met766, Leu777, Thr790, Thr854, Phe856, and Leu858. The aniline nitrogen and the ether oxygen are not involved in any direct hydrogen bonding interactions with the protein. The methyl-sulfonyl-ethyl-aminomethylfuryl group, at the C6 position of the quinazoline, is positioned at the solvent interface and does not make any significant interactions with the protein. The methyl-sulfonylethylamino group is bound near Asp800 but is poorly defined.[44]

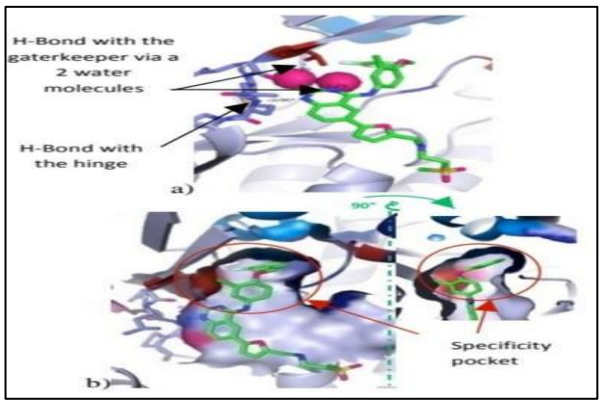

Fig. (12). Docking of lapatinib (green) in EGFR active site (purple). a) We can see the H-Bonds between lapatinib and the Thr790 via two water molecules(pink). b) The specificity pocket of EGFR is enlarged when lapatinib is docked into. (PDB code: 1XKK)

3.5.2. Irreversible Inhibitors:

The irreversible inhibitors (also called second-generation inhibitors) are compounds, which form covalent, and therefore permanent, bonds with their target. These bonds should theoretically increase the efficiency of the compounds by prolonging the inhibition of EGFR. These molecules are similar to reversible inhibitors with almost the same central scaffolds and hydrophobic moieties. However, they have a Michael acceptor on their hydrophilic side chain that can link the sulfur of cysteine 797. In cell culture systems, such irreversibly binding TKIs can effectively kill the cells that have acquired resistance to first-generation TKIs. Currently, dacomitinib, afatinib, and neratinib are the only second-generation EGFR TKIs in advanced clinical development for cancers.

I. Dacomitinib:

Dacomitinib is an irreversible TKI of EGFR, HER-2,and HER-4 with IC50 values of 6.0, 45.7, and 73.7 nM respectively. As it is a pan-ErbB inhibitor, it is able to inhibit three of the four ErbB family members. This class

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of inhibitors was developed in order to block not only EGFR but also HER-2 and HER-4. Indeed the activation of EGFR signaling requires dimerization of EGFR with the other members of the family. Moreover, they could also inhibit HER-3 which has no intrinsic kinase activitybut allows the activation of other ErbB receptors during the dimerization process.

Furthermore, phases I/ II revealed a maximum tolerated dose (MTD) of 45 mg daily, the most commonly reported adverse events were diarrhea and skin toxicity. Importantly, dacomitinib appeared to be a potent CYP2D6 inhibitor (cytochrome P450 (CYP) 2D6), the most important enzyme involved in the metabolism. This means that a drug-drug interaction could occur when it is concomitantly administered with drugs metabolized by CYP2D6.

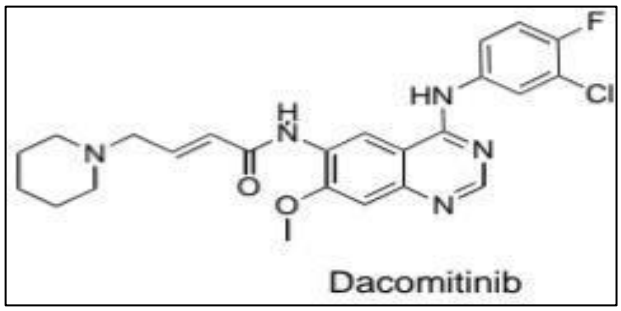

Fig no.13. Structure of Dacomitinib

Structural Analysis Dacomitinib possesses a structure similar to that of gefitinib, a quinazoline core substituted by a 3-chloro-4-fluoro aniline and a methoxy group. However, it is characterized by its second hydrophilic piperidinylbut-2-enamide substituent. This 2-enamide is used as a Michael acceptor to link the Cys797 of the active site[45]

II. Afatinib:

Afatinib an aniline quinazoline-based derivative, is a highly selective and irreversible inhibitor of both EGFR and HER2 kinases (IC50= 0.5 and 15 nms. respectively). Phase II studies showed an MTD of 50 mg once daily and the most common side effects are gastrointestinal events (diarrhea, nausea, vomiting), fatigue, and rash. It is being systemically investigated in several major trials in NSCLC (LUX-Lung trials) employing various treatment strategies.

