CONCOMITANT BOOST IRRADIATION WITH WEEKLY LOW DOSE CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEADANDNECK

Institution

DEPARTMENT OF RADIOTHERAPY
MADRAS MEDICAL COLLEGE &
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CERTIFICATE

This is to certify that Dr. S. SELVALAKSHMI has been a Post Graduate MD Student during the period from May 2014 to April 2016 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled "CONCOMITANT BOOST IRRADIATION WITH WEEKLY LOW DOSE CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK" is a bonafide work done by her during her study period and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch IX Radiotherapy examination.

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DECLARATION

I solemnly declare that the dissertation titled **"CONCOMITANT BOOST IRRADIATION WITH WEEKLY LOW DOSE CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK"** a SINGLE ARM PROSPECTIVE STUDY was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during **January 2015 to August 2015** under the guidance and supervision of Prof. Dr.S. SHANMUGAKUMAR.

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CONTENTS

CONCOMITANT BOOST IRRADIATION WITH WEEKLY LOW DOSE CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEADANDNECK

Dr.S.SELVALAKSHMI*; Prof.Dr.S.Shanmugakumar; Prof.Dr.N.V.Kalaiyarasi;

Dr.Baskar, Dr.Madhumathi, Dr.Sundaresan, Dr.Prabakaran. Dr.Sanjal, Dr.Karthick

INTRODUCTION:

65% patients with head and neck tumors present with locally advanced disease. Concurrent chemo radiotherapy is a treatment program for locoregionally advanced squamous cell carcinomas of the head and neck with established benefits in both organ preservation and survival.

AIMS AND OBJECTIVES:

To assess the immediate locoregional response rates of locally advanced squamous cell carcinomas of the head and neck treated with concomitant boost radiotherapy and chemotherapy using low dose weekly cisplatin and paclitaxel. To assess acute toxicity to the treatment.

MATERIALS AND METHODOLOGY:

Single arm prospective study with 30 consecutive patients with locally advanced head and neck cancer presented to the department of radiotherapy, Madras medical college, Chennai.

All patients were treated with Radiotherapy using concomitant boost 45gy/1.8gyper# /25# - 5 weeks ,22.5gy/ 1.5gy per# /15# given as a boost only to small field including primary and involved node at an interval of 6 hrs during last 3 weeks of treatment along with weekly CDDP and low dose PACLITAXEL.

RESULTS:

Among 30 patients, Ca Oropharynx was 9 patients, followed by Ca Hypopharynx 8 patients, Ca Oral cavity with 5 patients and Ca Supraglottis 8 patients. 83% of patients had complete response and 17% had partial response. Toxicities observed in the study were Mucositis grade 3 in 6 patients and grade 4 in 1 patients; Skin reactions grade 3 in 2 patients. Leucopenia grade 1 in 4 patients grade 2 in 3 patients. There was no renal toxicity in this study. There was no treatment related deaths in this study.

CONCLUSION: Concomitant Boost Irradiation with weekly low dose chemotherapy in locally advanced squamous cell carcinoma of head and neck cancer is better regimen with manageable toxicity with higher complete response.

Keywords: concurrent chemoradiation, concomitant boost, cisplatin, paclitaxel

INTRODUCTION

The term “Head and Neck cancer” refers to neoplasms arising from below the base of the skull to the region of thoracic inlet. Majority among the head and neck malignancies arise from the different anatomic subsites and air spaces within this region. Most of the lesions arise from the upper respiratory and digestive tracts. Since the Head and neck is responsible for various important functions such as vision, taste, hearing, smell, deglutition, and breathing, various malignancies can jeopardize these functions. This is also the most visible part of the individual’s physical appearance and therefore the cosmetic disturbance affects the person both mentally and physically. The management of the Head and neck cancer is therefore an important aspect of oncology in India.

As the life expectancy of the population rises, there is an increasing incidence in the trend of cancer in the world. They pose a significant health problem especially in developing countries, including India. Due to high exposure to smokeless and smoke tobacco among Indian people, head and neck cancers in India

continues to be a major public health problem and it causes significant morbidity and mortality.

Head and neck region cancers represent a heterogeneous group of cancers arising from the mucosa of upper aerodigestive organs, lined by squamous epithelium. It comprises the cancers in the following anatomical regions, nasalcavity, nasopharynx, oral cavity, oropharynx, hypopharynx, the larynx, the salivary glands and the paranasal sinuses.

EPIDEMIOLOGY

The Head and neck cancers comprises 5% of all the malignancies worldwide.[1] The geographical distribution of head and neck cancers varies significantly among different parts of the world. In western Europe and USA the incidence is relatively low. The incidence is high in the countries of South East Asia , parts of Africa and South America. The overall male to female ratio is 4;1. It usually occurs in the 5th decade and above, except for salivary gland tumours and nasopharyngeal tumours which tend to occur commonly in younger age group.

GLOBAL INCIDENCE

Overall, head and neck cancer constitutes more than 550,000 cases annually worldwide.[2] Head and neck cancer incidence is

about 3% of all cancers in the United States. In the current year, approximately 59,340 people (43,390 men and 15,950 women) will develop head and neck cancer. It is also calculated that 12,290 deaths (8,900 men and 3,390 women) will occur this year. The laryngeal cancer incidence is , but not oral cavity and pharyngeal cancer, is approximately 50 percent higher in African American men. To draw the world's attention on effective care and control on head and neck cancer**,** the International Federation of Head and Neck Oncologic Society proposed **27th July as the World Head and Neck Cancer Day.**

INDIAN SCENARIO

Head and Neck Cancer is one of the leading cause of death and disability in India, while oral cancer is the most common malignancy of all head and neck cancers and is the primary cause of cancer related deaths in India in men. India has an increase in the incidence of head and neck cancers. Infact, they are among the top cancers affecting men and are the third most common cancers affecting women. Since 90% of these tumours are related to risk factors such as tobacco, alcohol and areca-nut usage, they are highly preventable.

TAMILNADU SCENARIO

In southern India, the common cancers among male were found to be stomach, oral, esophagus and leukemia whereas females were mainly affected by cervix, breast, oral and esophageal cancers. In Tamilnadu, MMTR states that most common cancer in men is head and neck cancer (19.23%) followed next by stomach cancer (13.98%) and lung cancer (12.46%). In women, breast cancer is the most common (20.87%) followed by cervical cancer (11.46%), stomach cancer (8.11%) and head and neck cancer (7.53%).

In our institute Barnard Institute of Radiology & Oncology, head and neck cancers constitute the majority of cases registered in our OPD. Majority of them are squamous cell carcinomas (~95%) with other histologies making up the remaining. Nearly 75% of them present in the locally advanced stage. Only around 20 to 25% of the cases present in the early stages. Most of them belong to poor socioeconomic status, tobacco users either in smoked form such as cigarettes, beedis or non-smoked forms such as pan etc.

RISK FACTORS

TOBACCO

Tobacco use remains one of the leading causes of death worldwide. Data from the Global Adult Tobacco Survey (GATS), which conducted representative household surveys in 14 low- and middle-income countries such as Bangladesh, Brazil, China, Egypt, India, Mexico, Philippines, Poland, Russia, Thailand, Turkey, Ukraine, Uruguay, and Vietnam), suggest 41% of men and 5% of women across these countries currently smoke. [3] Among youth, there is some evidence of growth in use of other forms of tobacco (e.g., cigars, water pipes, electronic cigarettes) in 2011 to 2012 that may be displacing cigarette use.[4]

A common index of cancer risk is pack-years, or the number of packs of cigarettes smoked per day multiplied by the number of years smoked in the lifetime. In general, the higher the number of pack-years, the greater the cancer risk. The level of tobacco exposure is ultimately driven by use behaviors, including the number of cigarettes smoked, the patterns of smoking on individual cigarettes, and the number of years smoked. The primary driver of smoking behavior is **nicotine,** the major addictive substance and primary reinforcer of continued smoking. Nicotine is metabolized

primarily to cotinine, which is further metabolized to trans-3â€²-hydroxycotinine (3HC), catalyzed by the liver cytochrome P450 2A6 enzyme. The ratio of 3HC to cotinine in plasma or saliva can be used as a reliable noninvasive phenotypic marker for CYP2A6 activity. CYP2A6 activity is known to vary across racial/ethnic groups, with those of African or Asian descent showing slower metabolism than those of Caucasian descent.[5] In these analyses, the N-nitrosamines, benzene, 1,3-butadiene, aromatic amines, and cadmium often rank highly. Smokeless products available in India are often far higher in nitrosamines. PAH and nitrosamines are also likely to be implicated in cancers along the respiratory tract and the cervix. Smoke carcinogens are known to cause G:A and G:T mutations, and mutations in the *KRAS* oncogene and the *P53* tumor suppressor gene are strongly associated with tobacco-caused cancers.[6]

SMOKELESS TOBACCO

Globally there is a 60% increase in alternative nicotine delivery systems like snuff, lozenges. Betel quid is extensively used in India. It is also called as*pan* which consists of pieces of areca nut, tobacco and slaked lime. Added to this are

spices,cardamom,cloves,according to the localpreferences and are varyingly called as *gutkha, zarda, mawa, khaini.*

HUMAN PAPILLOMA VIRUSES

Viral infections are estimated to play a causal role in at least 11% of all new cancer diagnoses worldwide. A vast majority of cases (>85%) occur in developing countries, where poor sanitation, high rates of cocarcinogenic factors such as HIV/AIDS, and lack of access to vaccines and cancer screening all contribute to increased rates of virally induced cancers. A common feature of DNA viruses that depend on host cell DNA polymerases for replication (e.g., papillomaviruses, herpesviruses, and polyomaviruses) is the expression of viral gene products that promote progression into the cell cycle. A typical mechanism of direct oncogenic effects is through the **inactivation of tumor suppressor proteins,** such as the guardian of the genome, p53, and retinoblastoma protein (pRB). This effectively primes the cell to express the host machinery necessary for replicating the viral DNA.

