" Efficacy and Safety of Low Dose Celecoxib with Chemoradiation in Locally advanced Head and Neck Squamous Cell Carcinoma "

A DOUBLE ARM PROSPECTIVE STUDY

Dissertation submitted in partial fulfillment of

DOCTOR OF MEDICINE
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DEPARTMENT OF RADIATION ONCOLOGY
MADRAS MEDICAL COLLEGE
&
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CERTIFICATE

This is to certify that **Dr. T. RETHINESH KUMAR D.M.R,T.,** has been a postgraduate student during the academic period 2018 to 2020 in the Department of Radiation Oncology , Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai - 03.

This Dissertation titled **" Efficacy and Safety of Low Dose Celecoxib with Chemoradiation in Locally advanced Head and Neck Squamous Cell Carcinoma "** is a bonafide work done by him during the study period and is being submitted to The Tamil Nadu Dr.M.G.R Medical University in partial fulfillment of M.D Branch IX Radiotherapy Examination.

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DECLARATION

I hereby declare that the dissertation entitled **" Efficacy and Safety of Low Dose Celecoxib with Chemoradiation in Locally advanced Head and Neck Squamous Cell Carcinoma "** is a double arm prospective study done by me under the guidance and supervision of Prof. Dr. R.Giridharan D.M.R.D., M.D.R.T., is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment for the Degree of Doctor of Medicine in M.D., Degree Examination, Branch IX, RADIOTHERAPY is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

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CONTENTS

INTRODUCTION

INTRODUCTION

EPIDEMIOLOGY:

Head and neck cancer is common in several regions of the world. Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth leading cancer by incidence worldwide. The primary risk factors associated with head and neck cancer include tobacco use, alcohol consumption, human papilloma virus (HPV) infection (for oropharyngeal cancer), and Epstein-Barr virus (EBV) infection (for nasopharyngeal cancer). The chronic exposure of the upper aerodigestive tract to these carcinogenic factors can result in dysplastic or premalignant lesions and ultimately result in head and neck cancer. The relative prevalence of these risk factors contributes to the variations in the observed distribution of head and neck cancer in different areas of the world.

Worldwide :

Head and neck cancer accounts for more than 550,000 cases and 380,000 deaths annually. In the United States, head and neck cancer accounts for 3 % of malignancies, with approximately 63,000 Americans developing head and neck cancer annually and 13,000 dying from the disease. In Europe, there were approximately 250,000 cases (an estimated 4 % of the cancer incidence) and 63,500 deaths in 2012.

In Asia :

Mouth and tongue cancers are more common in the Indian subcontinent, nasopharyngeal cancer is more common in Hong Kong, and pharyngeal and / or laryngeal cancers are more common in other populations; these factors contribute disproportionately to the overall cancer burden in these Asian countries.

In India :

India has one third of oral cancer cases in the world. Head and neck cancer in India has distinct demographic profile, risk factors, food habits, personal and family history. They are emerging as major health problem accounting for 30 % of all cancers in India. 60 to 80 % of patients presents in advanced stage. Over 200,000 cases occur each year and nearly 2/3 rd are located in the gingivobuccal sulcus due to betel quid which warrant the term " The Indian Oral Cancer ". As per Globocan 2018 estimation, in India 1,19,992 new cases and 72,616 deaths are due to oral cancers.

In Tamil Nadu :

As per the Cancer Registry in Tamilnadu, the incidence of HNSCC are attributable to 29 % of men compared to 11 % in women.

Most of them are presented in a very advanced stage constituting around 70 to 80 % of cases.

Sex Ratio :

Males are affected significantly more than females, with a ratio ranging from 2:1 to 4:1. The incidence rate in males exceeds 20 per 100,000 in regions of France, Hong Kong, the Indian subcontinent, Central and Eastern Europe, Spain, Italy, and Brazil, and among African Americans in the United States. The incidence of laryngeal cancer, but not oral cavity and pharyngeal cancer, is approximately 50 percent higher in African American men . The mortality associated with both laryngeal and oropharyngeal cancer is significantly higher in African American men, which may reflect the lower prevalence of human papilloma virus (HPV) positivity.

ETIOLOGY :

During the past few decades, several countries have witnessed a decline in oral cavity cancer incidence correlating to a decline in tobacco use. However, Canada, Denmark, the Netherlands, Norway, Sweden, the United States, and the United Kingdom, have seen an increasing rate of

oropharyngeal and oral cavity cancers despite declines in smoking rates since the 1980s. This has led to theories that human papilloma virus (HPV) infection might be an additional risk factor for developing certain head and neck cancers.

Historically , HNSCC is mainly associated with the chronic use of the following :

1. Tobacco in various forms
2. Alcohol Consumption
3. Poor Diet
4. Bad dentition
5. Betel and Areca nut chewing
6. Human papilloma Virus
7. Genetic factors
8. Environmental & Occupational exposures

Tobacco Use :

Smoking is identified as an independent risk factor in 80% to 90% of patients who present with cancer of the oral cavity. Tobacco users have a 5 - fold to 25 - fold higher risk of oral cavity and oropharyngeal

cancer. Tobacco use remains one of the leading causes of death worldwide. A preponderance of the death and disease associated with tobacco use is associated with its combusted forms, particularly the cigarette.

However, all forms of tobacco use have negative health consequences, the severity of which can vary among products. Smokers tend to consume a relatively stable number of cigarettes per day and to smoke those cigarettes in a relatively consistent manner in order to maintain an acceptable level of nicotine in their system across the day.

The number of cigarettes smoked per day and the smoking pattern of an individual may be influenced by the rate of nicotine metabolism.

In India, apart from cigarettes, tobacco is consumed in other forms like beedis, betel quid, cigars, pipes, chutka, pan masala, etc. The habit of chewing betel nut leaves rolled with lime and tobacco (mixture known as " pan "), which results in prolonged carcinogen exposure to the oral mucosa, is thought to be the leading cause of oral cancer.

The International Agency for Research on Cancer (IARC) has classified both cigarette smoke and smokeless tobacco as Group 1 carcinogens. IARC has also identified 72 measurable carcinogens in

cigarette smoke where evidence is sufficient to classify them as Group 1 (carcinogenic to humans), 2A (probably carcinogenic to humans), or 2B (possibly carcinogenic to humans).

Alcohol Consumption :

The combined use of alcohol and tobacco may have a synergistic effect on carcinogenesis. International Head and Neck Epidemiology Consortium (INHANCE) pooled analysis data demonstrate a greater than multiplicative joint effect between tobacco and alcohol on head and neck cancer risk, which is most pronounced in carcinoma of the pharynx and oral cavity.

Poor Diet :

Vegetable and fruits consumption along with fish which are rich in antioxidants are believed to have protective effect in head and neck cancers. There is two fold higher risk of cancer among those who are non consumers.

Bad Dentition :

Poor oral hygiene associated with bad dentition (Sharp tooth or teeth , ill - fitting dentures) are associated with increased risk of oral cancers.

Betel and Areca nut Chewing :

In India, betel and areca nut chewing, as quid with tobacco is most common risk factor leading to various premalignant lesions mainly submucous fibrosis and leukoplakia, which later turns into invasive cancers.

Human Papilloma virus :

The relationship between HPV and oropharyngeal cancer has been well established. However, oral cavity carcinoma, unlike oropharyngeal carcinoma, does not appear to be typically associated with HPV. The increasing incidence of oral tongue carcinoma in young individuals is unlikely due to an HPV - related etiology and may represent a unique and emerging oral cancer patient population.

A significant increase in rates of oropharyngeal cancers in nonsmokers and nondrinkers caused by oncogenic human papilloma viruses (HPVs) is occurring, predominantly among men. Although both HPV - associated and HPV - unassociated malignancies are classified as squamous cell carcinomas, the behavior of these cancers markedly differs as HPV - associated cancers have a significantly more favorable prognosis.

The recognition that HPV - associated oropharyngeal cancer is a distinct clinical entity, and the adverse effects of standard therapies on speech, swallowing, and psychological well being, has lead to significant multidisciplinary interest in defining different treatment paradigms for HPV - associated and HPV - unassociated oropharyngeal cancers. Treatment recommendations for these two clinical entities currently remain the same, pending the outcomes from ongoing clinical investigations.

The HPV genome encodes three onco proteins (E5, E6, and E7), in addition to regulatory genes (E1 and E2) as well as capsid protein genes (L1 and L2). Oncogenesis is primarily mediated via the E6 and E7 proteins. HPV E6 complexes with E3 ubiquitin ligase and E6 - associated protein, promoting ubiquitin - mediated destruction of p53.

Loss of cellular p53 function results in dysregulation of the G1 / S and G2 / M checkpoints. An E7 / cullin 2 complex ubiquitinates the Rb protein, resulting in loss of G1 / S checkpoint control. E7 is believed to be the major transforming oncogene during early carcinogenesis, with E6 functioning later.

Although E6 and E7 oncoprotein function is necessary for development of an HPV - associated malignancy, it is not sufficient. It is

believed that as yet undefined genetic events are required for HPV malignant transformation.

Genetic Factors :

Certain syndromes such as Xeroderma pigmentosum, Li - Fraumeni, Ataxia telangiectasia, Bloom syndrome, and Fanconi anemia, because of inherent genetic instability, have been associated with a predisposition to oral cancer.

Plummer Vinson Syndrome, manifested with iron deficiency anemia, dysphagia and postcricoid webs : is associated with higher risk of head and neck and esophageal cancers.

Environmental & occupational Exposure :

Ultraviolet radiation has been associated with carcinoma of the lip. In geographic regions where there are long daily periods of sun exposure, cancer of the lip may represent up to 60% of all cancers of the oral cavity.

Patients with occupational exposure to coal dust, steel dust, iron compounds, and fumes have also shown an increased risk for developing hypopharynx cancer.

PREMALIGNANT LESIONS :

Leukoplakia :

Leukoplakia and erythroplakia are gross clinical descriptors that do not always correspond directly to specific pathologic entities. The World Health Organization defines leukoplakia as a white patch or plaque that cannot be rubbed off or characterized clinically or pathologically as any other disease. Leukoplakia is not related to the presence or absence of dysplasia ; however, it is the most common precursor of cancer of the oral cavity.

Leukoplakia is primarily a clinical entity, with certain key pathologic features. These features include hyperkeratosis and acanthosis. Leukoplakia may begin as a thin gray or gray / white plaque that may appear translucent, is sometimes fissured or wrinkled, and typically soft and flat. They frequently have sharply demarcated borders but occasionally blend gradually into normal surrounding mucosa.

Homogenous leukoplakia is a uniform white lesion that is prevalent in the buccal mucosa ; it is the most common variety of leukoplakia and has a low malignant potential. Conversely, high - risk oral leukoplakia demonstrates abnormal orientation of cells, nuclear hyperchromatism, increased mitosis, and nuclear cytoplasmic ratio.

Clinically, these lesions are nonhomogenous, nodular, speckled, or verrucous, with central ulceration or erosion. Followup studies demonstrate that between <1 % and 18 % of oral leukoplakias develop into oral cancer, with the latter clinical subtype conferring a higher risk of malignant transformation.

Leukoplakia may regress spontaneously without therapy. A baseline biopsy may be performed to establish diagnosis and rule out malignant transformation. Leukoplakia with clinically or histologically aggressive features, demonstrating dysplasia, should be excised.

Erythroplakia :

Erythroplakia describes a chronic, red, generally asymptomatic lesion or patch on the mucosal surface that cannot be attributed to a traumatic, vascular, or inflammatory cause. Erythroplakia, like leukoplakia, is a clinical diagnosis of exclusion that requires the clinician to rule out all other erythematous oral lesions. However, erythroplakia is associated with a higher risk of malignant transformation than leukoplakia.

Transformation rates are considered to be the highest among all precancerous oral lesions and conditions. Histopathologically, it has been documented that in homogenous oral erythroplakia, 51% showed invasive

carcinoma, 40% carcinoma *in situ*, and 9% mild or moderate dysplasia. The treatment of choice for erythroplakia is surgical excision.

Oral Submucous Fibrosis :

The term describes a generalized fibrosis of the oral cavity tissues resulting in marked rigidity and trismus. At early stages, these premalignant lesions are characterized by blanching of the mucosa with a marble - like appearance. At more advanced stages, palpable fibrous bands become evident around the buccal mucosa and the mouth opening.

Once oral submucous fibrosis reaches advanced stages, approximately 25% of cases biopsied demonstrate epithelial dysplasia in addition to subepithelial alterations. Oral submucous fibrosis is associated with the use of betel quid (with or without tobacco) or pan masala. In India, it is estimated that as many as 5 million individuals are afflicted with oral submucous fibrosis.

ANATOMY :

ORAL CAVITY :

The oral cavity consists of the lips, oral tongue, floor of the mouth, retromolar trigone, alveolar ridge, buccal mucosa, and hard palate.

The anterior boundary of the oral cavity is the skin – vermilion junction. The superior portion of the oral cavity extends posteriorly to the junction between the hard and soft palate, whereas the inferior portion extends to the circumvallate papillae. The specific anatomic subsites of this region are noted below

Lip :

The lips begin at the junction of the vermilion border with the skin and form the anterior aspect of the oral vestibule. The lips are comprised of the vermilion surface, which is the portion of the lip that comes in contact with the opposing lip. The lips are well defined into an upper and lower lip.

Oral Tongue :

The anterior two - thirds of the tongue is mobile and considered part of the oral cavity. The oral tongue extends anteriorly from the circumvallate papillae to the undersurface of the tongue at the junction of the floor of the mouth. The fibrous septum divides the tongue into right and left halves. The oral tongue can be demarcated into four anatomic areas : the tip, lateral borders, dorsal surface, and under surface (ventral surface).

There are six pairs of muscles that form the oral tongue. Three of these muscles are extrinsic, whereas the other three are intrinsic. The extrinsic muscles include the genioglossus, hyoglossus, and styloglossus. The intrinsic muscles include the lingual, vertical, and transverse muscles. The former primarily move the body of the tongue, whereas the latter alter the shape and conformation of the tongue during speech and swallowing.