Afatinib is currently involved in several phases of clinical research including phase III for NSCLC, breast cancer, and also in head and neck neoplasm.

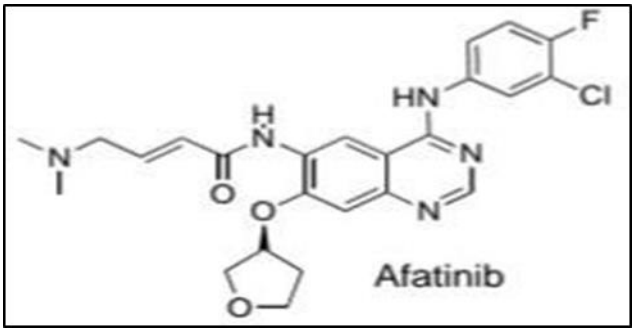

Fig no.14. Structure of Afatinib

Structure The chemical structure of Afatinib is similar to that of gefitinib and dacomitinib since it contains a quinazoline ring as a central scaffold substituted by a 3-3-chloro-4-fluoroaniline. However, its two hydrophilic substituents, tetrahydrofuran-3- yloxy and dimethylaminobut-2-enamide, are different from those of the other drugs.[46]

III. Pelitinib

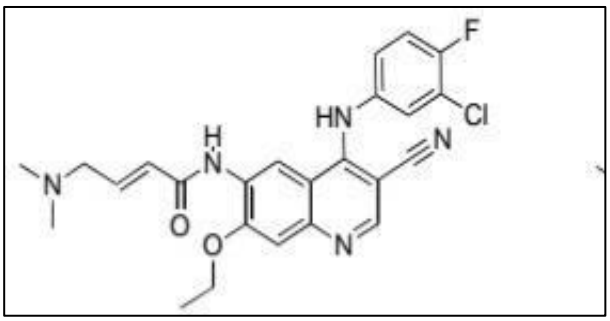

Fig No.15. StructureE of PElitinib

Pelitinib is a potent and selective irreversible inhibitor of the EGFR tyrosine kinase (IC50= 14.5 nM). Pelitinib is efficient against tumor cell lines resistant to gefitinib and expressing T790M. As expected for other irreversible drugs, in vivo studies confirmed that pelitinib is rapidly cleared from the plasma and the inhibition of EGFR signaling is prolonged. A phase I study found an MDT of 75 mg/day with adverse events including diarrhea, rash, nausea, vomiting, and asthenia. Structure Pelitinib was built with a quinoline core substituted by a 3-chloro-4-fluoroaniline at the 4 positionsas gefitinib, and two hydrophilic substituents, i.e., anethoxy moiety and (dimethylamine)but-2-enamide

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as a Michael acceptor. It differs from the other drugs by the cyan quinolinyl moiety at position 3 of the quinoline ring. The nitrogen of this moiety forms an H-Bond with the catalytic site of EGFR.[47]

IV.Canertinib:

Canertinib is an irreversible pan-ErbB inhibitor, which inhibits EGFR and HER-2, as well as ErbB-4 (in vitro IC50= 0.3, 30 [35] and 7 nM, respectively,). Canertinib is also able to inhibit different EGFR mutants (IC50 on L858R and L858R/T790M EGFR kinases are 0.4 and 26 nM, respectively). It has been shown that canertinib is more effective than erlotinib, gefitinib, and lapatinib. However, it is less effective than afatinib in inhibiting the survival of lung cancer cell lines harboring L858R or L858R/T790M mutations of EGFR (IC50 = 1 and 101 nM, respectively).