Many of the tumors found in nonsmokers were found to have wild-type p53 genes, raising the possibility that the tumor might be dependent on a p53-suppressing viral oncogene (as seen in cervical cancer). Gillison and colleagues went on to show that nearly half of

all tonsillar cancers contain HPV DNA, most commonly HPV16. Interestingly, HPV-positive oropharyngeal cancers tend to be less lethal than tobacco-associated HPV-negative tumors. This finding has important considerations for treatment of HPV-positive head and neck cancers.[7] Recent studies suggest an ongoing increase in the incidence of HPV-associated cancers of the tonsils and the base of the tongue. By 2025, the number of new HPV-induced head and neck cancer cases in the United States is expected to roughly equal the number of new cervical cancer cases. Based in part on these observations, the U.S. Centers for Disease Control and Prevention recommends that boys, in addition to girls, should be vaccinated against high-risk HPVs.

HPV-positive oropharyngeal cancers show improved response to therapy when compared to HPV-negative cancers of the same site.[8] Patients presenting with HPV-positive oropharyngeal cancers also tend to be younger, healthier, and have a much lower frequency of smoking and alcohol abuse. However, some studies have shown that a history of smoking in patients with HPV-positive oropharyngeal cancer may increase the likelihood of recurrence or metastasis after treatment. This has prompted many to consider

reducing the intensity of treatment to decrease treatment-related morbidity.

GENETIC FACTORS

The genes associated with an inherited predisposition to head and neck cancer include the master regulator, *TP53* (Li-Fraumeni syndrome),- and Fanconi anemia genes, the *FANC* family of DNA repair genes that are inturn associated with the development of HNSCC.[9] Head and neck cancers arising in young patients and others that are independent of tobacco exposure provide a rich area for an in-depth molecular assessment to determine the underlying genetic factors.

OTHER FACTORS

The effects of alcohol and tobacco seems to be additive. It might also mediate through common malnutrition and vitamin deficiency. Alcohol intake increases the risk by 2 to 6 fold.

The inhalation of dusts and chemical constituents give rise to cancer of nasal cavity and paranasal sinuses. Occupational exposure to wood dust, textile fiber, nickel and radium also predispose to cancer.

Low socioeconomic status leading to improper nutrition and poor vitamin intake are associated with higher risk of head and neck cancer. It is known that vitamins such as Retinoic acid are important in preventing the occurrence of cancer in the upper aerodigestive tract. Other factors include poor orodental hygiene, ill fitting dentures etc.

HISTOPATHOLOGY

Most head and neck malignant neoplasms arise from the surface epithelium and are **squamous cell carcinoma** (SCC) or one of its variants, including lymphoepithelioma, spindle cell carcinoma, verrucous carcinoma, and undifferentiated carcinoma. Lymphomas and a wide variety of other malignant and benign neoplasms make up the remaining cases. Head and neck squamous cell carcinoma (HNSCC) accounts for 90% of all malignant disease in the head and neck region of the body.

Lymphoepithelioma is an SCC with a lymphoid stroma and occurs in the nasopharynx, tonsillar fossa, and base of tongue; it may also occur in the salivary glands. In the spindle cell variant, there is a spindle cell component that resembles sarcoma intermixed with SCC. It is generally managed like other high-grade SCCs.

Verrucous carcinoma is a low-grade SCC found most often in the oral cavity, particularly on the gingiva and buccal mucosa. It usually has an indolent growth pattern and is often associated with the chronic use of snuff or chewing tobacco. Small cell neuroendocrine carcinoma occurs rarely throughout the head and neck.

CLINICAL FEATURES

Oral ulceration, unusual bleeding in the mouth,sore throat, dysphagia, hoarseness of voice, otalgia, growth in tongue, pain, numbness of the face,dyspnea, difficulty in speaking or opening the mouth and headache are the varied symptomatology at presentation.

DIAGNOSTIC WORKUP

- History and Physical Examination
- Biopsy from the lesion
- Pan Endoscopy
- Contrast Enhanced CT scan from base of skull to root of neck **or** MRI to know the extent of the disease and involvement of lymphnodes.
- CBC, RFT , LFT , BLOOD GROUPING AND TYPING

❖ Viral Markers

❖ Chest X RAY

Patients with N3 neck disease, as well as those with N2 disease with nodes below the level of the thyroid notch, have a 20% to 30% risk of developing distant metastases and are considered for a chest CT or positron emission tomography (PET).

PROGNOSTIC FACTORS

Prognosis of patients with head and neck cancers depends most importantly on the stage of the disease at presentation. Involvement of nodes in head and neck cancers upgrades it to stage III and also the survival of these patients is decreased by as much as 50 %. Involvement of regional lymph nodes and also advanced T stages have higher incidence of locoregional recurrences and also distant metastasis. They also require multimodality treatment than the early stage cancers in which single modality will achieve cure in more than 90% of cancers. Even with these aggressive approaches more than 50 – 60% will fail the treatment and have local recurrences and in the rare cases develop distant metastasis. Death in such cases are usually due to locoregional recurrences.

TREATMENT OVERVIEW

Most of the cases present in locally advanced stage in developing countries like India because of poor socio economic status, illiteracy, increased use of tobacco , and inadequate screening and early detection. Therefore multimodality treatment is the best option foe treating squamous cell carcinoma of head and neck. The sequencing of the modalities depend on the tumour stage,

Bulk of the disease, performance status of the patient. Commonly used modalities are

1)Surgery followed by RT / ChemoRT.

2)Chemoradiation followed by surgery

3)Induction chemotherapy followed by concurrent chemoRT.

4)Defnitive radiotherapy with targeted agents.

SURGERY

The advantages of surgery compared with RT, assuming similar cure rates, may include the following:

1) tumour with adequate clearance is alone removed

2) the treatment time is shorter,

3) the risk of immediate and late RT sequelae is avoided, and

4) RT is reserved for a head and neck second primary tumour , which may not be as suitable for surgery

Different types of surgical procedures in the treatment of head and neck cancers include wide local excision with adequate clearance, partial or total glossectomy, composite resection with flap reconstruction, total laryngopharyngectomy, segmental or marginal mandibular resection with or without mandibular reconstruction using fibula. Surgery remains the main modality for nasal cavity and paranasal tumours, major and minor salivary gland tumours, and thyroid malignancies whereas radiotherapy still plays the major role in the management of ca nasopharynx.

NECK NODES MANAGEMENT

The neck node dissection is of many types which depend mainly on the clinically positive or negative nodes, the presence of ipsilateral or contralateral nodes, levels of nodes involved, presence of extracapsular extension, the primary site with preponderance of nodes.

TYPES OF NECK DISSECTION

In a classic ***radical neck dissection***, the superficial and deep cervical fascia with its enclosed lymph nodes (levels I to V) is

removed in continuity with the sternocleidomastoid muscle, the omohyoid muscle, the internal and external jugular veins, cranial nerve XI, and the submandibular gland. The radical neck dissection can be *modified* to spare certain structures with the intent of decreasing morbidity and improving functional outcome without compromising disease control. There are three main types of **modified radical neck dissections**

Type I, CN XI is spared;

Type II, CN XI and the internal jugular vein are spared; and

Type III (functional), CN XI, the internal jugular vein, and the sternocleidomastoid muscle are spared.

Selective **neck dissections** are more limited and include the resection of lymph node levels that are at greatest risk for nodal metastatic spread. Examples include the lateral, posterolateral, and supraomohyoid, which include resections of lymph node levels II through IV, II through V, and I through III, respectively. The extended supraomohyoid neck dissection includes level IV nodes along with level I , II, III nodes.

A modified or selective neck dissection is recommended for the cN0 neck, for selected clinically positive necks (mobile, 1 to 3

cm lymph nodes), and for removing residual disease after RT when there has been excellent regression of N2 or N3 disease.[10] The more extensive the neck dissection, the higher the risk of complications. Both RT and neck dissection are approximately 90% efficient at eradicating subclinical regional disease. The salvage rate for patients developing clinically positive lymph nodes with the primary lesion controlled is 50% to 60%. Elective neck irradiation (ENI) and elective neck dissection are equally effective in the management of the N0 neck, with control rates exceeding 90%. Treatment of the entire neck is advised for primary lesions with a high rate of subclinical disease, such as the base of tongue, soft palate, supraglottis, and hypopharynx. In general, RT precedes surgery if the primary site is to be treated by RT or if the node was fixed. The operation precedes RT if the primary site is to be treated surgically. Modified neck dissection is sufficient treatment for the ipsilateral neck for patients with N1 or N2A disease without ECE. RT, often combined with concurrent chemotherapy, is added for those with more advanced neck disease. Complications after neck dissection include hematoma, seroma, lymphedema, wound infections and dehiscence, damage to the 7th, 10th, 11th, and 12th

cranial nerves, carotid exposure, and carotid rupture. Pain and dysfunction in the neck or shoulder may occur.