Floor of the Mouth :

The floor of the mouth is a semi lunar space extending from the lower alveolar ridge to the under surface of the tongue. The floor of the mouth overlies the mylohyoid and hyoglossus muscles. The posterior boundary of the floor of the mouth is the base of the anterior tonsillar pillar. This region is divided into right and left by the frenulum of the tongue and contains the ostia of the submandibular and sublingual salivary glands. A sling formed by the mylohyoid muscles medially supports the anterior floor of the mouth, and the hyoglossus supports the posterior floor of the mouth.

Hard Palate :

The hard palate extends from the inner surface of the superior alveolar ridge to the posterior edge of the palatine bone. This is a semi

lunar area between the superior alveolar ridge and the mucous membrane covering the palatine process of the maxillary palatine bones.

Alveolar Ridge :

The alveolar ridges include the alveolar processes of the maxilla and mandible and the overlying mucosa. The mucosal covering of the lower alveolar ridge extends from the line of attachment of mucosa in the buccal gutter to the line of free mucosa of the floor of the mouth. The lower alveolar ridge extends to the ascending ramus of the mandible posteriorly. The superior alveolar ridge mucosa extends from the line of attachment of mucosa in the upper gingival buccal gutter to the junction of the hard palate. The posterior margin is the upper end of the pterygopalatine arch.

Retromolar trigone :

The retromolar trigone is the triangular area overlying the ascending ramus of the mandible. The base of the triangle is formed by the posterior most molar, and the apex lies at the maxillary tuberosity.

Buccal Mucosa :

The buccal mucosa includes the mucosal surfaces of the cheek and lips from the line of contact of the opposing lips to the

pterygomandibular raphe posteriorly. This extends to the line of attachment of the mucosa of the upper and lower alveolar ridge superiorly and inferiorly.

OROPHARYNX :

The oropharynx is contiguous with the oral cavity anteriorly, the larynx and hypopharynx posterior / inferiorly, and nasopharynx superiorly. Three main subregions compose the oropharynx including the tonsil, base of tongue, and soft palate. Normal function of the oropharynx is critical for speech and swallowing.

Tonsil :

The tonsillar region contains the anterior and posterior tonsillar pillars and the palatine tonsil. The palatine tonsils are lymphoid aggregates incompletely encapsulated with a keratinized stratified squamous epithelial mucosal lining positioned in the tonsillar bed, a part of the tonsillar cleft between the anterior (palatoglossal) and posterior (palatopharyngeal) tonsillar pillars.

Base of Tongue :

The base of tongue comprises the posterior third of the tongue and is bounded anteriorly by the circumvallate papillae, sitting in front of

the sulcus terminalis. It is bounded posterior – inferiorly by the hyoid and epiglottis and laterally by the glossopharyngeal sulci. Underlying the mucosa of the base of tongue are lymphatic nodules collectively known as the lingual tonsil. The vallecula is a 1- cm mucosal strip that serves as a transition between the base of tongue and epiglottis and is considered a part of the base of tongue.

Soft Palate :

The soft palate is a fibromuscular structure bounded anteriorly by the hard palate, laterally coursing into the anterior tonsillar pillars and posterior / inferiorly forming a free edge, and the midline uvula. The soft palate is composed of five muscles (levator veli palatini, tensor veli palatini, palatoglossus, palatopharyngeus, and musculus uvulae) posteriorly and the palatine aponeurosis an expanded tendon of the tensor veli palatini anteriorly.

HYPOPHARYNX :

The hypopharynx, sometimes referred to as the laryngopharynx, is contiguous superiorly with the oropharynx and inferiorly with the cervical esophagus. As general landmarks, the superior border of the hypopharynx is demarcated by the hyoid bone and the inferior border by the cricoid cartilage. With regard to cancer diagnosis and staging, there

are three primary anatomic subsites within the hypopharynx: the bilateral pyriform sinuses, the postcricoid region, and the posterior pharyngeal wall.

Pyriform Sinus :

The pyriform sinuses are essentially inverted pyramids with the medial, lateral, and anterior walls narrowing inferiorly to form the apices. Posteriorly, the pyriform sinuses are open and contiguous with the pharyngeal walls. Superiorly, the sinuses are surrounded by the thyrohyoid membrane through which passes the internal branch of the superior laryngeal nerve. Tumor involvement of the sensory branches of this nerve can result in referred otalgia.

Post Cricoid Region :

The postcricoid region is composed of the mucosa overlying the cricoid cartilage, with the arytenoid and esophageal mucosa forming the superior and inferior borders, respectively.

Posterior Pharyngeal Wall :

The posterior pharyngeal wall predominantly comprises the squamous mucosa covering the middle and inferior pharyngeal constrictor muscles and is separated from the prevertebral fascia by the

retropharyngeal space. Typically, the mucosa lining the pharyngeal wall is < 1 cm in thickness and provides a minimal barrier to direct tumor infiltration. The posterior pharyngeal wall is contiguous with the lateral wall of the pyriform sinus .

There is a rich network of lymphatics within the hypopharynx that drain directly through the thyrohyoid membrane and into the jugulodigastric lymph nodes, most commonly involving the subdigastric node. Additionally, there may be direct drainage into the spinal accessory nodes.

Tumors involving the posterior pharyngeal wall can also drain to the retropharyngeal nodes, including the most cephalad retropharyngeal nodes of Rouviere.

LARYNX :

The larynx is divided into the supraglottis, glottis, and subglottis. The supraglottis consists of the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and the arytenoids. The glottis includes the floor of the ventricle, interarytenoid area, true vocal cords, and the anterior commissure. The subglottis is located below the vocal cords .

The axial line of demarcation between the glottic and supraglottic larynx is the apex of the ventricle. The demarcation between

the glottis and subglottis is ill defined, but the subglottis is considered to extend from a point 5 mm below the free margin of the vocal cord to the inferior border of the cricoid cartilage or 10 mm below the apex of the ventricle.

The vocal cords vary from 3 to 5 mm in thickness and terminate posteriorly with their attachment to the vocal process or the arytenoid cartilage. The posterior commissure is the mucosa between the arytenoids (interarytenoid area).

The shell of the larynx is formed by the hyoid bone, thyroid cartilage, and cricoid cartilage; the cricoid cartilage is the only complete ring of the upper airway. The more mobile interior framework is composed of the heart-shaped epiglottis and the arytenoid, corniculate, and cuneiform cartilages. The corniculate and cuneiform cartilages produce small, rounded bulges at the posterior end of each aryepiglottic fold. The epiglottis is elastic cartilage; ossification does not occur, and even focal calcification is rare.

The external laryngeal framework is linked together by the thyrohyoid, the cricothyroid, and the cricotracheal ligaments or membranes . The epiglottis is joined superiorly to the hyoid bone by the hyoepiglottic ligament. The epiglottis is joined to the thyroid cartilage by the thyroepiglottic ligament at a point just below the thyroid notch and

above the anterior commissure. This area of attachment is the *petiole* of the epiglottis.

The arrangement of the ligaments that connect the cricoid and arytenoid cartilages and form the vocal ligaments . The conus elasticus (cricovocal ligament) is the lower portion of the elastic membrane that connects the inferior framework. It connects the upper surface of the cricoid, the vocal process of the arytenoid, and the lower thyroid cartilage; its free border is thickened into the vocal ligament.

The quadrangular membrane is the upper portion of the elastic membrane that connects the superior framework. It connects the false vocal cords, aryepiglottic folds, and the epiglottis. The vocal ligaments and thyroarytenoid / vocalis muscle complex attach to the vocal process of the arytenoid posteriorly and the thyroid cartilage anteriorly.

The intrinsic muscles of the larynx primarily control the movement of the cords. The extrinsic muscles are concerned primarily with swallowing. The cricothyroid muscle draws the larynx anteriorly and inferior when contracting. The consequence is increased vocal cord tension leading to increased pitch of the voice. It is innervated by the external branch of the superior laryngeal nerve.

The intrinsic muscles of the larynx are innervated by the recurrent laryngeal nerve. The pre - epiglottic and paraglottic fat spaces are essentially one contiguous space lying between the external framework of the thyroid cartilage and hyoid bone and the inner framework of the epiglottis and intrinsic muscles.

The space is traversed by blood and lymphatic vessels as well as nerves. Because few capillary lymphatics arise in this area, invasion of the fat space seldom leads to lymph node metastases. The fat space is limited by the conus elasticus inferiorly; the thyroid ala, thyrohyoid membrane, quadrangular membrane, and hyoid bone anterolaterally; the hyoepiglottic ligament superiorly; and the fascia of the intrinsic muscles medially. Posteriorly, it is adjacent to the anterior wall of the pyriform sinus.

The laryngeal surface of the epiglottis and the free margin of the vocal cords are squamous epithelium, and the remaining mucosa is usually pseudostratified ciliated columnar epithelium. Beneath the epithelium of the free edge of the vocal cord is the lamina propria, which can be divided into three layers. There is no true submucosal layer along the free margin of the vocal fold.

The supraglottic structures have a rich capillary lymphatic plexus; the trunks pass through the preepiglottic space and the thyrohyoid

membrane and terminate mainly in the jugulodigastric (Level II) lymph nodes; a few drain to the middle internal jugular chain (Level III) lymph nodes. There are essentially no capillary lymphatics of the true vocal cords; as a result, lymphatic spread from glottic cancer occurs only if tumor extends to supraglottic or subglottic areas.

The subglottic area has relatively few capillary lymphatics. The lymphatic trunks pass through the cricothyroid membrane to the pretracheal (Delphian) lymph nodes in the region of the thyroid isthmus.

The subglottic area also drains posteriorly through the cricotracheal membrane, with some trunks going to the paratracheal (Level VI) lymph nodes and others continuing to the inferior jugular (Level IV) chain.

LYMPHATIC DRAINAGE :

The neck is traditionally divided into five primary nodal levels (i.e., levels I–V) plus the retropharyngeal nodes that are relevant to the staging and management of oral cavity carcinoma. The classification of neck nodal regions, initially popularized by Robbins et al., has served as a surgical reference system based on visible landmarks. Gregoire et al. published consensus guidelines for the CT - based delineation of nodal

levels in the node - negative neck that were revised in 2014 to serve as a guide in the practice of radiation oncology.

Level I :

Level I includes the submental (Ia) and submandibular (Ib) triangles.

Level Ia is limited anteriorly by the mandibular symphysis, posteriorly by the body of the hyoid bone, and cranially by the geniohyoid muscle. The medial border is virtual because this region continues to the contralateral Ia station.

Level Ib is located within the space bounded by the inner table of the mandible laterally, the digastric muscle medially, the mandibular symphysis anteriorly, and the submandibular gland posteriorly.

Level II :

Level II includes the upper jugular chain lymph nodes from the base of the skull to the carotid bifurcation (surgical landmark) or the caudal body of the hyoid bone (clinical landmark); this nodal station extends from the posterior edge of the submandibular gland anteriorly to the posterior border of the sternocleidomastoid posteriorly.

The level II nodal region is further subdivided into IIa and IIb. The vertical plane defined by the spinal accessory nerve (surgical landmark) or the posterior edge of the internal jugular vein (radiographic landmark) defines each the subdivision within this level; level IIa lies anterior, whereas IIb lies posterior to this plane.

Level III :

Level III is the caudal extension of level II. It includes the midjugular nodes, of which the surgical landmarks extend from the carotid bifurcation to the omohyoid muscle inferiorly, the sternohyoid medially, and the posterior aspect of the sternocleidomastoid posteriorly. The corresponding radiographic landmarks are the caudal edge of the hyoid bone superiorly and the caudal edge of the cricoid cartilage inferiorly.

Level IV :

Level IV includes the inferior jugular nodes located around the inferior third of the internal jugular vein. Level IV is bounded by the omohyoid muscle superiorly, the clavicle inferiorly, and the posterior aspect of the sternocleidomastoid posteriorly.

Level V :

Level V includes nodes in the posterior triangle, which are located posterior to the sternocleidomastoid muscle. This space is bordered by the base of the skull superiorly, clavicle inferiorly, and posterior aspect of the sternocleidomastoid anteriorly.

Therefore, from a practical standpoint, the radiolographic cranial border of level V has been accepted as a horizontal plane crossing the cranial edge of the hyoid bone.

From a surgical perspective, level V is further subdivided into Va and Vb, and the caudal edge of the cricoid arch is the anatomic landmark denoting this subdivision (Vb lies below this boundary).

Retropharyngeal Nodes :

The retropharyngeal space, which contains the retropharyngeal nodes, extends from the skull base (cranially) to the hyoid bone (caudally). The anterior boundary of the retropharyngeal space is the pharyngeal constrictor muscles and the posterior boundary is the prevertebral fascia.

The retropharyngeal nodes are further divided into medial and lateral groups. The lateral retropharyngeal nodes lie medial to the carotid artery and lateral to the longus capitis and longus coli muscles, whereas

the medial group consists of one or two nodes intercalated along the midline lymphatics.

DISTANT METASTASIS :

Distant metastasis occurs in approximately 15 % to 20 % of patients who eventually die of their disease. The risk of distant metastases increases with the degree of lymph node involvement. Patients with recurrent disease are also at higher risk for distant metastases. Patients without clinically appreciable neck disease rarely fail distantly after treatment.

In general terms, with respect to head and neck cancer, 66 % of distant metastases are to the lungs, 22 % to the bones, and 9.5 % to the liver. On rare occasion, the oral cavity will serve as a site for distant metastasis from another anatomic primary tumor site.

MOLECULAR BIOLOGY :

Cancer progression models describe several steps that occur during tumor development: oncogenes become activated and tumor suppressor genes become deactivated, and a series of these alterations are required for carcinogenesis.

In the oral mucosa, this genetic progression is reflected histologically by the transformation from normal mucosa to dysplastic epithelium and ultimately to frankly invasive squamous cell carcinoma. Data to support this model come from studies that reveal genetic alterations in histologically normal tissues and in premalignant lesions, including loss of heterozygosity at chromosomes 3p14 and 9p21. Furthermore, mutations in the region of chromosome 17p13, which encompasses the tumor suppressor gene *TP53*, are among early events that contribute to malignant transformation.