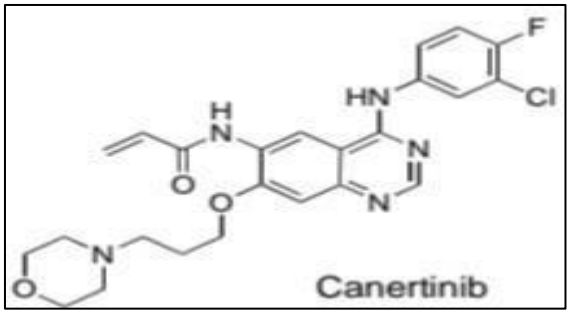

Fig no.16. Structure Canertinib

Several phase I studies measured the MTD as 150 mg/day on continuous daily dosing. Diarrhea and rash have been the most common observed side effects, and thrombocytopenia has also been reported. As the others pan-ErbB, canertinib blocks the TK activity of EGFR, HER-2, and ErbB-4. A phase I trial of canertinib in combination with carboplatin and paclitaxel chemotherapy has also been completed. Finally, the strategy of administering canertinib intravenously has been evaluated in a phase I trial since the bioavailability by this route is three times more important than in oral administration.[48]

3.5.3 Phosphoinositide 3- Kinase/MechanisticTarget of Rapamycin:

Once activated, receptor tyrosine kinases initiate several signal transduction cascades, including activation of the phosphoinositide 3-kinase (PI3K) pathway. PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP_3), which in turn activates PDK1 and AKT. Activated AKT phosphorylates the mechanistic target of rapamycin (mTOR), leading to cell cycle progression, proliferation, and cell survival. Aberrant hyperactivation of the PI3K pathway has been observed in half of HNSCC cases. The PI3K enzyme is comprised of multiple catalytic and regulatory isoforms, but mutations in *PIK3CA*, the gene encoding the p110α catalytic subunit, have been detected in 35% of HNSCC tumors. *In vivo* studies have shown that patient-derived xenograft tumors harboring these mutations are sensitive to a PI3K inhibitor, suggesting opportunities for future clinical investigations. Downstream of PI3K, mTOR is activated in >70% of HNSCC specimens and therefore presents another favorable target for therapy.[49]

3.5.4 Signal Transducer and Activator of Transcription

The ultimate target site of most signal transduction cascades is gene expression in the nucleus, where transcription factors can drive oncogenic signaling. The signal transducer and activator of the transcription (STAT) family of proteins mediate various cellular functions related to oncogenesis. Increased activation of STAT3 in particular has been observed in many cancers and is a well-validated target for therapeutics. Activation of STAT3 is associated with negative prognoses in many malignancies including colorectal, cervical, and gastric cancers. Unlike enzymatic targets (egg. kinases), however, transcription factors like STAT3 lack the catalytic pockets amenable to small-molecule inhibition. Moreover, their intracellular localization makes them difficult to target with mAbs.[50]

4.Conclusion:

Head and neck cancers, particularly oral cancers, are a significant health concern in developing countries, with a higher prevalence in males due to behavioral risk factors such as tobacco, areca nut, and alcohol consumption. The management of these cancers is challenging due to socioeconomic factors like poverty, limited healthcare access, and a lack of awareness, which often leads to late-stage diagnosis. The financial burden of cancer treatment is substantial, underscoring the need for health programs that focus on prevention, early detection, and improving

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access to care.Diagnostic tools for head and neck cancers include imaging techniques such as X-rays, CT scans, MRI, PET scans, and bone scans, as well as endoscopic examinations and biopsies. These methods are essential for detecting the presence of cancer, determining its extent, and guiding treatment decisions. The type of biopsy and imaging modality used depends on the location and characteristics of the suspected cancer. In conclusion, the multifaceted approach to diagnosing and managing head and neck cancers in developing countries requires a concerted effort to address both the medical and socioeconomic aspects of the disease. Innovative health programs and advancements in diagnostic technologies offer hope for improving patient outcomes and reducing the impact of these cancers on individuals and communities.

Declaration of Competing Interest-

All authors report no conflict of interest in any financial and personal relationships with other people or organizations.

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Ethics Approval Statement

No study involves an experiment on humans and animals.

Data Availability Statement

Not Applicable

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