RADIOTHERAPY

The advantages of RT may include

1) The risk of a major postoperative complication is avoided,

2) No tissues are removed so that the probability of a functional or cosmetic defect may be reduced,

3) Elective neck RT can be included with little morbidity, and

4) The surgical salvage of RT failure is probably more likely than the salvage of a surgical failure.

CONVENTIONAL FRACTIONATION

Standard fractionation for radiation therapy is defined as the delivery of one treatment of 1.8 to 2.25 Gy/d upto a dose of 66 – 70Gy over a period of 6 - 7 weeks.

ALTERED FRACTIONATION

Accelerated Radiotherapy:

Decreases the overall treatment time so that the tumor cells regenerate less during the treatment and hence better loco regional control is achieved.

Pure accelerated radiotherapy

There is a decrease in the overall treatment time but no change in the total dose or fraction size.

Hybrid accelerated fractionation:There are three types.

Type A: Drastic reduction in overall treatment time and a considerable decrease in the total dose.

Type B: Treatment time is decreased, total dose remains the same with an added break in between treatment.

Type C: Total dose is same; overall treatment time is reduced with an addition of a concomitant boost phase **(Accelerated concomitant boost).**

Hyper Fractionated Radiotherapy

In hyper fractionated radiotherapy, dose of radiation is increased, dose per fraction is significantly reduced, the numbers of fractions are increased and overall treatment time is significantly unchanged.

Hypo fractionated radiotherapy

Here the dose per fraction is increased, the number of fractions is reduced, total dose is decreased, and the overall

treatment time is significantly reduced. This is mainly used for palliative radiotherapy.

RATIONALE FOR ALTERED FRACTIONATION:

The most fundamental principles of fractionated radiotherapy:

- ❖ Repair,
- ❖ Reassortment
- ❖ Repopulation
- ❖ Reoxygenation,

Elkind et al. found that the survival of cells increased with increasing time between doses for up to a maximum of about 6 hours. This finding is consistent with the clinical observation that separation of radiation treatments by 6 hours produces similar normal tissue injury as a 24-hour separation.[11] The shoulder of a survival curve is strongly influenced by sublethal damage repair : the broader the shoulder the more SDR and the smaller α/β ratio.

Similar to repair, reassortment and repopulation are also dependent on the interval of time between radiation fractions. If cells are given short time intervals between doses, they can progress from a resistant portion of the cell cycle (e.g., S phase) to a sensitive portion of the cell cycle (e.g., G_2 phase). This transit between resistant and sensitive phases of the cell cycle is termed

reassortment. If irradiated cells are provided even longer intervals of time between doses, the survival of the population of irradiated cells will increase. This increase in split-dose survival after longer periods of time is the result of cell division and has been termed *repopulation*. Reassortment and repopulation appear to have more protracted kinetics in normal tissues than rapidly proliferating tumor cells and thereby enhance the tumor response to fractionated radiotherapy compared to normal tissues. Similarly Reoxygenation also plays a vital role in tumour control. The cells in the center part of tumour is usually hypoxic due to lack of oxygen because of impermeability of blood vessels till the center of the tumour. Once the cells in the periphery which is oxic gets destroyed, the cells in the center receives blood from the blood vessels and becomes oxic which is susceptible to further radiation.

Radiotherapy is incorporated in the various steps of management in the squamous cell carcinoma of head and neck. It can be given as

DEFNITIVE RT

Mainly for early stage disease as a single modality with good tumour control equivalent to that of surgery. It can be given as EBRT alone in the form of 2D conventional (whose usage has been

reduced now a days) , 3D Conformal radiotherapy, IMRT, IGRT. Conformal radiotherapy techniques increases the therapeutic ratio by increasing the tumour control and reducing the normal tissue toxicities. In other words they increase the tumour control propability and also decrease the normal tissue complication probability. They have mainly reduced the incidence of xerostomia, thereby increasing the quality of the patients till their survival.

EBRT can be combined with brachytherapy for certain accessible sites thereby increasing the tumour dose without additional toxicities with the help of sharp dose fall off to the surrounding tissues.

PRE OPERATIVE RT

Most of the tumours in locally advanced stage such as stage III and stage IV are upfront inoperable. But the chance of cure is impossible without surgery. In those patients RT is given along with chemotherapy to reduce the bulk of the disease thereby helping the surgical oncologists to resect the tumour with adequate clearance. The usual dose given for this purpose is around 50 Gy and the patient is taken up for surgery after 4 weeks with proper assessment of the reduction of disease.

POSTOPERATIVE

Postoperative RT is indicated in patients with high risk features following surgery such as

- Tumour stage T3 , T4
- Nodal positivity
- Margin positivity
- Extracapsular extension
- Lymphovascular invasion
- Perineural invasion

Margin positivity and the Extracapsular extension are the indications of chemoRT.

PALLIATIVE RT

Palliative RT is usually considered in very advanced disease with poor performance status for whom cure is impossible due to extensive nature of the disease. It is usually given as hypofractionated radiotherapy in high doses to palliate symptoms like bleeding , pain.

CONCURRENT CHEMORT

Radiation can be combined along with chemotherapy to increase the tumour control thereby increasing disease free survival and overall survival. So these are mainly used in the management of locally advanced cancers to get better therapeutic effect. Altered fractionation schedules of RT lead to a 7% to 10% improvement in locoregional control relative to once-daily treatment schemes. Even the most effective RT regimens result in local control rates of 50% to 70% and disease-free survivals (DFSs) of 30% to 40%. These results has stimulated the investigation of treatments combining RT and chemotherapy. Chemotherapy can be combined along with RT as

- Induction or Neoadjuvant chemotherapy
- Concurrent along with RT
- Palliative chemotherapy.

A meta-analysis of individual patient data from >17,346 participants in 93 trials conducted from 1965 to 2000 (Meta-Analysis of Chemotherapy on Head and Neck Cancer [MACH-NC]) demonstrated that the use of radiotherapy and concurrent chemotherapy (CRT) resulted in a 19% reduction in the risk of death and an overall 6.5% improvement in 5-year survival

compared to treatment with RT alone ($p < .0001$). This benefit was predominantly attributable to a 13.5% improvement in local regional control. The 2.9% reduction in the risk of distant metastases was not statistically significant. The MACH-NC also demonstated a 2% improvement in 5year survival with the use of induction chemotherapy followed by RT which is not significant.

Concurrent chemoRT is the most commonly accepted and beneficial because some chemotherapeutic agents may both radio sensitize cells and provide additive cytotoxicity. The superiority has also been demonstated in other squamous cell carcinomas of other anatomic sites including oesophagus and cervix. Also a thorough understanding of toxicity is essential since the morbidity of loss of function due to surgery is better avoided with concurrent chemoRT. A recent analysis of phase III trials comparing RT with chemoRT suggests that concurrent chemotherapy provides the equivalent of a 10- 12 Gy dose escalation. Also chemotherapy addition shows better response when added to altered fractionation though there is mild increase in acute toxicity.

Some drugs which are commonly used along with RT includes Platinum compounds, antimetabolites, taxanes, mitomycin, bleomycin, vinca alkaloids, etc. Among these CDDP has got a

proven role in the management of head and neck scc at advanced stage.. Among the recent studies taxols also play a vital role along with RT.

CISPLATIN

Cisplatin and its analogs react preferentially at the N7 position of guanine and adenine residues and forms a variety of monofunctional and bifunctional adducts. The monoadducts may form intrastrand or interstrand cross-links. The formation of adducts and cross-links has been associated with therapeutic efficacy.[12] These adducts are responsible for the drug's cytotoxicity because they impede certain cellular processes that require the separation of both DNA strands, such as replication and transcription.though the combination chemotherapy of CDDP and 5 FU yield good results, the toxicities such as mocositis is still high in the combination arm than single agent chemotherapy arm.

THREE WEEKLY CHEMO VS WEEKLY CHEMO

Cisplatin is given as a single agent the dose as 100 milligrams per square metre of body surface area every three weekly. This high dose is associated with increased mucositis, increased vomiting and renal toxicity. This necessitates more intensive care and has attendant resource implications. This also results in treatment delay

or at least decrease in patient compliance. Therefore it is logical to split high dose three weekly cisplatin into weekly cisplatin schedule so that the toxicities are decreased and patient compliance is increased while maintaining dose intensity. Many trials have showed that weekly cisplatin is a safe alternative to three weekly cisplatin without compromising the efficacy. More over in weekly cisplatin arm we can monitor patients every week and dose adjustments can be made if necessary. Hence weekly cisplatin is a more acceptable regimen than three weekly cisplatin. Also the total dose of cisplatin 200mg is essential to achieve the therapeutic effect similar to that of 3 weekly regimen.

PACLITAXEL

This is an antimicrotubule agent which acts by arresting the cells at G2M phase thereby increasing the cells exposed to radiation. This is first tried along with other drugs for induction chemotherapy and proved to be effective. Later due to its radosensitization effect, weekly paclitaxel trials have tried and proved to be effective along with RT. The addition of paclitaxel to carboplatin or cisplatin in weekly therapy with CRT has great appeal because of the synergy between these drugs and the significant radiation-sensitizing properties of the taxanes.

TARGETTED AGENTS

Most of the head and neck cancers in Indian population have EGFR overexpression and the molecules targeting this have a great impact in the management of head and neck cancers. Of these tyrosine kinase inhibitors and monoclonal antibodies are upcoming. The drug approved by phase III STUDIES is Cetuximab. Other drugs commonly used in trials are Nimotuzumab, Geftinib, Erlotinib. These drugs have been proved effective and less toxic when compared to chemotherapy in HPV positive oropharyngeal cancers.