Indeed, biopsies of normal mucosa from patients with upper aerodigestive tract carcinomas frequently harbor *TP53* mutations. Comprehensive studies of whole - genome sequencing, gene copy number analysis, and mRNA and protein expression of head and neck squamous cell carcinoma have been performed and have helped to provide an unbiased characterization of the genomic alterations seen in this disease. Known tumor suppressor genes and oncogenes were found to be mutated, including *TP53, PIK3CA, PTEN, HRAS,* and *CDKN2A*.

It was observed that HPV - positive tumors had a reduction in mutation rate of at least 50 % relative to smoking associated tumors. Moreover, they were inversely correlated with *TP53* mutations, suggesting that HPV - positive tumors are genomically distinct. However,

very few oral cavity tumors (~ 4%) appear to be driven by high - risk HPV.

The first genomic analyses have identified loss - of - function mutations in *NOTCH1* that suggest that *NOTCH* may act as a tumor suppressor gene in head and neck cancers rather than as an oncogene, as it had been identified in other malignancies. Subset analysis of patients with oral cancer has found that reduced copy number alterations and activating mutations in *HRAS* or *PIK3CA* are associated with improved clinical outcomes.

The use of whole - exome sequencing has also been applied to evaluate genomic alterations in younger, nonsmoking patients, and this analysis surprisingly found no significant difference in mutation frequencies, types of mutations, or copy number between younger and older patients with oral tongue cancers. Smoking was seen to have a minimal effect on genomic changes.

FAT1 and *TP53* mutations were not significantly increased in the younger cohort and may represent a novel area of study. Although the genomic characterization has allowed clinicians to better understand the molecular alterations underlying the development of oral cancers, the majority of known mutations represent non targetable tumor suppressor genes.

Therefore, further studies of these alterations as potential prognostic and predictive biomarkers and synthetic lethality approaches are needed to fully realize the immense potential of assessment of the genomic alterations in an individual oral cancer patient's tumor.

More recent analyses have focused on recurrent and metastatic head and neck cancers that suggest the potential for precision approaches to treating these advanced tumors with more than 20 % showing " actionable " mutations. Liquid biopsy approaches analyzing tissue fluids including saliva and blood also hold tremendous promise in the early detection of recurrence of oral cancers.

Furthermore, immuno profiling of squamous cancers of the head and neck inclusive of oral cavity tumors indicates that immune - oncologic approaches to treating these tumors should be considered in future clinical investigations.

HISTOLOGY :

The predominant histopathologic type of cancer in the oral cavity is squamous cell carcinoma. There are several variants of squamous cell carcinoma, including

Basaloid and

Verrucous carcinoma.

Basaloid SCC :

Basaloid squamous cell carcinoma is believed to have a worse prognosis than traditional squamous cell carcinoma. In a retrospective comparison between basaloid squamous cell carcinoma and traditional poorly differentiated squamous cell carcinoma, the former had a higher incidence of advanced disease at presentation, distant metastases, and poorer overall survival rate.

Verrucous Carcinoma :

Verrucous carcinoma is a less common variant of squamous cell carcinoma. It is generally considered a low - grade malignancy with low metastatic potential and good overall prognosis, although often with challenges for local control in elderly patients.

Sarcomatoid carcinomas can be found in the oral cavity and larynx. This variant of squamous cell carcinoma carries a poor prognosis with a mean survival of approximately 2 years.

Less than 10 % of neoplasms of the oral cavity have nonsquamous histology.

1. Adenoid cystic carcinoma
2. Adenocarcinomas

3. Melanoma

4. Ameloblastoma,

5. Lymphoma - Most lymphomas in the head and neck arise in Waldeyer ring (tonsil, base of the tongue, and nasopharynx). Only 2 % of all lymphomas are found in the oral cavity

6. Kaposi sarcoma - Approximately 50 % of acquired immuno deficiency syndrome – related cases of Kaposi sarcoma have oral cavity involvement.

Fortunately, melanoma of the oral cavity is very rare and represents only 0.2 % to 8 % of all melanomas.

Mucosal melanomas generally have a worse prognosis than cutaneous melanomas.

CLINICAL FEATURES :

Despite this fact, many patients with oral cavity tumors present with advanced - stage disease as initial symptoms may be vague and painless.

Tumors of the oral tongue often present as small ulcers and gradually invade the musculature of the tongue. Advanced lesions may be either ulcerative or exophytic and are usually quite evident. Cervical metastases occur early in the natural history of the disease, with 30 % to 40 % of patients harboring cervical lymph node metastases at diagnosis.

Lesions of the floor of the mouth are often infiltrative and may invade bone, the muscles of the floor of the mouth, and the tongue. The frenulum is frequently a site of involvement. Clinical fixation of the tumor to the mandible suggests periosteal involvement, which may occur early.

Tumors of the alveolar ridge may present with pain while chewing, loose teeth, or ill - fitting dentures in edentulous patients. These cancers often arise in edentulous areas or along the free margin of the mandibular alveolus. Anesthesia of the lower lip and teeth may indicate involvement of the mandibular canal and inferior alveolar nerve.

Tumors involving the retromolar trigone region may present with an exophytic growth pattern and limited involvement of underlying bone or they may infiltrate cortical bone and spread along regional tissue planes to involve the pterygoid complex and parapharyngeal space. These latter lesions often induce trismus early in the clinical course.

Carcinoma of the buccal mucosa is rarely symptomatic early in its course. Lesions may be papillary or erosive and located near the dental occlusal line. These tumors are often relatively asymptotic and therefore seldom come to medical attention as T1 lesions. Often, these tumors manifest associated leukoplakia. Multiple primary sites and local recurrence are also common. These tumors most frequently arise adjacent to the lower molars along the occlusal line of the teeth.

Carcinoma of the hard palate is often painless, and the sole presenting symptom may be an irregularity in the mucosa or ill - fitting dentures. Other presenting symptoms include nonhealing ulcers of the hard palate, intermittent bleeding, and pain.

Oropharyngeal cancers present with a painless neck mass, which is usually mobile, firm, and nontender, but can be fixed, indicating extranodal extension and invasion into surrounding structures. Some patients complain of a deep - seated otalgia located within the auditory canal. This is mediated via irritation of the glossopharyngeal nerve (CN IX) with referral via the Petrosal ganglion to the tympanic nerve of Jacobson.

Regurgitation of foods can occur with invasion of the soft palate, inhibiting its ability to elevate during swallowing. Trismus is seen with more advanced tumors and reflects invasion of the pterygoid fossa and /

or musculature. Odynophagia and dysphagia are other common presenting symptoms that occur with invasion into the pharyngeal musculature or obstruction by pathologic lymphadenopathy.

Carcinoma arising on the true vocal cords produces hoarseness at a very early stage. Odynophagia, otalgia, pain localized to the thyroid cartilage, and airway obstruction are features of advanced lesions. Hoarseness is not a prominent symptom of cancer of the supraglottis until the lesion becomes extensive. Odynophagia, usually mild, is the most frequent initial symptom, often described as a sore throat.

Some patients report a sensation of a " lump in the throat ". Pain is referred to the ear by way of the Arnold branch of the vagus nerve. A neck mass may be the first sign of a supraglottic cancer.

Late symptoms include weight loss, halitosis, dysphagia, and aspiration.

DIAGNOSTIC EVALUATION :

A detailed history and physical examination including complete head and neck examination with biopsy is necessary to establish the diagnosis.

Examination with a mirror or fiberoptic scope is essential in diagnosing and staging lesions involving the larynx and pharynx.

Imaging can complement the physical examination in determining the extent of disease.

A chest x - ray should be performed to exclude lung metastases or a second primary cancer.

CT is the modality most commonly used to determine the extent of soft tissue and bony involvement and occult disease in the neck.

A panoramic radiograph of the mandible or MRI of the neck may be done as indicated and are useful to assess the extent and stage.

Pretreatment dental evaluation and audiological examinations are recommended.

For patients with advanced stage disease who will receive concurrent chemotherapy and radiation, blood counts and chemistries may be done to assess critical organ function including renal and hepatic function.

A multidisciplinary consultation should be sought as indicated.

STAGING (AJCC 8th Edition) :

Oral Cavity :

Definition of Primary Tumor :

T Category		T Criteria
TX	-	Primary tumor cannot be assessed
Tis	-	Carcinoma in situ
T1	-	Tumor ≤ 2 cm in greatest dimension, ≤ 5 mm depth of invasion (DOI)
T2	-	Tumor ≤ 2 cm in greatest dimension, DOI > 5 mm and ≤ 10 mm, *or* tumor > 2 cm, but ≤ 4 cm, and ≤ 10 mm of DOI
T3	-	Tumor > 4 cm in greatest dimension. Any tumor > 10 mm DOI
T4	-	Moderately advanced or very advanced local disease
T4a (Lip)	-	Tumor invades through cortical bone, inferior alveolar nerve, floor of the mouth, or skin of the face (i.e., chin or nose).

T4a (oral cavity) - Tumor invades adjacent structures (e.g., through cortical bone of the mandible or maxilla, maxillary sinus, or skin of the face).

Note: superficial erosion of bone / tooth socket by a gingival primary is not sufficient to classify a tumor as T4. T4b Tumor invades masticator space, pterygoid plates, or skull base and / or encases carotid artery.

Definition of Regional Lymph Node (N) :

Clinical N (cN) :

N Category		**N Criteria**
Nx	-	Regional lymph nodes cannot be assessed
N0	-	No regional lymph node metastases
N1	-	Metastases in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension, ENE (−)
N2	-	Metastases in a single ipsilateral lymph node > 3 cm, but ≤ 6 cm in greatest dimension and ENE (−); in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE (−); *or* in bilateral or contralateral lymph

nodes, ≤ 6 cm in greatest dimension and ENE (−)

N2a - Metastases in a single ipsilateral lymph node > 3 cm, but ≤ 6 cm in greatest dimension and ENE (−)

N2b - Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension, and ENE (−)

N2c - Metastases in bilateral or contralateral lymph nodes ≤ 6 cm in greatest dimension and ENE (−)

N3 - Metastases in a lymph node > 6 cm in greatest dimension and ENE (−) *or* in any node with clinically overt ENE (+)

N3a - Metastases in a lymph node > 6 cm in greatest dimension and ENE (−)

N3b - Metastases in any lymph node(s) and clinically over ECE (+)

Definition of Regional Lymph Node (N) :

Pathologic N (pN) :

N Category		N Criteria
Nx	-	Regional lymph nodes cannot be assessed
N0	-	No regional lymph node metastases
N1	-	Metastases in a single ipsilateral lymph node ≤ 3 cm in greatest dimension and ENE (−)
N2	-	Metastases in a single ipsilateral lymph node ≤ 3 cm in greatest dimension and ENE (+); > 3 but ≤ 6 cm in greatest dimension and ENE (−); in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE (−); *or* in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE (−)
N2a	-	Metastases in a single ipsilateral or contralateral lymph node ≤ 3 cm in greatest dimension and ENE (+), *or* in a single ipsilateral lymph node, > 3 but ≤ 6 cm in greatest dimension and ENE (−)
N2b	-	Metastases in multiple ipsilateral lymph nodes ≤ 6 cm in greatest dimension and ENE (−)

N2c - Metastases in bilateral or contralateral lymph nodes ≤ 6 cm in greatest dimension and ENE (−)

N3 - Metastases in a lymph node > 6 cm in greatest dimension and ENE (−); in a single ipsilateral lymph node, > 3 cm in greatest dimension and ECE (+); *or* multiple ipsilateral, contralateral, or bilateral lymph nodes, any with ENE (+)

N3a - Metastases in a lymph node > 6 cm in greatest dimension and ENE (−)

N3b - Metastases in a single ipsilateral lymph node > 3 cm in greatest dimension and ECE (+), *or* in multiple ipsilateral, contralateral, bilateral lymph nodes, any with ENE (+)

Note. A designation of " U " or " L " may be used for any N category to indicate metastases above or below the lower border of the cricoid, respectively. Similarly, clinical or pathologic extranodal extension (ENE) should be recorded as ENE (−) or ENE (+).

Distant Metastasis (M) :

M0 - No distant metastasis present

M1 - Distant metastasis present

Histologic Grade (G) :

GX - Grade cannot be assessed

G1 - Well differentiated

G2 - Moderately differentiated

G3 - Poorly differentiated

G4 - Undifferentiated

AJCC Prognostic Stage Groups :

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1 - 3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1 - 4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0

Stage IVC	Any T	Any N	M1

Oropharynx (HPV +) :

Primary Tumor (T) :

T0	-	No primary identified
T1	-	Tumor 2 cm or smaller in greatest dimension
T2	-	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	-	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	-	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond

Clinical Regional Lymph Nodes (cN) :

NX	-	Regional lymph nodes cannot be assessed
N0	-	No regional lymph node metastasis
N1	-	One or more ipsilateral lymph nodes, none larger than 6 cm

N2 - Contralateral or bilateral lymph nodes, none larger than 6 cm

N3 - Lymph node(s) larger than 6 cm

Pathologic Regional Lymph Nodes (pN) :

NX - Regional lymph nodes cannot be assessed

pN0 - No regional lymph node metastasis

pN1 - Metastasis in 4 or fewer lymph nodes

pN2 - Metastasis in more than 4 lymph nodes

Distant Metastasis (M) :

M0 - No distant metastasis present

M1 - Distant metastasis present

Histologic Grade (G) :

No grading system exists for HPV - mediated oropharyngeal tumors

Prognostic Stage Groups :

Clinical :

Stage I	T0, T1, T2	N0,N1	M0

Stage II	T0, T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage III	T0, T1, T2, T3	N3	M0
	T4	N0, N1, N2, N3	M0
Stage IV	Any T	Any N	M1

Pathological :

Stage I	T0, T1, T2	N0, N1	M0
Stage II	T0, T1, T2	N2	M0
	T3, T4	N0, N1	M0
Stage III	T3, T4	N2	M0
Stage IV	Any T	Any N	M1

Oropharynx (HPV -) :

Primary Tumor (T) :

TX - Primary tumor cannot be assessed

Tis - Carcinoma *in situ*

T1 - Tumor 2 cm or smaller in greatest dimension

T2 - Tumor larger than 2 cm but not larger than 4 cm in greatest dimension

T3 - Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis

T4 - Moderately advanced or very advanced local disease

T4a - Moderately advanced local disease

Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*

T4b - Very advanced local disease

Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Hypopharynx :

T1 - Limited to 1 subsite of the hypopharynx and ≤ 2 cm in greatest dimension

T2 - Tumor invades more than 1 subsite of the hypopharynx or an adjacent site, or measures > 2 cm but ≤ 4 cm in greatest diameter without fixation of hemilarynx

T3 - Tumor measures > 4 cm in greatest dimension or with fixation of hemilarynx or with extension to the esophagus

T4a - Invades thyroid / cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue, which includes prelaryngeal strap muscles and subcutaneous fat

T4b - Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

Larynx :

Supraglottis :

TX - Primary tumor cannot be assessed

Tis - Carcinoma *in situ*

T1 - Tumor limited to one subsite of supraglottis with normal vocal cord mobility

T2 - Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of the base of the tongue, vallecula, medial wall of the pyriform sinus) without fixation of the larynx.

T3 - Tumor is limited to the larynx with vocal cord fixation and / or invades any of the following area: postcricoid space, preepiglottic space, paraglottic space, and/or inner cortex of the thyroid cartilage

T4 - Moderately advanced or very advanced

T4a - Moderately advanced local disease; tumor invades through the thyroid cartilage and / or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)

T4b - Very advanced local disease; tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis :

TX	-	Primary tumor cannot be assessed
Tis	-	Carcinoma *in situ*
T1	-	Tumor limited to the vocal cord(s) (may involve the anterior or posterior commissure) with normal mobility
T1a	-	Tumor limited to one vocal cord
T1b	-	Tumor involves both vocal cords.
T2	-	Tumor extends to the supraglottis and / or subglottis with impaired vocal cord mobility.
T3	-	Tumor limited to the larynx with vocal cord fixation and / or invasion of paraglottic space and / or inner cortex of the thyroid cartilage
T4	-	Moderately advanced or very advanced
T4a	-	Moderately advanced local disease; tumor invades through the outer cortex of the thyroid cartilage and / or invades tissues beyond the larynx (e.g., trachea, cricoid cartilage, soft tissues of the neck

including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b - Very advanced local disease; tumor invades the prevertebral space, encases the carotid artery, or invades mediastinal structures

Subglottis :

T1 - Tumor limited to the subglottis

T2 - Tumor extends to vocal cord(s) with normal or impaired mobility

T3 - Tumor limited to larynx with vocal cord fixation and / or inner cortex of the thyroid cartilage

T4 - Moderately advanced or very advanced

T4a - Moderately advanced local disease

Tumor invades cricoid or thyroid cartilage and / or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)

T4b - Very advanced local disease; Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

MANAGEMENT :

General :

The five - year overall survival rate of patients with HNSCC is about 40 - 50 %. About one third of patients present with early stage disease (T1-2, N0). Treatment for early HNSCC usually involves single modality therapy with either surgery or radiation. Survival is comparable for the two approaches. Early stage cancers have a very favorable prognosis with high cure rates with surgery or radiation alone and chemotherapy or concurrent chemotherapy / radiation is not indicated.

For patients with pathologically staged III, IVA / B head and neck cancer, postoperative concomitant chemoradiation with cisplatin has shown improvement in local regional control and survival rates for those with positive microscopic surgical margins and / or extra - capsular nodal extension .

Decision of treatment is based on different factors, including tumor accessibility, functional outcome, patient's health and preference, and the availability of treatment expertise. A multidisciplinary team evaluation is vital to optimize the outcome of these patients.

Surgery is the preferred treatment modality for early stage oral cavity cancers and involves resection of the primary tumor with or without lymph nodal dissection. Patients who are medically inoperable or refuse surgery can be treated with definitive radiation therapy.

Definitive radiation therapy is the preferred approach for many patients with non - oral cavity tumors, in particular to hypopharynx and supraglottic and glottic larynx, since it appears to provide a better functional outcome in comparison to larynx - sparing surgical approaches.

For those with residual disease after radiation therapy, salvage surgery is recommended; for those managed by surgery, post operative radiation therapy is indicated in the presence of close or positive margins, lymphovascular or perineural invasion, or when a positive lymph node is identified, upstaging the tumor.

Administration of cisplatin requires intravenous infusion capacity. Adequate IV hydration and anti - emetics should accompany the infusion of cisplatin. Blood counts and chemistries should be serially

monitored during the course of treatment. Concurrent chemotherapy increases the risk for radiation related adverse effects including mucositis, dysphagia, dermatitis etc. Patients should be carefully monitored for these and supportive care provided as indicated. Care should be taken to maintain adequate hydration, nutrition and analgesia before, during and after completion of treatment. Optimal monitoring and supportive care requires trained clinicians experienced in the management of these cancers with access to inpatient care and laboratory services.

Late treatment related toxicities such as xerostomia, dysphagia, speech dysfunction, gastric tube dependence, tracheostomy dependence, neuropathies, depression, and cosmetic disfigurement can significantly impact quality of life and psychosocial wellbeing and therefore need to be identified and addressed.

Concurrent radiation with 3 doses of cisplatin are recommended. The following excludes ancillary medications pertaining to the management of cisplatin administration and side effects. Standard Regimen Concomitant Chemotherapy - Radiation Cisplatin 100 mg / m2 IV, q 3 weeks x 3 cycles (days 1, 22, and 43).

Early stage head and neck cancers are highly curable with either surgery or radiation therapy. Certain high risk features have been shown to significantly increase the risk of recurrence.

Two randomized trials have demonstrated improved outcomes with the addition of concomitant cisplatin to postoperative radiation in patients with locally advanced disease or certain adverse risk features. Both studies compared the addition of concomitant cisplatin (100 mg / m2 on days 1, 22, and 43) to radiotherapy versus radiotherapy alone given after surgery in patients with advanced stage cancers of the oral cavity, oropharynx, larynx, or hypopharynx.

The RTOG 9501 / Intergroup trial randomized 459 patients and showed significant improvement in localregional control rates and disease free survival but not overall survival in the chemo radiation arm . Two year rate of local and regional control was 82 % in the combined - therapy group versus 72 % in the radiotherapy group. Disease - free survival was significantly longer in the combined - therapy group (HR for disease or death, 0.78; 95 % CI, 0.61 to 0.99; P = 0.04).

The EORTC 22931 trial randomized 334 patients and showed improved 5 - year progression free survival of 47 % vs 36 % and overall survival of 53 % vs 40 % respectively, in favor of the concomitant cisplatin group . The estimated 5 - year cumulative incidence of local or regional relapses was 31 % with radiation versus 18 % after combined therapy.

A comparative analysis of data pooled from the two trials showed that extracapsular extension and / or microscopically involved surgical margins were the only risk factors for which the impact of concomitant chemoradiation was significant in both trials . There was also a trend in favor of the combined modality arm in the group of patients who had stage III - IV disease, perineural infiltration, vascular embolisms, and / or clinically enlarged level IV - V lymph nodes secondary to tumors arising in the oral cavity or oropharynx. A ten - year follow up of the RTOG 9501 / Intergroup trial confirmed the superiority of the combined arm for local regional control and disease - free survival in the subgroup of patients with microscopically involved margins and / or extracapsular nodal spread.

Primary combined chemotherapy with cisplatin and radiation is also the standard for patients with locally advanced, unresectable tumors. In this setting, the addition of cisplatin to radiation improves disease control and overall survival. A meta - analysis including 50 studies showed an absolute benefit of 6.5 % in overall survival with a HR of 0.81, $p < 0.0001$, for patients who received combined chemoradiation .

Cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor, EGFR, has been shown to improve outcomes when compared to radiation alone in the primary treatment setting of

patients with locally advanced disease but has not been shown to be superior to cisplatin and it is much more costly .

Neoadjuvant chemotherapy approaches have been studied in several trials with controversial and inconclusive findings to date. While this approach cannot be recommended as a standard for all patients, it is a reasonable alternative for patients with very large burden of disease who would not be candidates for surgery or primary chemotherapy + radiation. Common Nausea and vomiting occur in almost all patients treated with cisplatin and is often severe, necessitating the use of anti - emetic medications.

Major dose limiting toxicities of cisplatin include renal impairment (28 - 36 %), ototoxicity (40 - 60 % children; 10 - 31 % adults) and myelosuppression. Ototoxicity usually manifests as tinnitus and high frequency hearing loss. Myelosuppression can lead to anemia, leucopenia and thrombocytopenia with associated complications.

In the RTOG 9501 trial, the incidence of acute toxicity of grade 3 or greater was 34 % in the radiotherapy group versus 77 % in the concomitant cisplatin arm. Similarly, in the EORTC trial, severe adverse effects were more frequent after combined therapy (41 %) than after radiotherapy (21 %, P = 0.001). Serious Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities.

Intravenous hydration both before and after administering cisplatin is necessary to reduce the incidence of renal toxicity. This should be particularly considered in elderly patients and patients with compromised renal function. Combining cisplatin chemotherapy with radiation significantly increases the rates of grade 3 and 4 radiation related toxicity including dysphagia, dermatitis and mucositis.

Chemotherapy benefit was higher for concomitant administration for all tumour locations, but the interaction test between chemotherapy timing and treatment effect was only significant for oropharyngeal ($p < 0.0001$) and laryngeal tumours ($p = 0.05$), and not for oral cavity ($p = 0.15$) and hypopharyngeal tumours ($p = 0.30$). The 5 - year absolute benefits associated with the concomitant chemotherapy are 8.9 %, 8.1 %, 5.4 % and 4 % for oral cavity, oropharynx, larynx and hypopharynx tumours, respectively. Carboplatin is not an acceptable alternative to cisplatin.

CELECOXIB :

Celecoxib, is a COX - 2 selective nonsteroidal anti - inflammatory drug (NSAID). Celecoxib was patented in 1993 and came into medical use in 1999. It is available as a generic medication.

It is used to treat the pain and inflammation in osteoarthritis, acute pain in adults, rheumatoid arthritis, ankylosing spondylitis, painful menstruation, and juvenile rheumatoid arthritis.

It may also be used to decrease the risk of colorectal adenomas in people with familial adenomatous polyposis. It is taken by mouth. Benefits are typically seen within an hour.

Common side effects include abdominal pain, nausea, and diarrhea. Serious side effects may include heart attacks, strokes, gastrointestinal perforation, gastrointestinal bleeding, kidney failure, and anaphylaxis.

Use is not recommended in people at high risk for heart disease. The risks are similar to other NSAIDs, such as ibuprofen and naproxen . Use in the later part of pregnancy or during breastfeeding is not recommended.

Pharmacokinetics :

Bioavailability : Unknown

Protein Binding : 97 % mainly to serum albumin

Metabolism : Liver (mainly CYP 2C9)

Elimination T1/2 : 7.8 hours

11 hours (mild hepatic impairment)

13 hours (moderate - severe hepatic impairment)

Excretion : Faeces (57 %)

Urine (27 %)

Indications :

1. Osteoarthritis
2. Rheumatoid arthritis
3. Acute pain, musculoskeletal pain and painful menstruation
4. Ankylosing spondylitis
5. Reduce the number of colon and rectal polyps in people with familial adenomatous polyposis.
6. In children with juvenile rheumatoid arthritis who are older than two years of age and weigh more than 10 kg (22 lb).

For postoperative pain, it is more or less equal to ibuprofen. For pain relief, it is similar to paracetamol. And in osteoarthritis, acetaminophen is the first line treatment. In knee and hip osteoarthritis, acetaminophen may be ineffective.

7. Mental illness : major depression, bipolar disorder, and schizophrenia.

Adverse effects :

1. **Cardiovascular events:**

NSAIDs are associated with an increased risk of serious (and potentially fatal) adverse cardiovascular thrombotic events, including myocardial infarction and stroke. Risk may be increased with duration of use or pre - existing cardiovascular risk factors or disease. Individual cardiovascular risk profiles should be evaluated prior to prescribing.

New - onset hypertension or exacerbation of hypertension may occur (NSAIDs may impair response to thiazide or loop diuretics), and may contribute to cardiovascular events; monitor blood pressure and use with caution in patients with hypertension.

May cause sodium and fluid retention, use with caution in patients with edema or heart failure.

Long-term cardiovascular risk in children has not been evaluated. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternative therapies should be considered for patients at high risk. The increased risk is about 37 %.

2. **Gastrointestinal events:**

NSAIDs may increase risk of serious gastrointestinal (GI) ulceration, bleeding, and perforation (may be fatal). These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and / or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients.

Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

When used concomitantly with ≤ 325 mg of aspirin, a substantial increase in the risk of gastrointestinal complications (e.g., ulcer) occurs; concomitant gastroprotective therapy (e.g., proton pump inhibitors) is recommended. The increased risk is about 81 %.

3. Hematologic effects :

Anemia may occur; monitor hemoglobin or hematocrit in people on long-term treatment.

Celecoxib does not usually affect prothrombin time, partial thromboplastin time or platelet counts; it does not inhibit platelet

aggregation at approved doses. People with prior history of ulcer disease or GI bleeding require special precaution.

Moderate to severe liver impairment or GI toxicity can occur with or without warning symptoms in people treated with NSAIDs.

4. Allergy :

Celecoxib contains a sulfonamide moiety and may cause allergic reactions in those allergic to other sulfonamide - containing drugs. This is in addition to the contraindication in people with severe allergies to other NSAIDs. However, it has a low (reportedly 4 %) chance of inducing cutaneous reactions among persons who have a history of such reactions to aspirin or nonselective NSAIDs.

NSAIDs may cause serious skin adverse events, including exfoliative dermatitis, Stevens - Johnson syndrome, and toxic epidermal necrolysis; events may occur without warning and in patients without prior known sulfa allergy. Use should be discontinued at first sign of rash (or any other hypersensitivity).