CHEMOPREVENTION

Chemoprevention is the administration of natural or synthetic agents to reduce the risk of getting SPTs. Patients with head and neck SCC have an increased risk of developing an upper aerodigestive tract SPT because of exposure to carcinogens and/or genetic predisposition. The risk of developing an SPT is approximately 2.7% to 4% per year and may impact survival. High-dose13-*cis*-retinoic acid (100 mg/m^2 daily for 12 months) has been shown in a randomized, placebo-controlled trial to reduce the risk of SPTs in patients previously treated for stage I to IV, M0, cancers of head and neck. Retinoids and beta-carotene both may cause

regression of oral leukoplakia; the former appear more efficacious. Lesions commonly recur after cessation of drug therapy. There is no standard role for the use of HR-HPV vaccination in the prevention of head and neck cancer at this time, although the impact of current vaccination programs on the incidence of head and neck cancer requires follow-up.

LITERATURE REVIEW

Radiotherapy plays a major role in the management of unresectable locally advanced head and neck squamous cell carcinoma over decades. Delivery of radiotherapy using modern techniques has improved the local control along with adequate sparing of normal tissues so that the patients are very compliant with minimal toxicities. Apart from conventional fractionation, various altered fractionation modalities have been developed in order to achieve increased locoregional control without increasing the toxicities. Altered fractionation with or without concomitant chemotherapy result in improved outcomes in the form of tumour control and survival compared with conventionally fractionated definitive RT alone for stage III-stage IV HNSCC.[13]

Two important features that influence the effectiveness of radiation are 1) the dose given during each radiation treatment ie dose per fraction 2) total amount of time necessary to complete the treatment.

Accelerated fractionation used in the management of head and neck cancer was thought to arise from various analyses as a function of dose administered and total treatment time given. When

the total dose is increased there is improved locoregionl control but due to prolonged duration of treatment, the equivalent loss of local control was about 0.75 Gy per day. Study by withers et al showed that **accelerated repopulation** occurs usually after 28 days of treatment for head and neck cancers. A dose increment of 0.6 gy per day is necessary to compensate for this repopulation. Accelerated fractionation is defined as decrease in overall treatment time or an increase in the average dose per week above 10 gy given in conventional fractionation.

Concomitant boost irradiation is a technique where two radiation fractions are given from fourth week of radiation therapy in order to compensate accelerated repopulation in head and neck cancers. The boost is given only to the primary tumour site and the involved nodes. The main advantage of Concomitant Boost Radiotherapy is that

There is **increase in locoregional control** of the tumour with **minimal enhancement in acute toxicities** as compared to other accelerated fractionation regimens

It shortens the total treatment duration from seven weeks to five weeks.

ALTERED FRACTIONATION TRIALS

RTOG 90-03 TRIAL compared various altered fractionation schedules such as HYRERFRACTIONATION Vs CONCOMITANT BOOST RT Vs SPLIT COURSE RT to standard CONVENTIONAL RT in locally advanced squamous cell carcinoma of head and neck. In this study 4 arms were randomized including 1073 patients of Stage III-IV (oral cavity, oropharynx, or supraglottic larynx) or Stage II-IV (base of tongue, hypopharynx).

Arm 1) Conventional or standard fractionation 70/35 @ 2 Gy/fx vs.

Arm 2) HF hyperfractionated RT 81.6/68 @ 1.2 Gy BID vs.

Arm 3) AFX-S split course accelerated fractionation 67.2/42 @ 1.6 Gy BID with 2 week break after 38.4 Gy vs.

Arm 4) AFX-CB concomitant boost radiation 72 Gy given 54/30 @ 1.8 Gy + 18/12 @ 1.5 Gy concurrent BID boost

RESULTS: 2 year and 5 year locoregional control rates were found to be better in HYPER FRACTIONATED and CONCOMITANT BOOST arms than STANDARD FRACTIONATION. Though acute effects were found to be increased as expected , the late effects were found to be reduced.

There is no significant difference between progression free survival and overall survival[14].

M.D.ANDERSON TRIAL in 1985-1988 treated patients wth carcinoma oropharynx and nasopharynx with CONCOMITANT BOOST RT. The treatment schedule includes 6 weeks to a maximum dose of 69-72 Gy with the boost consisting of 10-12 fractions. They found better primary tumor control (p=0.11) if the boost is given during last the last 10-12 fractions versus the first 10-12 fractions or twice a week throughout the treatment.[15]

A Prospective phase II study of concomitant boost radiotherapy given for stage II nasopharyngeal carcinoma found that C-Boost radiotherapy regimen provides a substantially higher biologically effective dose compared with conventional radiation treatment. Preliminary locoregional control and survival rates are increased with no significant acute and/or late toxicities.[16]

Prospective studies show that biologic dose escalation with Modified fractionation (hyperfractionation or accelerated fractionation with concomitant boost) improves locoregional control (LRC) compared with standard fractionation in patients with advanced head and neck cancer . In a recent meta-analysis,

enhanced LRC with modified fractionation translated into a 3.4% improvement in overall survival (OS) at 5 years[18] .

GHOSHAL S conducted a phase III Randomized trial in a single institution in INDIA, in which Patients were randomised so that

Conventional radiotherapy was given with 2 Gy/fraction/day, to a dose of 66 Gy in 33 fractions over 6.5 weeks or

Accelerated radiotherapy in the form of CONCOMITANT BOOST to **a dose of 67.5 Gy/40 fractions over 5 weeks (phase 1: 45 Gy/25 fractions/5 weeks to the wide portal and phase 2: 22.5 Gy/15 fractions/3 weeks** as a second daily fraction ie the boostafter a 6h gap) to the tumour and the involved nodes.

The primary and secondary end points were disease-free survival and locoregional control respectively. Patients treated with concomitant boost had a better 2-year disease-free survival (**71.7% vs 52.17%,** P=0.0007) and locoregional control rates (**73.6% vs 54.5%,** P=0.0006) than with conventional fractionation.[19]

A study by **Shrivatsava** compared Concomitant boost radiotherapy vs conventional radiotherapy in advanced oral cavity and oropharynx cancers reported in the Department of

Radiotherapy, KGMC, Lucknow between Jan 1999 and Feb 2000. In Concomitant boost arm, 30 patients out of 40 patients (**75%)** and in Conventional RT arm 24 patients (60%) had complete response (CR) and the rest of the patients had partial response except for one patient in Group II who had no response (NR). Acute reactions were slightly higher in Concomitant boost arm and were easily managed by IVF support. There is no difference in the late reactions between the two groups. The main advantage of CONCOMITANT BOOST TECHNIQUE is that there **is very minimal enhancement in acute reactions** that can be managed well as compared to other accelerated fractionation regimens and another advantage is that **it shortens the total treatment duration** from seven weeks to five weeks[20].

Phase III randomised trial was conducted by **Anupam rishi and Sushmita Goshal** to compare concomitant boost radiotherapy against concurrent chemoradiation in locally advanced oropharyngeal cancers in single institution from INDIA : 216 patients with histologically proven Stage III–IVA oropharyngeal cancer were randomly assigned between June 2006 and December 2010 to receive either chemoradiation (CRT) to a dose of 66 Gy in 33 fractions over 6.5 weeks with concurrent cisplatin (100 mg/m^2 on

days 1, 22 and 43) or accelerated radiotherapy with concomitant boost (CBRT) to a dose of 67.5 Gy in 40 fractions over 5 weeks. The 2 year disease-free survival rates were similar with 56% in the chemo radiotherapy group and 61% in CBRT group ($p = 0.2$; HR-0.81, 95%CI-0.53–1.2). Subgroup analysis revealed that patients with nodal size >2 cm had significantly better DFS with CRT ($p = 0.05$; HR-1.59, 95%CI-0.93–2.7). Acute toxicities were comparatively higher in chemo radiotherapy arm when compared to concomitant boost arm. But the patients had improved quality of life with concomitant boost arm[21].

CONCURRENNT CHEMOTHERAPY WITH RADIATION

Locally advanced squamous cell carcinoma of head and neck cancers management usually incorporates chemotherapy along with radiation to improve the tumour control, disease free survival and overall survival. This is achieved by two mechanisms: **Radiosensitisation and Spacial additivity.** Radiosensitisation increases the effect of radiation on tumour by increasing the cell kill without increasing the dose of radiation. This radiosensitisation is achieved with many chemotherapeutic agents either single or combination agents such as Cisplatin, 5FU, paclitaxel, docetaxel , capecitabine, gemcitabine, vinorelbine. Selection of the regimen is

therefore important in order to achieve improved tumour control without causing any treatment related breaks due to increased toxicities thereby preventing the delay in treatment completion.

The MACH-NC conducted meta-analysis of 63 randomized trials (10,741 patients) that were published between 1965 and 1993 and revealed that adjuvant chemotherapy provided a 4% improvement ($P < .0001$) in 5-year overall survival. This benefit was limited to those who received concomitant chemotherapy (8%; $P < .001$) and was not observed in patients who received induction or maintenance chemotherapy. But this report was criticized for its heterogeneity and was recently updated to include 24 new trials, 85% of which explore concomitant chemotherapy. The results were unchanged:

1) There was an 8% improvement in overall survival with concurrent chemoradiotherapy;

2) Maintenance and induction schedules did not provide a significant survival benefit;

3) All tumor sites were benefited;

4) Platinum-containing regimens showed the greatest benefit (an 11% 5-year overall survival advantage); and

5) There was no difference between poly- and monochemotherapy.

A recent update of Meta- analysis of chemotherapy on head and neck cancer (MACH-NC) showed that by adding chemotherapy along with radiation results in 19 % reduction in risk of death and 8% improvement in overall survival compared to radiation therapy alone. Majority of these benefits are derived from concurrent chemo radiation. The 2 % improvement in survival by induction chemotherapy is not statistically significant[22 , 23].

Budach and coworkers published a meta-analysis of modern chemotherapy regimens and curative intent RT doses (>60 Gy). The analysis included 32 trials (10,225 patients) published between 1975 and 2003. Their report showed an overall survival benefit of 12 months for chemotherapy concurrent with conventional or altered fractionation RT[24].

Even though concurrent chemo radiation increases the toxicities of radiation, it exerts a good loco regional and systemic control. **Hence concurrent chemo radiation is standard of care in locally advanced squamous cell carcinomas of head and neck.**

EQUIVALENCE OF CHEMOTHERAPY TO RADIOTHERAPY

From RTOG 90-03, a 1% increase in BED is associated with a 1.1% increase in Locoregional control. The mean BED of standard fractioned radiotherapy was found to be 60.2 Gy10 and 66 Gy10 for modified fractionation. The mean BED of standard fractionated chemoradiotherapy was found to be 71 Gy10 (10.8 Gy10 contributed by chemotherapy). The mean BED of modified fractionated chemoradiotherapy was found to be 76 Gy10 (10.4 Gy10 contributed by chemotherapy)[25]. Chemotherapy increases BED by approximately 10 Gy10 in both standard and modified fractionated radiotherapy, equivalent to a dose escalation of 12 Gy in 2 Gy daily or 1.2 Gy twice daily. Such an escalation could not be safely achieved by increasing radiation dose alone. Thus, combined-modality therapy should be the preferred method to enhance LRC and OS in locally advanced head-and-neck cancer. Efforts should be made to investigate the mechanisms underlying the unique biologic benefit achieved with chemotherapy or targeted therapy in combination with RT.

CHEMOTHERAPY ALONG WITH CONCOMITANT BOOST

RTOG 99-14 enrolled locally advanced squamous cell carcinoma of head and neck and treated with chemoradiation in the

form of concomitant boost radiation along with INJ Cisplatin to evaluate the feasibility of combining concomitant boost accelerated radiation regimen (AFX-C) with cisplatin and to assess its toxicity and the relapse pattern and survival in patients with advanced head and neck carcinoma.

76 patients were treated with Radiation which consisted of 72 Gy in 42 fractions over 6 weeks (daily for 3.5 weeks, then twice a day for 2.5 weeks) along with Cisplatin dose 100 mg/m^2 on days 1 and 22. **Complete response** to therapy was found in 63 patients (**83%**). The estimated 2-year locoregional relapse and distant metastasis rates were 34.7% and 16.1%, respectively. The estimated 2-year overall survival and disease-free survival rates were 71.6% and 53.5%, respectively. LR failure noted was 33% (2 yr) and 36% (4 yr). OS was found to be 70% (2 yr) and 54% (4 yr). Grade 3 – 4 late toxicity found was 42%. Though the acute toxicities were increased, patients were very compliant with the treatment[26].

Another study by **Teh BS** using concurrent chemotherapy of cisplatin 100mg/m^2 in the frst and last week of treatment along with Concomitant boost radiotherapy upto a dose of 70 Gy in 6 weeks showed 65% of complete response and 35% of partial response[27]. Though there were increased acute confluent mucositis

in 50% of patients, there were no enhanced treatment related late toxicity. They concluded that this combined chemoradiotherapy is safe and efficacious.

Another study conducted in our institute during the year 2006 using concomitant boost radiotherapy of 72Gy in 6 weeks along with Inj Cisplatin 100mg/m^2 on day 1 and 22 showed complete response rate of 79.1% with a partial response of 16.7%and progressive disease was noted in 4.2%. The study concluded that this study is very compliant to the patient with enhanced locoregional control and manageable acute toxicities.

WEEKLY CISPLATIN

HEATHER E NEWLIN did a trial with Concomitant weekly cisplatin and altered fractionation radiotherapy in locally advanced head and neck cancer. The routine chemotherapy schedule includes 3 weekly cisplatin 100 mg/m2. Both altered fractionation and cisplatin causes increased acute toxicity. But there is a debate whether weekly cisplatin can be used along with altered fractionation. The authors' purpose of this study was to evaluate the efficacy and toxicity after weekly cisplatin (30 mg/m^2/wk) given along with altered fractionation RT.

One hundred twenty-one patients with American Joint Committee on Cancer stages II (3%), III (13%), or IV (84%) squamous cell carcinomas of the oropharynx (70%), hypopharynx (20%), or larynx (10%) were treated between 2000 and 2006 at the University of Florida with hyperfractionated RT (55 patients) or concomitant boost RT (66 patients) and concomitant cisplatin (30 $mg/m^2/wk$).

The 5-year outcomes were: local control of 83%; locoregional control of 79%; distant metastasis-free survival of 88%; cause-specific survival of 76%; and overall survival of 59%. They concluded that Concomitant weekly cisplatin with altered fractionation RT is a safe and effective treatment regimen[28].

PACLITAXEL TRIALS

Initially paclitaxel was given for head and neck cancers in a recurrent and metastatic settings and proved to be beneficial. Later paclitaxel was tried in concurrent setting along with radiation either as a single chemo or in combination. The main dose limiting toxicity was febrile neutropenia. So various doses were tried in concurrent settings. **Hoffman et al** did an interesting study to define the maximum tolerated dose of paclitaxel given as weekly intravenous infusion concomitant with radiation by describing the

dose limiting toxicity in Head and neck cancer patients and he concluded that 30 mg/m2 is the maximum tolerated dose of weekly paclitaxel concomitant with radiation with mucositis as the dose limiting toxicity and only mild haematological toxicities[30]. By causing mitotic arrest and accumulating cells in radiosensitive phases like G2 and M phase (redistribution of cells), by eliminating hypoxic cells in the tumour and by causing programmed cell death, Paclitaxel act as 10 times more radio sensitizer than cisplatin.

Garden et al conducted a study in concurrent chemo radiotherapy with 3 arms – one arm with weekly cisplatin 20mg/m^2 and weekly paclitaxel 30mg/m^2 . this showed equal response rate with that of cisplatin and 5FU arm[29]. The toxicities were also comparable. But large randomised trial was not continued with this study.

RATIONALE FOR THIS STUDY

This study is mainly based on combining chemotherapy with Altered Fractionation regimen to get enhanced locoregional control in advanced setting.

Concomitant Boost technique is chosen thereby to increase the response rate without excessive toxicities and also the treatment time is reduced from 7 weeks to 5 weeks. Cisplatin and paclitaxel was chosen as weekly regimen inorder to potentiate the effects of radiation. Cisplatin is the drug proved to be effective in metaanalyses with dose of 200mg in 5 weeks is comparable to 3 weekly cisplatin. Paclitaxel by arresting the cells at G2M phase increases the sensitising effects of radiation. The study is planned to increase the total dose within the short period of time with enhanced effects of low dose chemotherapy without increasing the morbidity due to toxicities.

AIMS AND OBJECTIVES

The main aim of this study is to evaluate the use of Altered fractionation in the form of Concomitant boost along with low dose chemotherapy in the form of weekly CDDP and Paclitaxel.

PRIMARY OBJECTIVE (S)

To assess the immediate locoregional response rates of locally advanced squamous cell carcinomas of the head and neck treated with concomitant boost radiotherapy and chemotherapy using low dose weekly cisplatin and paclitaxel.

SECONDARY OBJECTIVE(S)

To Evaluate the acute toxicity to the treatment.

MATERIALS AND METHODS

STUDY DESIGN

This was a Single arm prospective study with a Phase II design.

STUDY DURATION

January 2015 - August, 2015

STUDY CENTRE

Department of Radiotherapy, Barnard Institute of Radiology & Oncology, Madras Medical college, Chennai.

SAMPLE SIZE

30 consecutive patients with histopathologically proven squamous cell carcinoma of head and neck who were fit for inclusion criteria were recruited in the study from the outpatient department.

The intent of treatment was to be radical, aiming for cure, considering their disease stage, co- morbidities and performance status

ETHICAL COMMITTEE APPROVAL

Approval from the institute ethical committee was obtained on 20.01.2015.

INFORMED PATIENT CONSENT

All patients enrolled in the study were informed about the merits and demerits of participating in this study and signed an informed consent form in their regional language,which is Tamil.

INCLUSION CRITERIA

- Biopsy proven newly diagnosed squamous cell carcinoma of the head & neck.
- Primary tumor sites: oral cavity, oropharynx, hypopharynx, larynx.
- Age 20- 60 years
- Stage III or IV locally advanced squamous cell carcinoma
- Previously not exposed to any chemo or radiotherapy
- ECOG 1-2
- No major life threatening comorbidities

EXCLUSION CRITERIA

- Non Squamous Histopathology
- Tumors of nasal cavity, paranasal sinuses and nasopharynx.
- Bone and cartilage involvement.

- ❖ Inadequate hepatic and renal functions, bone marrow reserve.
- ❖ Patient not consenting to chemotherapy at any point in the treatment.
- ❖ Previously received treatment for any other malignancy.
- ❖ Metastatic or recurrent disease.
- ❖ Patients with uncontrolled co morbid conditions like diabetes, hypertension.
- ❖ Pregnant females.