4. **Heart attack and stroke :**

A 2013 meta - analysis of hundreds of clinical trials found that coxibs (the class of drugs that includes celecoxib) increase the risk of major cardiovascular problems by about 37 % over placebo. In 2016, a randomized trial provided strong evidence that treatment with celecoxib

is not more likely to result in poor cardiovascular outcomes than treatment with naproxen or ibuprofen. As a result, in 2018 an FDA advisory panel concluded that celecoxib poses no greater risk for causing heart attacks and strokes than the commonly - used NSAIDs ibuprofen or naproxen and recommended that the FDA consider changing its advice to physicians regarding celecoxib's safety.

The COX - 2 inhibitor rofecoxib (Vioxx) was removed from the market in 2004 due to its risk. Like all NSAIDs on the US market, celecoxib carries an FDA - mandated " black box warning " for cardiovascular and gastrointestinal risk. In February 2007, the American Heart Association warned that with respect to " patients with a prior history of or at high risk for cardiovascular disease... use of COX - 2 inhibitors for pain relief should be limited to patients for whom there are no appropriate alternatives, and then, only in the lowest dose and for the shortest duration necessary".

In 2005, a study published in the *Annals of Internal Medicine* found that cardiovascular effects of COX - 2 inhibitors differ, depending on the drug. Other COX - 2 - selective inhibitors, such as rofecoxib, have significantly higher myocardial infarction rates than celecoxib. In April 2005, after an extensive review of data, the FDA

concluded it was likely " that there is a ' class effect ' for increased CV risk for all NSAIDs ".

In a 2006 meta - analysis of randomized control studies, the cerebrovascular events associated with COX - 2 inhibitors were examined, but no significant risks were found when compared to nonselective NSAIDs or placebos.

Drug interactions :

Celecoxib is predominantly metabolized by cytochrome P450 2C9. Caution must be exercised with concomitant use of 2C9 inhibitors, such as fluconazole, which can greatly elevate celecoxib serum levels.

If used concomitantly with lithium, celecoxib increases lithium plasma levels.

If used concomitantly with warfarin, celecoxib may result in increased risk of bleeding complications. The risk of bleeding and gastric ulcers also increase further when SSRIs are used in combination with celecoxib.

The drug may increase the risk of kidney failure with angiotensin converting enzyme inhibitors, such as lisinopril, and diuretics, such as hydrochlorothiazide.

Pregnancy :

In the US FDA's pregnancy categories, the drug is category C prior to 30 weeks gestation, and category D starting at 30 weeks gestation.

Mechanism of action :

1. Anti-inflammatory :

A highly selective reversible inhibitor of the COX - 2 isoform of cyclooxygenase, celecoxib inhibits the transformation of arachidonic acid to prostaglandin precursors. Therefore, it has antipyretic, analgesic and anti - inflammatory properties. Nonselective NSAIDs (such as aspirin, naproxen, and ibuprofen) inhibit both COX - 1 and COX - 2.

Inhibition of COX - 1 (which celecoxib does not inhibit at therapeutic concentrations) inhibits the production of prostaglandins and the production of thromboxane A2, a platelet activator. COX - 1 is traditionally defined as a constitutively expressed " housekeeping " enzyme and plays a role in the protection of the gastrointestinal mucosa, kidney hemodynamics, and platelet thrombogenesis.

COX - 2, on the contrary, is extensively expressed in cells involved in inflammation and is upregulated by bacterial lipopolysaccharides, cytokines, growth factors, and tumor promoters.

Celecoxib is approximately 10 - 20 times more selective for COX - 2 inhibition over COX - 1. It binds with its polar sulfonamide side chain to a hydrophilic side pocket region close to the active COX - 2 binding site. In theory, this selectivity allows celecoxib and other COX - 2 inhibitors to reduce inflammation (and pain) while minimizing gastrointestinal adverse drug reactions (e.g. stomach ulcers) that are common with nonselective NSAIDs.

2. **Anti-cancer :**

For its use in reducing colon polyps, celecoxib affects genes and pathways involved in inflammation and malignant transformation in tumors, but not normal tissues. Celecoxib binds to Cadherin - 11 (which may explain the reduction in cancer progression).

Structure - activity relationship :

The Searle research group found the two appropriately substituted aromatic rings must reside on adjacent positions about the central ring for adequate COX - 2 inhibition. Various modifications can

be made to the 1, 5 - diarylpyrazole moiety to deduce the structure - activity relationship of celecoxib.

A parasulfamoylphenyl at position 1 of the pyrazole was found to have a higher potency for COX - 2 selective inhibition than a paramethoxyphenyl. In addition, a 4 - (methylsulfonyl) phenyl or 4 - sulfamoylphenyl is known to be necessary for COX - 2 inhibition. For instance, replacing either of these entities with a SO_2NHCH_3 substituent diminishes COX - 2 inhibitory activity as noted with a very high inhibitory concentration. At the 3 - position of the pyrazole, a trifluoromethyl or difluoromethyl provides superior selectivity and potency compared to a fluoromethyl or methyl substitution.

Celecoxib is compound 22; the 4 - sulfamoylphenyl on the 1 - pyrazol substituent is required for COX - 2 inhibition and the 4 - methyl on the 5 - pyrazol system has low steric hindrance to maximize potency, while the 3 - trifluoromethyl group provides superior selectivity and potency. To explain the selectivity of celecoxib, it is necessary to analyze the free energy of binding difference between the drug molecule and COX - 1 compared to COX - 2 enzymes.

The structural modifications highlight the importance of binding to residue 523 in the side binding pocket of the cyclooxygenase enzyme, which is an isoleucine in COX - 1 and a valine in COX - 2. This

mutation appears to contribute to COX - 2 selectivity by creating steric hindrance between the sulfonamide oxygen and the methyl group of Ile523 that effectively destabilizes the celecoxib-COX-1 complex. Thus, it is reasonable to expect COX - 2 - selective inhibitors to be more bulky than nonselective NSAIDs.

Availability :

Celecoxib is available as oral capsules containing 50, 100, 200 or 400 mg of celecoxib.

Cancer prevention :

The role celecoxib might have in reducing the rates of certain cancers has been the subject of many studies. However, no current medical recommendation exists to use this drug for cancer reduction.

The use of celecoxib to reduce the risk of colorectal cancer has been investigated, but neither celecoxib nor any other drug is indicated for this use. Small - scale clinical trials in very high - risk people (belonging to FAP families) showed celecoxib can prevent polyp growth. Hence, large - scale randomized clinical trials were undertaken. Results show a 33 to 45 % polyp recurrence reduction in people treated with celecoxib each day. However, serious cardiovascular events were significantly more frequent in the celecoxib - treated groups.

Aspirin shows a similar (and possibly larger) protective effect, has demonstrated cardioprotective effects and is significantly cheaper, but no head - to - head clinical trials have compared the two drugs.

Cancer treatment :

Different from cancer prevention, cancer treatment is focused on the therapy of tumors that have already formed and have established themselves inside the patient. Many studies are going on to determine whether celecoxib might be useful for this latter condition. However, during molecular studies in the laboratory, it became apparent that celecoxib could interact with other intracellular components besides its most famous target, COX - 2.

The discovery of these additional targets has generated much controversy, and the initial assumption that celecoxib reduces tumor growth primarily by the inhibition of COX - 2 became contentious. Certainly, the inhibition of COX - 2 is paramount for the anti - inflammatory and analgesic function of celecoxib. However, whether inhibition of COX - 2 also plays a dominant role in this drug's anticancer effects is unclear. For example, a recent study with malignant tumor cells showed celecoxib could inhibit the growth of these cells *in vitro*, but COX - 2 played no role in this outcome; even more strikingly, the

anticancer effects of celecoxib were also obtained with the use of cancer cell types that do not even contain COX - 2.

Additional support for the idea that other targets besides COX - 2 are important for celecoxib's anticancer effects has come from studies with chemically modified versions of celecoxib. Several dozen analogs of celecoxib were generated with small alterations in their chemical structures. Some of these analogs retained COX - 2 inhibitory activity, whereas many others did not.

However, when the ability of all these compounds to kill tumor cells in cell culture was investigated, the antitumor potency did not at all depend on whether or not the respective compound could inhibit COX - 2, showing the inhibition of COX - 2 was not required for the anticancer effects. One of these compounds, 2, 5 - dimethyl - celecoxib, which entirely lacks the ability to inhibit COX - 2, actually displayed stronger anticancer activity than celecoxib.

AIM OF THE STUDY

AIMS & OBJECTIVES

Primary Objectives (s) :

To determine the Efficacy in terms of clinical response, of Low Dose Celecoxib with Concurrent Chemoradiation in Locally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC).

Secondary Objective (s) :

To evaluate the Safety of Low Dose Celecoxib with chemoradiation in HNSCC.

Study Centre :

Department Of Radiation Oncology,

Madras Medical College and

Rajiv Gandhi Govt General Hospital,

Chennai-03.

Duration of the Study :

One year.

Study Design :

Double arm prospective study

MATERIALS
&
METHODS

MATERIALS & METHODS

Sample Size :

- Arm 1 (Study Arm) - 30 Patients
- Arm 2 (Control Arm) - 30 Patients

Randomization :

Simple Randomization.

Location, size, and extension of the primary tumor and the cervical lymph nodes are assessed by computed tomography (CT) scans.

Stages are assigned according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM 2018 staging system.

Patients are randomized using simple randomization, to receive concurrent chemoradiation of 66Gy in 33 fractions at 2 Gy per fraction over 6 weeks & 3 days with weekly Inj. Cisplatin 30 mg / m2 with either Cap. Celecoxib 100 mg twice daily oral (study group) or without (control group).

Treatment is to be delivered using a Telecobalt 60 machine in conventional 2D planning technique.

Patients are simulated and treated with a thermoplastic head and neck immobilization device.

Radiotherapy (Both Arms) :

Radiotherapy given in the form of **Phase I** to include the primary and the draining lymph node regions and a dose of ***40 Gy / 20 fractions / 4 weeks is delivered 5 days in a week at 2Gy / fraction*** (Monday to Friday).

In **phase II** off - cord reduction will be done, and a dose of **26 *Gy / 13 fractions / 2 weeks and 3 days at 2Gy / fraction*** is delivered 5 days in a week (Monday to Friday).

In two parallel opposed fields.

Chemotherapy (Both Arms) :

Inj CDDP (30 mg / m2) every week from Day 1 of RT along with proper pre - medications will be given for a ***total of 6 Cycles*** **.**

Study Arm (Arm 1) :

Cap. Celecoxib 100 mg twice daily oral is given on all days from day 1 of RT to till the end of course of radiotherapy.

Control Arm (Arm 2) :

Cap.Celecoxib 100 mg is not given.

Material & Methods	Arm 1 CCRT with Celecoxib	Arm 2 CCRT without Celecoxib
Drug	**Cap. Celecoxib 100 mg bid from Day 1 to till end of course on all days.**	**Nil**
Dosage	2 Gy / # Total 33 fractions	2 Gy / # Total 33 fractions
Duration	6 Weeks 3 days	6 Weeks 3 days
Total Dose	66 Gy (Off cord after 40 Gy)	66 Gy (Off cord after 40 Gy)
Chemo therapy & dosage	Inj.Cisplatin 40mg / m2	Inj.Cisplatin 40mg / m2
Duration	Weekly (6 cycles)	Weekly (6 cycles)
Investig--ations (Weekly)	CBC, RFT, LFT & Sr. Electrolytes	CBC, RFT, LFT & Sr. Electrolytes

Inclusion Criteria :

- Biopsy proven newly diagnosed locally advanced [stage III, IVA, & IV B] Squamous Cell Carcinoma of head and neck
- Primary tumor sites : Oral cavity, Oropharynx, Hypopharynx, Larynx
- ECOG Status : 1 - 2
- Karnofsky's performance score > 70
- Age - between 18 - 80 years
- Hemoglobin > 10gm %
- Total WBC count > 4000 / mm3
- Platelets > 1,00,000 cells / mm3
- Previously not exposed to any chemo or radiotherapy
- No major life threatening co - morbidities with normal or acceptable kidney, liver, and cardiovascular functions.

Exclusion Criteria :

- Non Squamous Histopathology.
- Tumors of Nasal cavity, Paranasal sinuses, Nasopharynx, Unknown Primary, Parotid and other Salivary Gland tumours.
- Deranged hepatic and renal functions (more than twice the upper limit), reduced bone marrow reserve.
- History of allergic reaction to NSAIDs
- Uncontrolled hypertension, gastrointestinal bleeding, and gastrointestinal ulcer.
- Presence of severe inflammatory bowel disease, or coagulation disorders.
- Any Previous Malignancies diagnosed or treated.
- Metastatic [Stage IV C] or recurrent disease.
- Pregnant and lactating women
- Inability to receive celecoxib or chemotherapy for any reason
- Patient not co - operating at any point in the treatment.
- Patients' refusal to participate in the trial or to sign on the consent form.

Investigation Details :

- Biopsy from the tumour lesion for histopathological confirmation
- Complete Blood Count
- Renal Function Test
- Liver Function Test
- Serum Electrolytes.
- Viral markers.
- CT scan Neck (From base of skull to Root of Neck) – Plain and Contrast pre - treatment and post treatment (after 6 weeks).
- Chest X ray – PA view,
- Bleeding time, Clotting time , INR and Occult Blood test.
- ECG and Echocardiogram
- Blood grouping
- Cardiology evaluation and fitness
- Dental evaluation

Data Collection and Methods :

- Pretreatment dental prophylaxis will be done.
- Eligible patients will be treated in the form of

Radiotherapy (Both Arms) :

- RT will be given in the form of **Phase I** to include the primary and the draining lymph node regions and a dose of ***40 Gy / 20 fractions / 4 weeks is delivered 5 days in a week at 2 Gy / fraction*** (Monday to Friday).
- In **phase II** off - cord reduction will be done, and a dose of **26 *Gy / 13 fractions / 2 weeks and 3 days at 2 Gy / fraction*** is delivered 5 days in a week (Monday to Friday).
- In two parallel opposed fields.