PRE TREATMENT WORK UP

1) Detailed history including presenting symptoms, past history, personal and family history.
2) Complete physical examination by inspection, palpation.
3) Upper aerodigestive tract evaluation by direct and indirect laryngoscopy, anterior and posterior rhinoscopy and endoscopy if indicated to know the extent of disease and rule out a second primary.
4) Biopsy from the primary tumor and/or fine needle aspiration cytology from the metastatic lymph node.

5) Blood grouping and typing.

6) Complete blood count.

7) Renal function test.

8) Liver function test.

9) CT scan of the base of the skull to root of the neck plain and contrast, before initiating treatment and also after 6 weeks of treatment for response assessment.

10) Chest X ray postero-anterior view.

11) Viral markers.

12) Cardiac evaluation and fitness.

13) Naso-gastric tube insertion if indicated

14) Dental prohylaxis including scaling, dental filling and extraction if required.

15) Tumour stage, performance status , weight , body surface area, creatinine clearance were recorded. Staging was done based on American Joint Committee staging manual 7th edition (for head and neck cancers).

16) Weekly CBC, RFT, LFT before each cycle of chemotherapy.

PATIENT PREPARATION DURING TREATMENT

All patients included in the study were told about the nature of the disease, stage and prognosis, treatment options , benefits of this study and informed consent for the same.

All patients enrolled in this study were distributed pamphlets describing in brief the do's and don'ts while on treatment and later.

NO TOBACCO AND ALCOHOL

The harmful effects of tobacco, both in smoking and smokeless form, and alcohol were explained to the patient and draw backs of its addictions to treatment was explained. These addictions has poor outcome after treatment and has increased risk of second malignancy due to field cancerization effect.

DENTAL PROPHYLAXIS

All the patients with oral cavity and oropharynx malignancies were advised dental evaluation and further management such as scaling, filling and extraction of the tooth if required in situations such as sharp teeth causing continuous irritation, caries tooth. They were started on antibiotics and analgesics following tooth extraction. A gap of 2 weeks after last teeth extraction was given

prior to the treatment of radiotherapy for proper wound healing of the gums. They were advised to use soft brush and fluoride containing tooth pastes twice daily. Artificial dentures are placed after completion of treatment after resolvement of toxic reactions, only then proper measurements can be got. Edentulous patients were evaluated for their oral hygiene any retained root tips. Patients were advised not to wear dentures until the mucosa is healed from the effects of radiotherapy. Regular mouth goggling was adviced

Thus in this study patients were suggested following oral measures to improve their oral hygiene during radiation.

- Patients oral health were monitored daily twice during treatment.
- All patients were advised to gargle 20 to 25 mL of indigenously prepared mouthwash by dissolving three teaspoons of soda bicarbonate and three teaspoons of table salt (sodium chloride) in 200ml of distilled water, for every 4 to 6 hours.
- Morphine sulfate mouthwash was used as an alternative to produce pain relief .Alcohol free commercial mouth wash was also used.

- Patients who developed mucositis were managed in addition with antibiotics and low dose corticosteroids. Oral candidiasis was treated with tablet Fluconazole 150 mg per oral for 7 days. Oral lozenges was also given.

- Oral physiotherapy - in the form of mouth stretching and mouth opening exercise also advised to patients to avoid trismus.

NUTRITIONAL CARE

All the patients enrolled in the study were assessed for their nutritional status by their intake of the quality and the quantity of the food taken by them. They were advised to take high protein diet prepared in their homes. A protein supplement and vitamins were given since the beginning of the treatment. They were given eggs. They were advised to take a simple preparation containing banana , egg , milk and sugar.

Most of the patients in this study were presented with dysphagia and odynophagia. According to the grade of dysphagia, they were advised oral feeding or naso gastric tube feeding. 3 of my patients had feeding jejunostomy. They were given total parenteral nutrition also.

Most of the patients developed mucositis since third week of the treatment they find difficulty in maintaining the nutritional

status. They were threated with low dose steroids and supportive measures. Liquid preparations such as fresh fruits and vegetable juices were advised that time. Also eating of spicy foods was not encouraged. Periodical monitoring of weight of the patients were done and advises given to them accordingly.

Before initiation of treatment, it was made sure that all patients had normal blood, renal and liver function tests and everyone had given written consent for the treatment.

TREATMENT PROTOCOL

30 locally advanced squamous cell carcinoma of head and neck cancer patients were selected consecutively from the outpatient department, who then underwent the pre treatment work up as mentioned before.

RADIATION THERAPY

All 30 patients were treated with a Theratron Phoenix Tele Cobalt-60 machine.

PATIENT POSITION

Patients were made to lie in the supine position with neck slightly extended.

PATIENT IMMOBILIZATION

Strict immobilization was practiced while irradiating the patient.

RADIATION PORTALS

Patients were treated with opposing lateral radiation portals.

VERIFICATION

X-ray simulation was done after making the patient lie in the same treatment position to verify the treatment field.

RADIATION DOSE

Eligible patients are treated with Radiotherapy using concomitant boost technique consisting of **5gy/1.8gyper# /25# - 5 weeks,to a field 1** composing of tumour plus 2 cm clearance and invoved nodes along with possible microscopic nodes.

22.5gy/ 1.5gy per# /15# to a field 2 given as a boost only to small field including primary and involved node at an interval of 6 hrs during last 3 weeks of treatment to a total dose of 67.5 Gy within 5 weeks of treatment.

DOSE CONSTRAINTS

Following were considered:

- Tolerance dose of spinal cord- 45 Gy in conventional fractionation for 5 to 10 cm.

- Parotid - up to 26 Gy after which permanent xerostomia is expected to occur.

CHEMOTHERAPY SCHEDULE

Inj Paclitaxel 20mg/m^2 - day 1, 8 15, 22, 29 and

Inj CDDP 30mg/m^2 – day 1,8,15,22,29 given 1 hr prior to radiotherapy.

Renal and hematologic parameters were assessed prior to each cycle of chemotherapy.

PREMEDICATION

Premedication was given 12 hours before and 30 minutes prior to chemotherapy which included the following:

- Inj. Ondansetron 8 mg IV.

- Inj. Dexamethasone 8mg IV.

- Inj. Ranitidine 50 mg IV.

- Inj. Chlorpheniramine 4mg IV.

All the patients were hydrated with 1 pint of normal saline efore the start of chemotherapy. First Inj Paxlitaxel was given along with 500ml of normal saline over 2 hrs followed by 1 pint of normal saline. Then inj CDDP was given along with 500ml normal saline over 2 hours. Inj Mannitol was then given followed by one more pint of normal saline. Inj ondansetron and inj rantac were given for 2 days bd after chemotherapy. Inj pacltitaxel should be monitored carefully for acute hypersensitivity reactions and should be stopped immediately.

If reanal function tests found altered adequate hydration was given to the patient and the nephrologist opinion obtained for the the modification of dosage of drugs during subsequent cycles. But almost all the patients tolerated well the complete treatment.

ASSESSMENT DURING CHEMORADIATION

TOXICITY ASSESSMENT

All the patients were examined daily before radiotherapy for reactions like Mucositis.

LARYNGITIS

Dysphagia and Skin reactions. Also the toxicities related to chemotherapy such as nausea and vomiting were also assessed.

Complete blood count and biochemistry will be monitored on a weekly basis. Chemoradiotherapy induced toxicity will be graded using **Common Toxicity Criteria version 4.03** and **RTOG acute radiation morbidity scoring criteria.** In the case of WBC less than 1000/µl or platelets less than 50,000/µl for a period longer than 5 days, or in the case of any severe grade 3 or 4, radiation therapy will be interrupted until recovery and drug doses will be reduced by 10% in the next cycle. Mucositis grade III would need suspension of radiation.

Mucositis was best treated with low dose steroids and antibiotics. Superadded infections such as candidiasis should also be noted and were treated with antifungals clotrimazole lozenges and flucanozole tablets. Saliva supplements and regular mouthwash advised for dryness of mouth. Skin reactions were treated with cansafe cream after completion of the treatment.

Blood investigations were repeated every week before chemotherapy and hemoglobin < 10g% was corrected by blood transfusion. Colony stimulating factor G_CSF was given when the Absolute Neutrophil Count fell below 1000 cells/cubic millimeter in a dose of 300mg. Symptomatic thrombocytopenia was corrected by platelet transfusion.

RESPONSE EVALUATION

All patients were reassessed by clinical examination , ENT examination with laryngoscopy and with a contrast enhanced CT Neck, 6 weeks after completion of concurrent chemo radiation. Response to treatment was described which depends on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1 version) Criteria.

- ***Complete Response:*** Disappearance of all target lesions; malignant nodes <10 mm.

- ***Partial Response:*** A minimum of 30% reduction in the sum of the longest diameter of target lesions, taking the baseline study as reference; confirmed at 4 weeks.

- ***Stable Disease:*** Neither partial response nor progressive disease criteria are met, in a minimum time set by the protocol.

- ***Progressive Disease:*** At least 20% increase in the sum of the diameter, with a minimum absolute increase of 5 mm, taking as reference the smallest sum in the study or appearance of new lesions.

FOLLOW UP

- Patients after completion of concurrent chemoradiation were discharged from the hospital. Response evaluation was done based on RECIST criteria after 6 weeks.

- Chest imaging, dental evaluations were done when indicated clinically. Continued smoking cessation, counseling to the patient and attender, rehabilitation, speech and swallowing therapy.

- Patients with complete response were kept for follow up. Patients with partial response was assessed for salvage surgery and if not feasible was started on palliative chemotherapy.

STATISTICAL ANALYSIS

The patient factors, tumor factors, response to treatment, and toxicities were thoroughly analyzed. The results are expressed in percentage. Since this study is single armed one and also the sample size was only 30, the levels of significance cannot be commented on.

TREATMENT PROTOCOL

Patient Selection Based on inclusion criteria

↓

Pretreatment evaluation including blood investigations, Imaging and Dental prophylaxis

↓

Treatment administration- concomitant boost irradiation with weekly low dose cispatin and paclitaxel

↓

Response assessment every week and Regular monitoring of toxicities

↓

Treatment completion

↓

Review after 6 weeks for response assessment

RESULTS AND ANALYSIS

30 patients were enrolled in the study. All of them completed their treatment protocol completely and were available for analysis of results.

PATIENT CHARACTERISTICS:

AGE DISTRIBUTION

30 patients enrolled in the study were from age 36yrs to 60yrs with good performance status. Majority of them were in 5th decade followed by 4th decade which is usually common in HNSCC patients. [figure no:1]

Table No: 1 Age Distribution Of Study Population

Age group	Number	Percentage
31 – 40 yrs	4	13%
41 – 50 yrs	10	33%
51 – 60 yrs	16	54%

GENDER

There was a male preponderance in this study since males are highly exposed to common risk factors such as tobacco, alcohol etc and the incidence is also high in males. I recruited only 3 female patients since I selected patients with good performance status and body surface areato tolerate this intense regimen within 5 weeks. [figure no : 2]

Table No : 2 Gender Distribution Of Study Population

Sex	Number	Percentage
Male	27	90%
Female	3	10%

PERFORMANCE STATUS

All the patients enrolled in this study were in a good performance status with ECOG (Eastern Cooperative Oncology Group) grade 0 or 1. [figure no : 3]

Table No : 3 ECOG Performance Status

ECOG	No of patients	Percentage
ECOG 0	17	57%
ECOG 1	13	43%

RISK FACTORS

Majority of the patients were exposed to risk factors such as tobacco both smoking and smokeless , alcohol. One female patient with chronic irritating ulcer due to sharp tooth had give rise to carcinoma.

Table No: 4 Risk Factors Exposure

Habits	No of patients	Percentage
Tobacco(smoking)	17	57%
Tobacco (smokeless)	9	30%
Alcohol	20	66%
None	4	13%

SYMPTOMS AND SIGNS

The most common presenting symptom among the study population was dysphagia followed by odynophagia since most of them are hypopharyngeal and oropharyngeal malignancies. [FIGURE NO :4]Table No: 5 Symptoms And Signs

Presenting symptoms/signs	Number	Percentage
Dysphagia	19	63%
Odynophagia	16	53%
Ulcer or growth	9	30%
Neck swelling	8	26%
Voice change	11	37%
Pain	11	37%

PRIMARY SITE

In this study Oropharynx were 9 patients, followed by Hypopharynx 8 patients then Oral cavity were 5 patients and larynx 8 patients.(figure no:) . the subsites requiring unilateral fields were not added to this study because of intense toxicity expected due to increased radiationdose of 3.3gy/day along with chemotherapy.[figure no: 5]

Table No: 6 Primary Site

Primary site	Number	Percentage
Orophaynx	9	30%
Hypopharynx	8	27%
Oral cavity	5	16%
Larynx	8	27%

SUBSITE ANALYSIS

In the subsite analysis, supraglottis and hypopharynx constitute the maximum number of cases. [figure no: 6]

Table no:7 subsite analysis

Subsite	Number	Percentage
Supraglottis	8	26.66%
Tonsil	6	20%
Post 1/3 tongue	3	10%
Pyriform fossa	8	26.66%
Ant 2/3 tongue	4	13.33%
Hard palate	1	3.33%

TUMOR STAGE

This study included only squamous cell carcinoma of head and neck in a locally advanced stage with T stages - T2 (with node positive), T3, T4a . [figure no: 7]

Table no: 8 Tumor stage

T stage	Number	Percentage
T1	0	0
T2	4	13.33%
T3	17	56.67%
T4	9	30%

NODAL STAGE

Most of them had N 2 nodal disease . N 3 is not included for study purpose. [figure no: 8]

Table no: 9 Nodal stage

Nodal stage	Number	Percentage
N0	4	13.33%
N1	10	33.33%
N2	16	53.34%

STAGE GROUPING OF THE STUDY SAMPLE

The staging grouping was done according to AJCC 7th edition.

Most of our patients present only in locally advanced stage. [figure no: 9]

Table no: 10 Stage Grouping

Stage grouping	Number	Percentage
STAGE III	14	46.67%
STAGE IV A	16	53.33%

HISTOLOGICAL DIFFERENTIATION

Most of the patients in this study belonged to moderately differentiated histology. [figure no: 10]

Table No: 11 Histological Differentiation

Histological differentiation	Number	Percentage
Well differentiated	9	30%
Moderately differentiated	13	43.33%
Poorly differentiated	8	26.67%

TREATMENT RESULTS

All 30 patients have completed the treatment protocol and were assessed at the end of 4-6 weeks after chemoRT. The evaluation was done clinically, which included ENT (Ear, Nose, Throat) examination with indirect laryngoscopy and direct laryngoscopy, and CT imaging (plain and contrast). The RECIST 1.1 criteria were used to classify the response type into a complete response, partial response, static or progressive disease.

RESPONSE RESULTS

In this study 73% of the patients had complete response and 27% had partial response. There was no static response or progression in the study. [figure no: 11]

Table no: 12 Response Results

Response	Number	Percentage
Complete response	25	83.33%
Partial presponse	5	16.67%
Static response	0	0
Progression	0	0

SUBSET ANALYSIS

All the patient characteristics were analyzed for response at the end of the treatment. The results are stated in percentage. Due to the single arm prospective analysis and small sample size of 30 patients, the study tests of significance cannot be relied on.

SITE VS RESPONSE

In this study Oropharynx , Hypophaynx, supraglottis had equal number of complete responses followed by oral cavity. [figure no: 12]

Table no:13, Site Vs Response

Site	Complete Response	Partial response
Oralcavity	3(60%)	2(40%)
Oropharynx	8(88.89%)	1(11.11%)
Hypopharynx	7(87.50%)	1(12.50%)
Larynx	8(88.89%)	1(11.11%)

SUBSITE VS RESPONSE

Among the subsites involved, tonsil show complete response in all patients. Only ant 2/3 patients have equal number of partial and complete response. [figure no:]. Subsites with well differentiated histology shows poor response when compared to others. [figure : 13]

Table no: 14 Subsite vs Response

Subsite	Complete response	Partial response
Supraglottis	7(87.5%)	1(12.5%)
Tonsil	6(100%)	0
Post 1/3 tongue	2(66.67%)	1(33.33%)
Pyriform fossa	7(87.5%)	1(12.5%)
Ant 2/3 tongue	2(50%)	2(50%)
Hard palate	1(100%)	0

TUMOR STAGE VS RESPONSE

3 patients of T4 stage and 2 patients of T3 stage showed partial response. All patients of T2 stage showed complete response. This denotes the bulk of the tumour and the advanced nature of the disease. [figure no : 14]

Table no: 15 Tumor Stage Vs Response

Tumor stage	Complete Response	Partial response
T1	0	0
T2	4(100%)	0
T3	15(88.24%)	4(11.76%)
T4	6(66.67%)	3(33.33%)

NODAL STAGE VS RESPONSE

5 patients of N2 disease showed partial response because of increased number of nodes and multiple matted nature of nodes with central hypoxia due to increased size of the node. [figure no: 15]

Table no: 16 Nodal Stage Vs Response

Nodal stage	Complete Response	Partial response
NO	4(100%)	0
N1	10(100%)	0
N2	11(68.75%)	5(31.25%)

HISTOLOGICAL DIFFERENTIATION VS RESPONSE

As already mentioned maximum numbers of the patients in our study were moderately differentiated in which 11 patients had complete response and 2 had partial response. All poorly differentiated cancer had complete response. Out of 9 well

differentiated tumors only 6 had complete, this is lower when compared to the other two differentiations. [figure no: 16]

Table no: 17 Histological differentiation Vs response.

Histologic differentiation	Complete response	Partial response
Well differentiated	6(66.67%)	3(33.33%)
Moderately differentiated	11(84.62%)	2(15.38%)
Poorly differentiated	8(100%)	0

STAGE GROUPING VS RESPONSE

Among the 14 patients in stage III, 13 patients showed complete response and 1 patient showed partial response. Stage IV patients had reduced complete response when compared to sage III. [figure no : 17]

Table no : 18 Stage Grouping vs Response

Stage Grouping	Complete Response	Partial Response
STAGE III	13(92.86%)	1(7.14%)
STAGE IV	12(75%)	4(25%)

PERFORMANCE STATUS VS RESPONSE

The ECOG performance status among the study patients did not show much difference in the response rates, as the study patients are in the ECOG 0 OR 1.

Table no: 19 ECOG Vs Response

ECOG	Complete response	Partial response
0	16(94.12%)	1(5.88%)
1	9(69.23%)	3(30.77%)

OTHER FACTORS AFFECTING RESPONSE

AGE

In this study the age were not randomized so its very difficult to interpret the results according to age group. Younger age because of their performance status had good outcome than old people with poor performance status. Also young age were well compliant to the treatment because of good performance status.