Chemotherapy (Both arms) :

Inj CDDP (30 mg / m2) every week from Day 1 of RT along with proper pre - medications will be given for a ***total of 6 Cycles.***

Study Arm (Arm 1) :

Cap.Celecoxib 100 mg twice daily oral is given on all days from day 1 of RT to till the end of course of radiotherapy.

Control Arm (Arm 2) :

Cap.Celecoxib 100mg is not given

Patients will be assessed clinically during treatment for toxicity and response. Also with CT Neck (From base of skull to root of neck) Plain & Contrast, 6 weeks after completing chemoradiation with or without celecoxib, for evaluating the locoregional response.

Efficacy in the form of Response assessment will be made both clinically and radiologically and response will be categorized as per RECIST criteria (version 1.1).

Safety assessment in the form of Acute toxicities (Hematological, Dermatitis and Mucositis) will be assessed from start of chemoradiation with or with celecoxib. Toxicities will be graded as per RTOG (Radiation Therapy Oncology Group) acute morbidity criteria.

Patients will be assessed as having complete, partial, static or progressive response.

Toxicity :

Complete blood count , RFT, LFT and serum electrolytes will be performed on a weekly basis. Acute toxicities will be assessed from the starting of treatment in both the arms. Toxicity assessment is made on

weekly basis during treatment, then on monthly basis and graded as per RTOG (Radiation Therapy Oncology Group) acute morbidity criteria and CTCAE (Common Terminology Criteria For Adverse Events) Version 5.0.

In the case of Hb less than 10 gm %, Absolute neutrophil count less than 1000 cells / µl or platelets less than 50,000 cells / µl , or in the case of any severe grade 3 or 4 toxicities, treatment will be interrupted until recovery.

Response Evaluation:

Patients are assessed both clinically and radiologically with CT Scan from the base of skull to root of Neck (plain & contrast) 6 weeks after completing chemo radiation in both the arms, for evaluation of locoregional response.. Response evaluation is done and categorized as per RECIST criteria (version 1.1)

Complete remission (CR) - No clinically detectable cancer is found after treatment.

Partial remission (PR) - Measurable tumor mass decreases by 50 % after

treatment, no new areas of tumor develop, and no area of tumor shows progression.

Minimal remission (MR) - is the same as partial remission, but the response does not meet the criteria of 50 % reduction.

Progression (PD) - The mass (product of diameters) of one or more sites of tumor increases more than 25 %, new lesions appear, or the patient dies as a result of the tumor.

Stable disease (SD) - Measurable tumor does not meet the criteria for CR, PR, MR, or progression

Follow up :

Patients will be assessed for disease status 6 weeks after the end of treatment and every month thereafter. During follow up, a thorough history, physical examination and a complete clinical examination will be done.

Analysis :

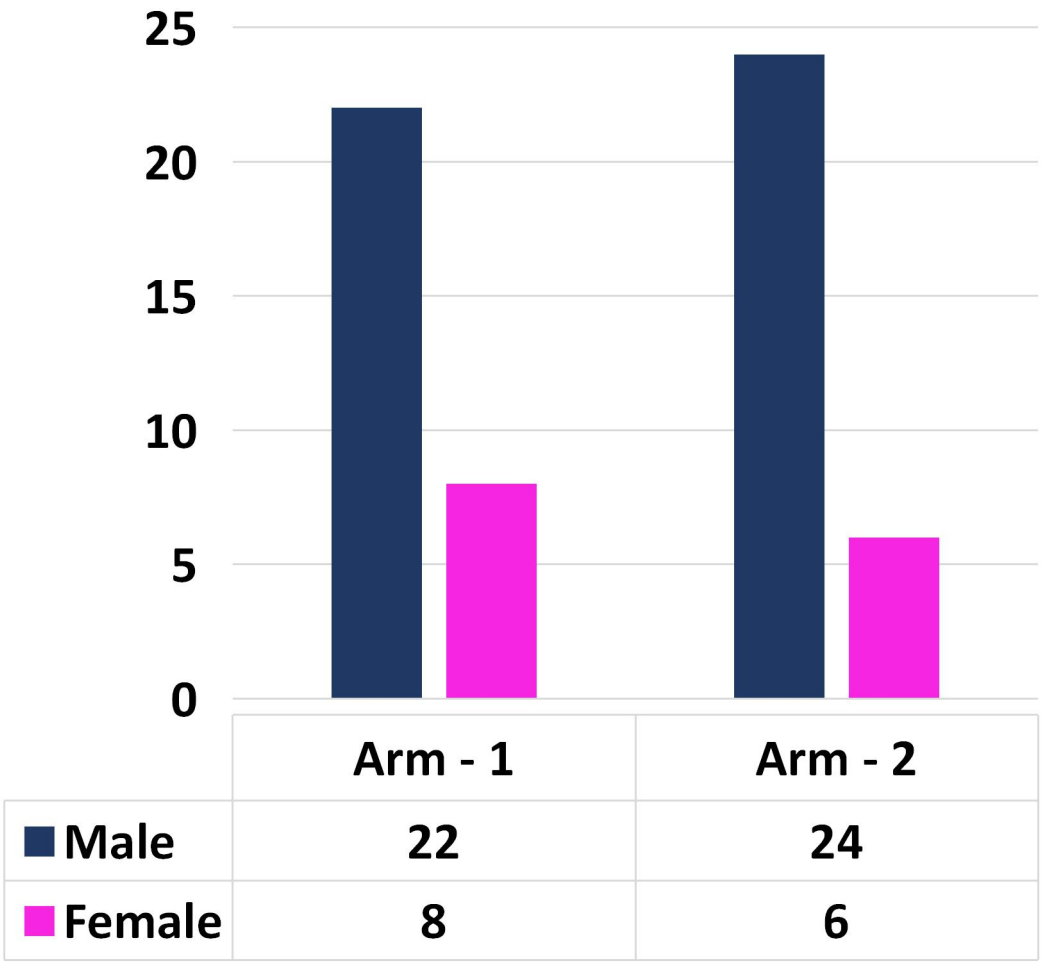
Patients will be assessed for immediate locoregional disease clinically at the end of course and after 6 weeks both clinically and radiologically. The toxicity of treatment and the factors affecting the treatment response will be analyzed.

RESULTS

RESULTS

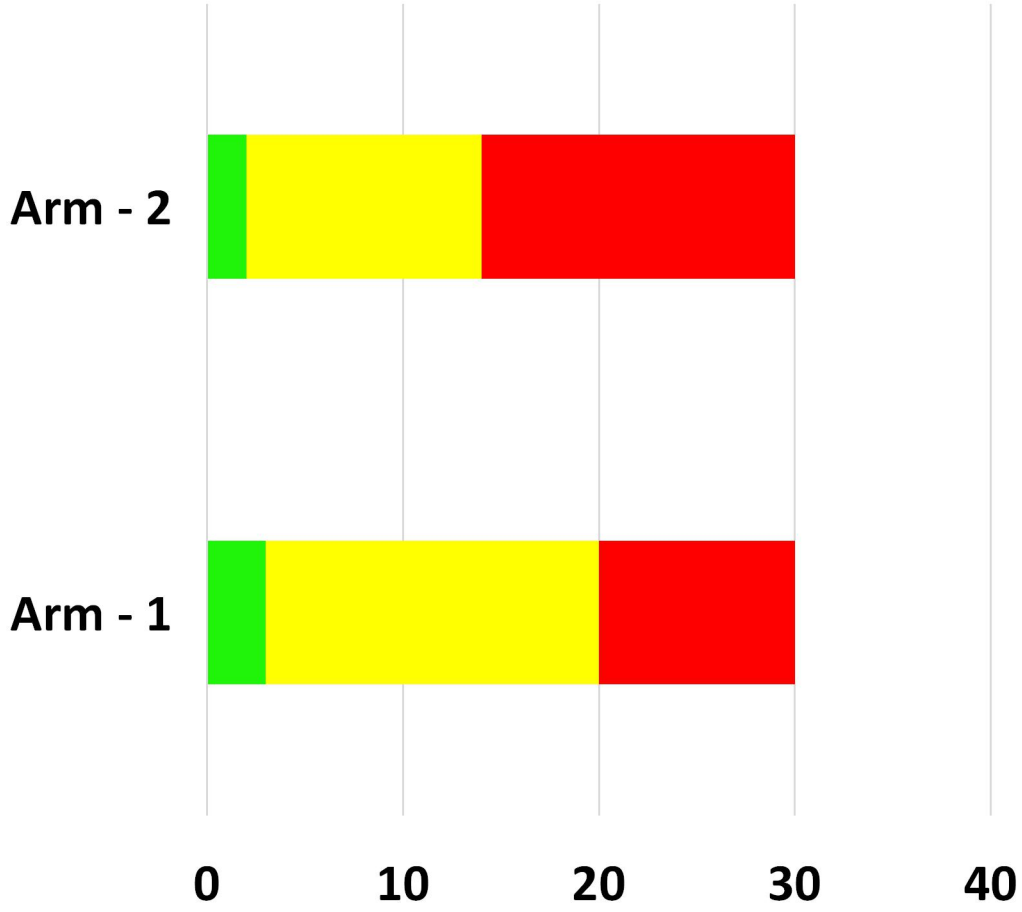
On analysis of the results observed in both arms, the following results were observed.

Sex Incidence:



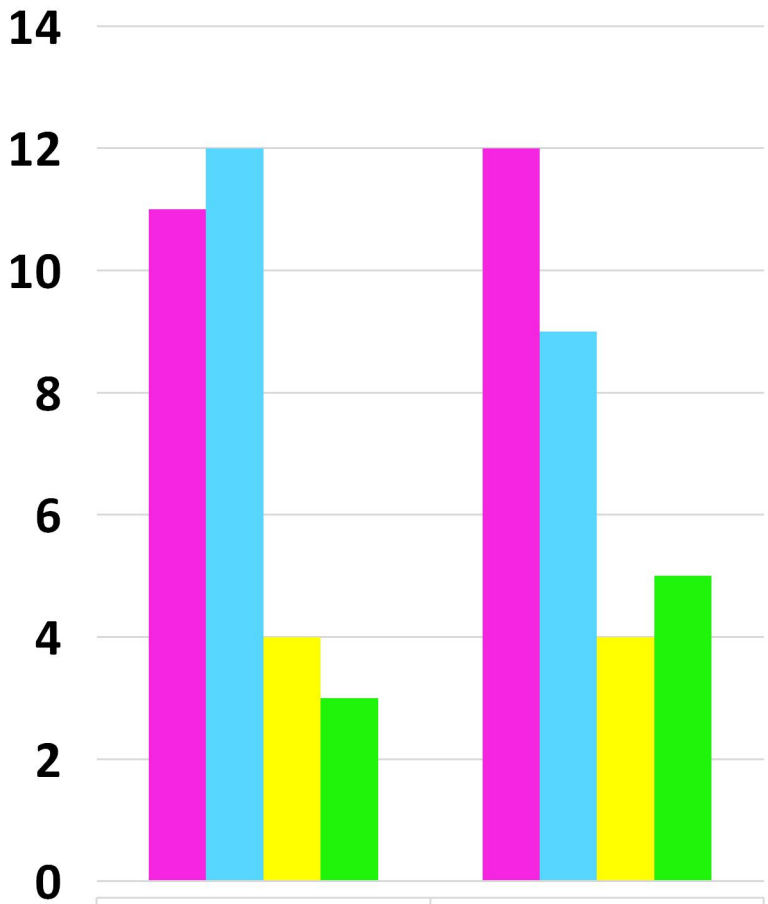
	Arm - 1	Arm - 2
Male	22	24
Female	8	6

Age Distribution :



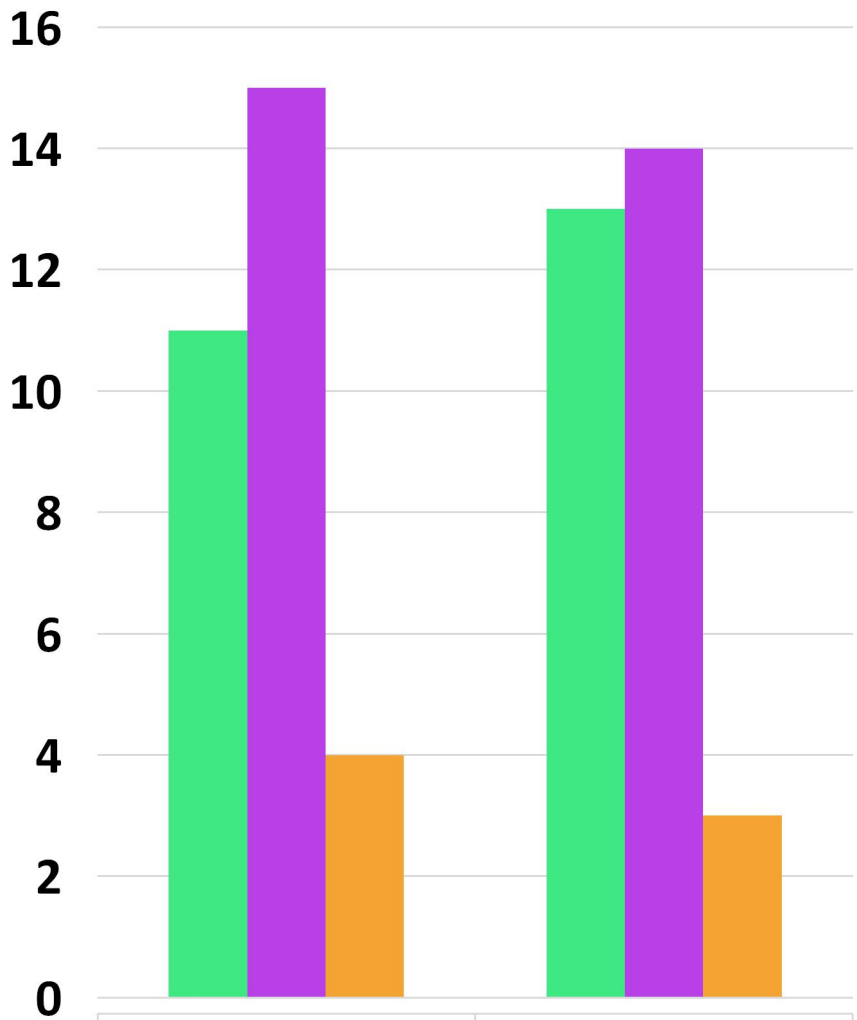
	Arm - 1	Arm - 2
18 - 40	3	2
40 - 60	17	12
> 60 yrs	10	16

Site wise distribution :



	Arm - 1	Arm - 2
Oral Cavity	11	12
Oropharynx	12	9
Hypopharynx	4	4
Larynx	3	5

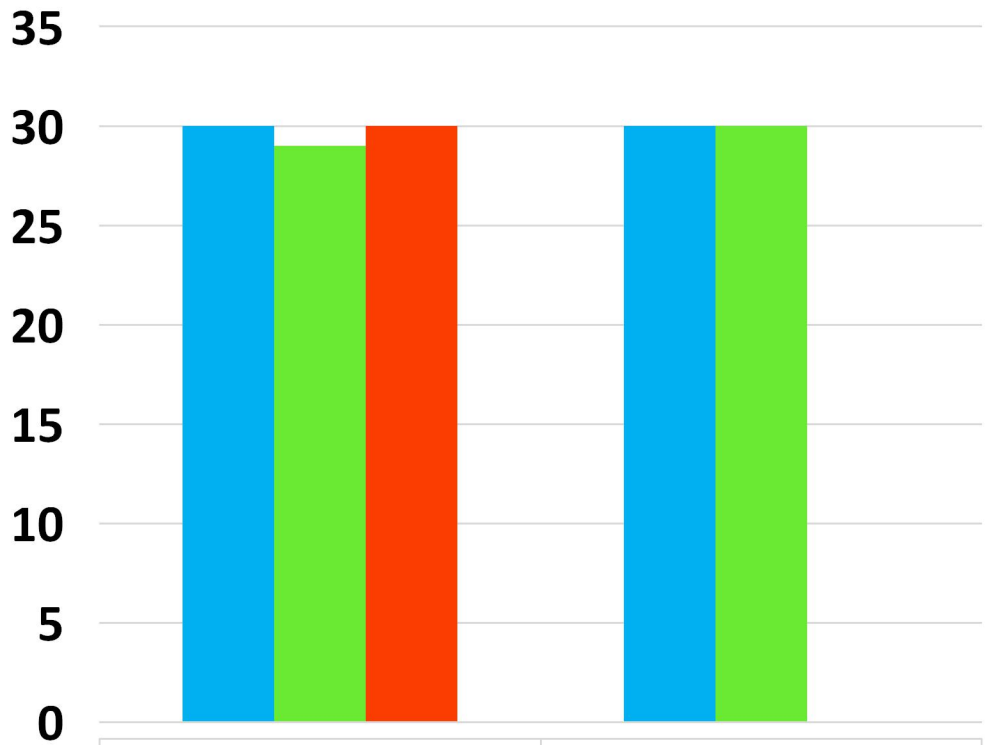
Stage wise Distribution :



	Arm - 1	Arm - 2
Stage III	11	13
Stage IVA	15	14
Stage IVB	4	3

Treatment Details :

One patient in Arm 1 could receive only 4 cycles of chemotherapy and further cycles deferred due to toxicity.



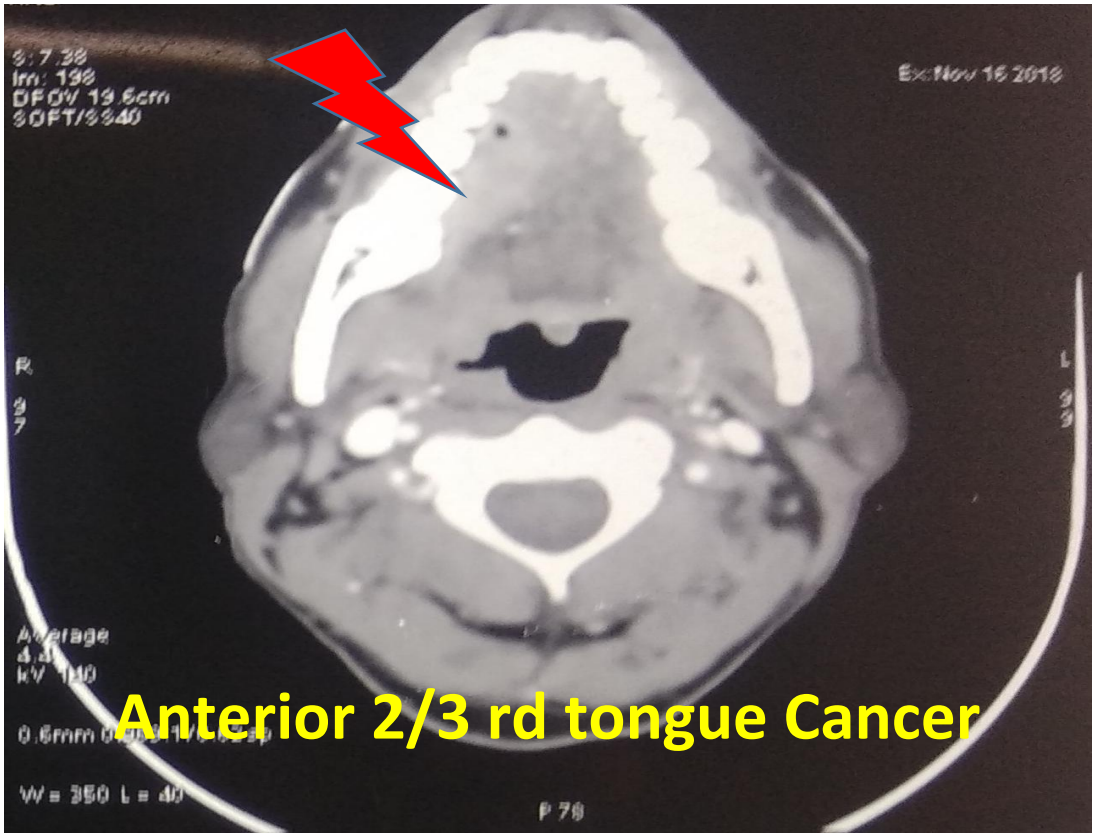
	Arm - 1	Arm - 2
RT	30	30
Chemo	29	30
Celecoxib	30	0

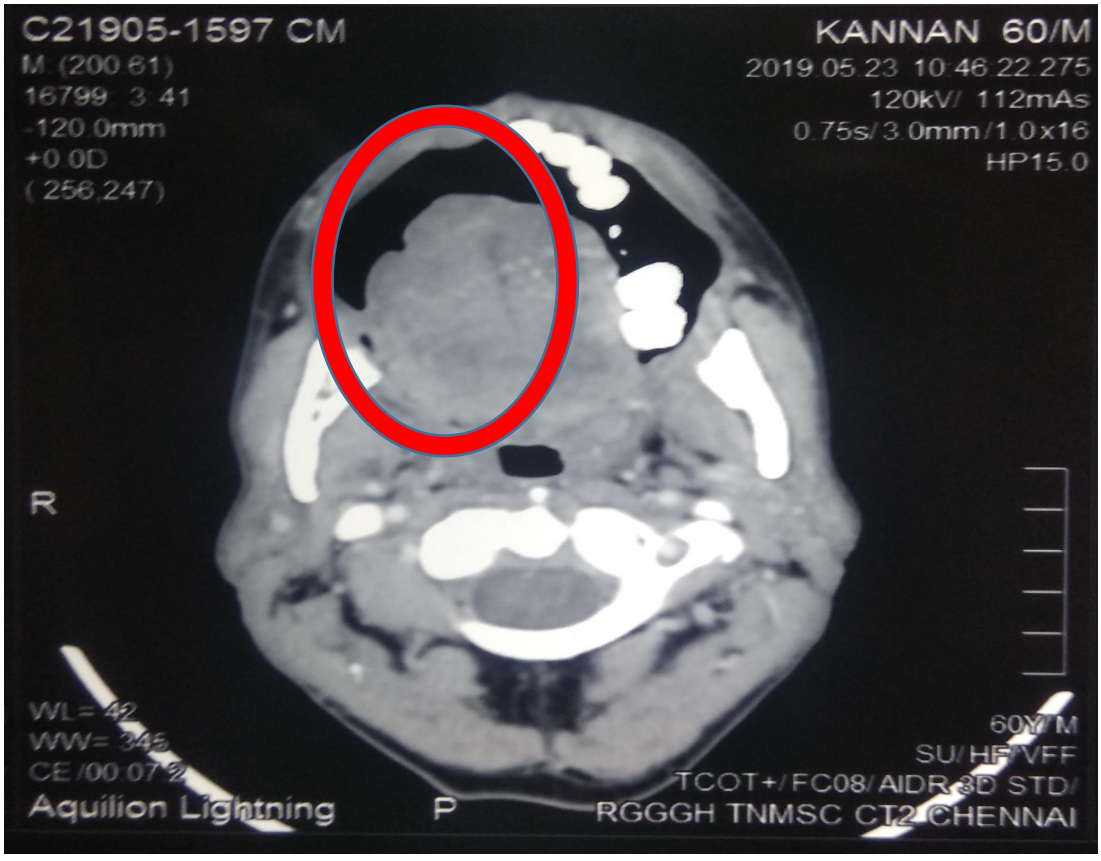
Tumour response :

In the study arm (Arm 1) of 30 patients, 19 (63.3 %) achieved Complete Response (CR), 9 (30 %) achieved Partial Response (PR) and 2 (6.7 %) had Stable disease compared to Control arm (Arm 2) with 13 (43.3 %), 16 (53.3 %) and 1 (3.4 %) having CR, PR and Stable disease respectively and no patients with disease progression were observed in both arms.

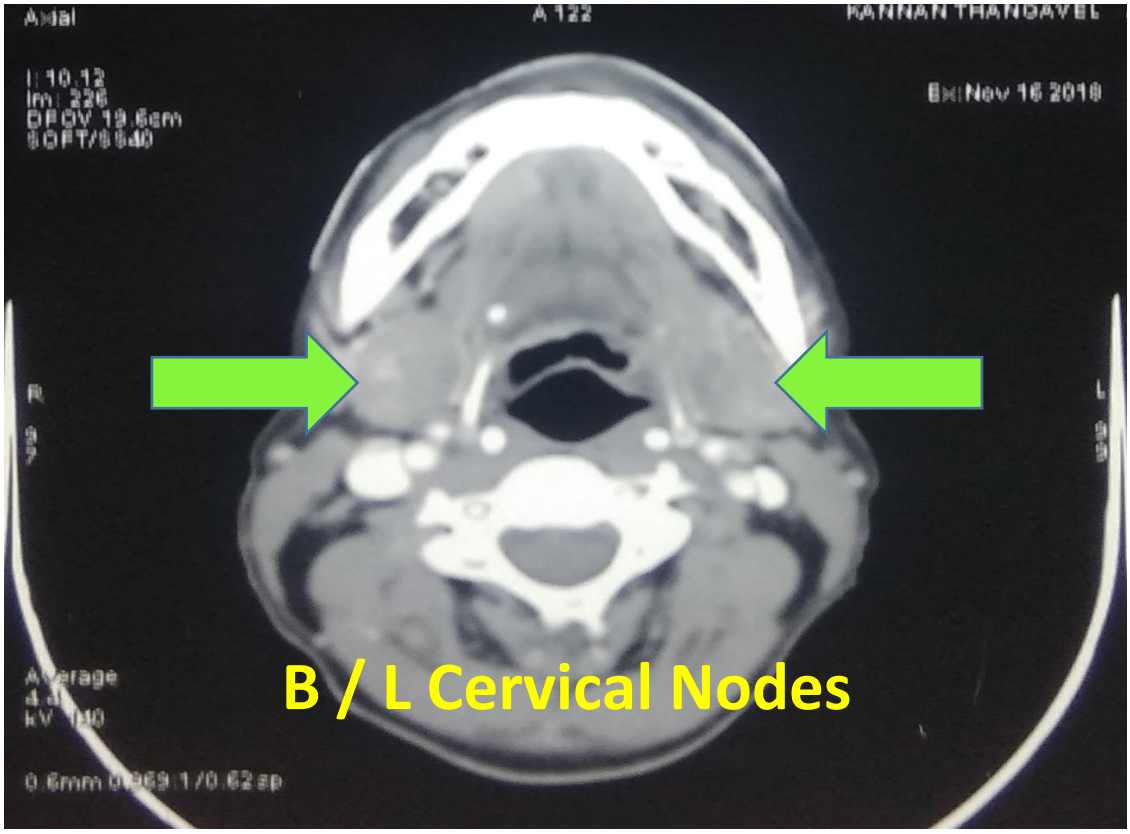
Response Evaluation	CR (%)	PR (%)	SD (%)	PD (%)
Arm - 1 30 Pts	19 (63.3%)	9 (30%)	2 (6.7%)	Nil
Arm - 2 30 Pts	13 (43.3%)	16 (53.3 %)	1 (3.4%)	Nil

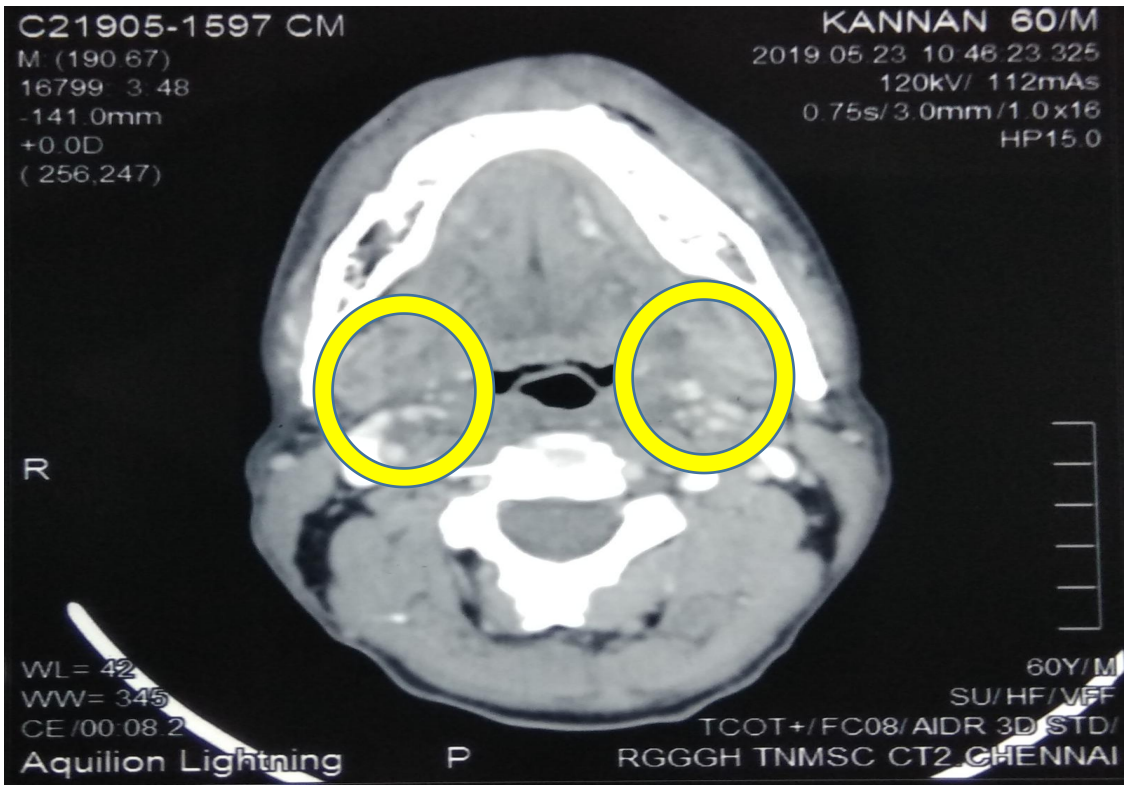
Tumour response CR (example) :





Nodal Response CR (example) :





Acute Toxicity :

The acute skin toxicity (Grade ≥ 2) and mucositis (Grade ≥ 2) were higher in Arm 1 than in Arm 2 (40 % vs 33.3 % and 80 % vs 73.3 % respectively).

Anorexia, nausea, vomiting, diarrhoea, and fatigue were also the treatment related toxicities in both groups.

Acute Toxicity RTOG criteria	Arm - 1	Arm - 2
Dermatitis (Grade≥2)	40%	33.3%
Mucositis (Grade≥2)	80%	73.3%

The patients in both the arms are in follow up to assess the late toxicity and overall survival .

CONCLUSION

CONCLUSION

Concurrent chemoradiation with weekly cisplatin is effective in locally advanced head and neck squamous cell carcinoma. The addition of celecoxib 100 mg twice daily to concurrent chemoradiation improved its effect on the response rates, with acceptable treatment - related toxicities.

DISCUSSION

DISCUSSION

Head and neck cancers constitute a substantial proportion of cancer patients in developing countries like India and most patients present with locally advanced disease. Locally advanced squamous cell carcinoma of head and neck (HNSCC), is treated by combined multimodality which includes surgery, radiotherapy, and chemotherapy.

The poor prognosis of locally advanced disease has led to increasing interests in exploring the use of novel antineoplastic agents in these patients. Cyclooxygenase - 2 (COX - 2) is one interesting potential target for the treatment.

COX - 2 enzyme overexpresses in many malignant tumors, and is associated with more aggressive tumor behavior and poor prognosis. Several preclinical studies on selective COX - 2 inhibitors, such as celecoxib, have shown that these agents have antitumor, antiangiogenesis, decreasing distant metastasis, inducing apoptosis and radiosensitizing effects.

In addition, there are evidences that COX - 2 inhibitors have been associated with significant reduction in vascular permeability and decrease in acute and chronic inflammation.COX - 2 enzyme

overexpresses in many different tumors, and its role in tumorigenesis, angiogenesis, transformation, and metastasis has been shown in several studies.

Many studies assessed the prophylactic role of COX - 2 inhibitors in various tumors, such as colon and breast cancer, and showed that non steroidal anti - inflammatory drugs and COX - 2 inhibitors decrease the incidence of colon and breast cancer via inhibiting cyclooxygenase - 1 and - 2 enzymes.

Lee *et al*. showed that COX - 2 enzyme was overexpressed in cultured cells of squamous cell carcinoma of the head and neck, when compared with normal cells. The authors concluded that COX - 2 inhibitors significantly decreased cell growth and increased apoptosis in cultured cells.

This study and several others have shown that COX - 2 inhibitors may have chemopreventive and therapeutic effects in squamous cell carcinoma of the head and neck.

In another study, Soo *et al*. found celecoxib 400 mg twice daily for 14 days reduced microvessel density and induced changes in gene expression in patients with newly diagnosed, untreated nasopharyngeal carcinoma.

In addition, several studies found that COX - 2 inhibitors significantly enhanced the response of tumor cells to radiotherapy. The exact mechanism(s) responsible for the antiproliferative effect of COX - 2 inhibitors remains to be defined; however, antiangiogenic effects of COX - 2 inhibitors seem to be mainly responsible for increasing the antitumor effects of ionizing radiation. Therefore, COX - 2 inhibitors have a potential role for improving response to radiotherapy.

Celecoxib has been progressively used in clinical studies for improving the response to therapy in many cancers. This study is aimed to determine the efficacy and safety of concurrent chemoradiation with weekly cisplatin ± celecoxib 100 mg twice daily in locally advanced head and neck squamous cell carcinoma.

COX -2 is extensively expressed in cells involved in inflammation and is upregulated by bacterial lipopolysaccharides, cytokines, growth factors and tumour promoters.

Celecoxib, a COX - 2 selective NSAID used to treat pain and inflammation, is also used to decrease (33 to 45 %) the risk of colorectal adenomas in FAP. It binds to Cadherin - 11, which may explain the reduction in cancer progression.

American Heart Association has recommended Celecoxib only in the lowest dose and shortest duration. In this study it is used in low dose

only and all patients received drug for a median duration of 45 - 50 days. No patient developed any coronary or cerebrovascular events.

No patient had deranged renal function, inspite of combining celecoxib and cisplatin, both being nephrotoxic drugs may be possibly due to reduced dosage of both drugs and reduced duration of celecoxib intake.

It costs a additional amount of rupees 700 to 800 per patient.

Analysis Plan :

On Intention to treat (ITT) basis.

Sponsorship (Yes/ No) :

NO

Conflict of Interest :

NO

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ANNEXURES

Annexure I

Zabrod / ECOG Status :

0 - Fully active, able to carry on all predisease activities without restriction (Karnofsky 90 - 100)

1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; for example, light housework, office work (Karnofsky 70 - 80)

2 - Ambulatory and capable of all self - care but unable to carry out any work activities; up and about more than 50 % of waking hours (Karnofsky 50 - 60)

3 - Capable of only limited self - care, confined to bed or chair 50 % or more of waking hours (Karnofsky 30 - 40)

4 - Completely disabled; cannot carry on self - care; totally confined to bed or chair (Karnofsky 10 - 20)

5 - Death (Karnofsky 0)

Annexure II

IEC Approval Form :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.**T.RETHINESH KUMAR,**
MDRT Post Graduate
Department of Radiation oncology,
Rajiv Gandhi Govt.General Hospital,
Madras Medical College,
Chennai-600003.

Dear Dr. T.RETHINESH KUMAR

The Institutional Ethics Committee has considered your request and approved your study titled **"EFFICACY AND SAFETY OF LOW DOSE CELECOXIB WITH CHEMORADIATION IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA"-NO.25012019.**

The following members of Ethics Committee were present in the meeting held on **08.01.2019** conducted at Madras Medical College, Chennai 3

1. Prof.P.V.Jayashankar :Chairperson
2. Prof.R.Jayanthi,MD.,FRCP(Glasg) Dean,MMC,Ch-3 : Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3 : Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch : Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3 : Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC : Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH : Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai : Member
9. Prof. S. Purushothaman, Associate Professor of Pharmacology, MMC,Ch-3 : Member
10. Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3 : Member
11. Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3: Member
12. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
13. Tmt.Arnold Saulina, MA.,MSW., :Social Scientist
14. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Annexure III

INFORMATION TO PARTICIPANTS

Title : **" Efficacy and Safety of Concurrent Chemoradiation with Weekly Cisplatin and Low-Dose Celecoxib in Locally Advanced Head and Neck Squamous Cell Carcinoma "**

Name of Participant :

Name of the Principal (Co- investigator) **: Dr.T.RETHINESH KUMAR**

Name of the institution **: Department of Radiation Oncology,**

RGGGH, MMC.

You are invited to take part in this research / study / procedures / tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

- Head and neck cancers constitute a substantial proportion of cancer patients in developing countries like India.
- Most patients presenting with Locally advanced squamous cell carcinoma of head and neck (HNSCC), are treated by combined

multimodality which includes surgery, radiotherapy, and chemotherapy.

- The poor prognosis of locally advanced disease has led to increasing interests in exploring the use of novel antineoplastic agents in these patients. Cyclooxygenase - 2 (COX - 2) is one interesting potential target for the treatment.
- COX - 2 enzyme overexpresses in many malignant tumors, and is associated with more aggressive tumor behavior and poor prognosis. Several preclinical studies on selective COX - 2 inhibitors, such as celecoxib, have shown that these agents have antitumor, antiangiogenesis, decreasing distant metastasis, inducing apoptosis and radiosensitizing effects. .
- In addition, there are evidences that COX - 2 inhibitors have been associated with significant reduction in vascular permeability and decrease in acute and chronic inflammation. COX - 2 enzyme overexpresses in many different tumors, and its role in tumorigenesis, angiogenesis, transformation, and metastasis has been shown in several studies.
- Many studies assessed the prophylactic role of COX - 2 inhibitors in various tumors, such as colon and breast cancer, and showed that nonsteroidal anti - inflammatory drugs and COX - 2 inhibitors

decrease the incidence of colon and breast cancer via inhibiting cyclooxygenase - 1 and - 2 enzymes.

- In addition, several studies found that COX - 2 inhibitors significantly enhanced the response of tumor cells to radiotherapy. The exact mechanism(s) responsible for the antiproliferative effect of COX - 2 inhibitors remains to be defined; however, antiangiogenic effects of COX - 2 inhibitors seem to be mainly responsible for increasing the antitumor effects of ionizing radiation. Therefore, COX - 2 inhibitors have a potential role for improving response to radiotherapy

STUDY DESIGN:

- Pretreatment dental prophylaxis will be done.
- Eligible patients will be treated in the form of

Radiotherapy (Both Arms) :

- RT will be given in the form of **Phase I** to include the primary and the draining lymph node regions and a dose of ***40 Gy / 20 fractions / 4 weeks is delivered 5 days in a week at 2 Gy / fraction*** (Monday to Friday).

- In **phase II** off - cord reduction will be done, and a dose of **26 *Gy / 13 fractions / 2 weeks and 3 days at 2 Gy / fraction*** is delivered 5 days in a week (Monday to Friday).
- In two parallel opposed fields.

Chemotherapy (Both arms) :

Inj CDDP (30 mg / m2) every week from Day 1 of RT along with proper pre - medications will be given for a ***total of 6 Cycles*** **.**

Study Arm (Arm 1) :

Cap.Celecoxib 100 mg twice daily oral is given on all days from day 1 of RT to till the end of course of radiotherapy.

Control Arm (Arm 2) :

Cap.Celecoxib 100mg is not given

We want to assess the " **Efficacy and Safety of Concurrent Chemoradiation with Weekly Cisplatin and Low - Dose Celecoxib in Locally Advanced Head and Neck Squamous Cell Carcinoma "** .We have obtained permission from the Institutional Ethics Committee.

The study design :

Double arm prospective study

Study Procedures :

The study involves evaluation of the **Efficacy and Safety of Concurrent Chemoradiation with Weekly Cisplatin and Low-Dose Celecoxib in Locally Advanced Head and Neck Squamous Cell Carcinoma** . Every week before RT and weekly chemotherapy, the study physician will examine you. Some [blood / urine / clinical examination other] tests will be carried out at each visit. [… … ml of blood will be collected at each visit. Blood collection involves prick with a needle and syringe.] These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.

In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document.

You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and / or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical

examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment / discontinuing of procedures etc.

Signature of Investigator Signature of Participant

Date Date

Annexure IV

INFORMED CONSENT FORM

TITLE OF THE STUDY: **Efficacy and Safety of Concurrent Chemoradiation with Weekly Cisplatin and Low-Dose Celecoxib in Locally Advanced Head and Neck Squamous Cell Carcinoma**

Name of the Participant:

Name of the Principal (Co – Investigator): **Dr.T.RETHINESH KUMAR**

Name Of The Instituition : MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in : **Efficacy and Safety of Concurrent Chemoradiation with Weekly**

Cisplatin and Low-Dose Celecoxib in Locally Advanced Head and Neck Squamous Cell Carcinoma

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him / her immediately if I suffer unusual symptoms. *****
8. I have not participated in any research study within the past 12 month(s). *****
9. I agree to under go complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck

10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understood that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for illiterate patients) :

Name _____ Signature_____

Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent

Name _____ Signature_____

Date_____

CERTIFICATE

This is to certify that the dissertation entitled **" Efficacy and Safety of Low Dose Celecoxib with Chemoradiation in Locally advanced Head and Neck Squamous Cell Carcinoma "** of the candidate **Dr. RETHINESH KUMAR . T** with the **Registration Number : 201819003** for the award of **M.D Degree** in the **Branch of Radiotherapy** is personally verified by me in the urkund.com website for the purpose of plagiarism check.

I found that the uploaded thesis file containing from Introduction to Conclusion pages is checked for plagiarism and the result shows **13 %** of Plagiarism in the Dissertation.

Guide & Supervisor Sign with Seal