GENDER VS RESPONSE

As the male population dominated the study 85% of the males had complete response in contrast to 66% of the females. As the male and female ratio was not equivalent it cannot be considered as significant.

TREATMENT BREAK VS RESPONSE

Treatment delay due to toxicities which caused prolongation of overall treatment time was analyzed for response. There was treatment delay in 30% of the patients compared to 70% who

proceeded without delay in overall treatment time. Among the 30% of the patients, most of the patients had 1-3 days treatment break had 83% complete response whereas only 62.5% had complete in case of treatment break for 4 days or more.

Though there was treatment break all patient completedchemoradiation.

Table no: 20, Treatment break Vs Response

Treatment break	Number	Complete response	Partial response
1-3 DAYS	5	3(60%)	2(40%)
> 4DAYS	4	1(25%)	3(75%)

TREATMENT RELATED ACUTE TOXICITIES

ACUTE LOCAL TOXICITY

Acute local toxicity is done by RTOG Acute morbidity scoring criteria.(Table 20, figure no: 18)

SKIN REACTION

In this study 21 patients had Grade 1 skin reactions in the form of dry desquamation, decreased sweating. Another 7 patients had patchy moist desquamation whereas only 2 patients had grade 3 confluent moist desquamation only during the last week of the treatment. All patients wee treated with aloe vera cream and cansafe at the end of the treatment.

MUCOSITIS

Among the study population , 6 patients had grade 3 mucositis and 1 patient had grade 4 mucositis for whom RT was suspended till it heals. Pt was on regular mouth wash and antibiotics and analgesics. 13 patients had grade 2 mucositis and 10 patients had grade 1 mucositis . These were best managed with antibiotics, analgesics such as mucopain ointment.

XEROSTOMIA

Some patients developed altered sensations of taste , hard sticky saliva during the treatment. Only 5 patients developed grade 2 reactions, 17 patients developed grade 1 reactions and rest of them didn’t have much effects.

PHARYNGITIS

Since many patients presented with dysphagia , many of them advised NG tube feeding from the beginning itself. During the couse of the treatment 18 patients had grade 2 phayngitis followed by 7 and 5 patients having grade 3 and grade 1 pharyngitis respectively. Even then the nutritional status was maintained due to proper advices.

Table no: 21 Acute Toxicity

Acute toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin reactions	0	21 (70%)	7 (23.33%)	2 (6.67%)	0	0
Mucositis	0	10 (33.33%)	13 (43.34%)	6 (20%)	1 (3.33%)	0
Salivary glands	8 (26.67%)	17 (56.67%)	5 (16.67%)	0	0	0
Pharyngitis	0	5 (16.67%)	18 (60%)	7 (23.33%)	0	0
Laryngitis	0	6 (20%)	16 (53.33%)	8 (26.67%)	0	0

LARYNGITIS

Some of the patients developed cough and symtoms of dyspnoea. Some petients with advanced laryngeal cancers had tracheostomy tube at the time of presentation in our department. Metal tracheostomy tube has been replaced with portex tracheostomy tube before starting radiotherapy. Grade 1, 2, 3, laryngitis were found in 6 , 16 , and 8 patients respectively.

SYSTEMIC TOXICITY

The treatment related systemic toxicity was assessed with CTCAE V 4.03 and presented. [Figure no: 19]. Only minor systemic toxicities occurred during the treatment.

Table no: 22 Systemic toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	20(%)	4	0	0
Vomiting	10	5	0	0

There are no diarrhea or cardiac toxicity during the treatment.

HAEMATOLOGICAL TOXICITIES

ANAEMIA

15 patients had adequate Hb levels during the treatment. 12 patients had Hb dropped between 11 and 9.5 gms and were given iron tablets. Only 3 patients had Hb less than 9 gms in the third and fourth week of treatment and they were given packed cell transfusions.

LEUCOPENIA AND NEUTROPENIA

Leucpenia and neutropenia were found only in 7 patients during the course of the treatment. They were given Inj G_CSF 300mg subcutaneously daily for 3 days along with antibiotics and home made foods. For this reason, chemotherapy schedule was little altered ie on the 4^{th} day of the week. No schedule has been missed by any of the patients. [figure no: 20]

THROMBOCYTOPENIA

There were no thrombocytopenia noted during the treatment among the study population.

RENAL TOXICITY

The patients had normal renal function tests through out the treatment.

Table no: 23 Haematological toxicity

Haem toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	15(50%)	12(40%)	3(10%)	0	0
Leucopenia	23(76.67%)	4(13.33%)	3(10%)	0	0
Thrombocytopenia	0	0	0	0	0

DISCUSSION

Most of the patients in India presented with advanced stage to the hospitals due to their poor socioeconomic status, illiteracy , fear of neglect by the family and society. Now a days Head and Neck squamous cell carcinomas are becoming more prevalent in younger age group commonly below 40 years due to increased use of smoking and smokeless tobacco in the form of pan , gudka , ganjha. So Oral cavity cancers have become more common among younger population. But since the patients present in locally advanced stage their management of cure is still challenging. Though most of them present in locally advanced stage , their performance status is still good because of their age. We are in a position to plan intense treatment regimen with multimodality management in order to achieve better local and regional control and disease free survival.

Various Altered fractionation regimens were found to be useful in achieving improved local and regional control and disease free survival due to the delivery of increased dose to the tumour without increasing the complications. Though the acute toxic effects are known to be slightly increased, they can be very well managed with best supportive measures since they are not life

threatening. Also the late toxic effects are found to be very low compared to standard fractionation. This is best achieved with hyper fractionation regimen and concomitant boost irradiation. Concurrent chemotherapy along with radiation gives improved locoregional control with minimal increased toxicities.

In our department also, many patients present with head and neck squamous cell carcinoma in a locally advanced stage. We prefer concurrent chemoradiotherapy for most of our patients. In this study we opted for concomitant boost irradiation in order to achieve increased dose for tumour control and to shorten the treatment time from 6.3 weeks to 5 weeks along with low dose chemotherapy cisplatin and paclitaxel for radiosensitisation and increased therapeutic effect.

This study included 30 patients with squamous cell carcinoma of head and neck in locally advanced stage presented to our department.

EPIDEMIOLOGICAL ASSESSMENT:

In this study, 54% of the patients were in 5^{th} decade followed by 33% and 13% in the 4^{th} and 3^{rd} decade respectively. This is the usual presentation in most of the studies.

90% of the patients in this study were males while only 10% constitute females. This is due to increased exposure of males to tobacco, smoking, alcohol. Among the females, one patient had shrp tooth as a risk factor due to chronic irritation.

Since this regimen has to be well tolerated patients with good performance status were only included in this study. Most of the them were in ECOG performance status 0 and 1.

57% of males had the habit of smoking and 30% had the habit of pan chewing which lead to oral cavity and oropharynx cancers. The most common symptom\ among the study patients was dysphagia (63%). Oral cavity and oropharyngeal tumours presented as ulcer or growth.(30%).

Only 4 primary sites were included in order to compare the results of the treatment. Tumours such as nasophaynx, nasal and paranasal tumours and salivary gland tumours behave differently and were not included in the study. Equal number of patients were found between oropharynx, hypopharynx and larynx malignancies (30%, 26%, 26%) respectively and oral cavity constitutes only 16%of cases.

Among the subsites, supraglottis and pyriform fossa comprised 27%of cases, followed by tonsil(20%), anterior 2/3rd tongue (13%), posterior 1/3rd tongue(10%) and hard palate – only one patient.(3%). The subsites requiring only ipsilateral irradiation such as buccal mucosa, alveolus were not included because high dose of radiation may increase acute effects to a larger extent.

Most of the patients belong to tumour stage T 3, T4A (57%, 30%), with varying nodal presentations and 13% patients had tumour stage T2 with nodal presentation. Among the nodal presentations, 54%, 33%, 13% of patients comprised of N0, N1, N2 (a,b,c) respectively. Stage III and stage IV A patients were only included in the study. Patients included in both the stages were almost equal 46% and 54% respectively. Most of the tumours are moderately differentiated (43%) followed by well differentiated and poorly differentiated (30% and 27%) respectively.

TREATMENT RESULTS ASSESSMENT

All the 30 patients completed the treatment and available for analysis. Their response to treatment were assessed immediately after completion of the treatment clinically and after 6 weeks of treatment clinically, and with the help of imaging.

Among the study population, 83% showed complete response ie 25 patients and 17% showed partial response (5 patients).none of the patients showed static disease or progressive disease.

The treatment results were also analysed in detail with respect to further subset analysis and the response outcomes were individually analsed in depth.

Among the primary sites , oropharynx, hypopharynx and laryngeal malignancies showed 87% – 88% complete response rates and only 11% - 12% showed partial response. But in case of oral cavity tumours, 60% had complete response and 40% had partial response. This may be arrtibuted to increase in the bulk of the disease.

Of the subsites involved, tonsil and hard palate showed complete response of 100%. Next to it, pyriform fossa and supraglottis had complete response of 88%. Carcinoma of tongue both anterior 2.3 rd and posterior 1/3rd tongue showed minimal complete response of 50% and 66% respectively. This is due to increased mucositis in these patients and treatment breaks which lead to delay in the completion of the treatment.

In respect of tumour stage , T2 showed 100% complete response while T3 and T4 showed 88% and 66% complete response respectively. This is explained by the advanced nature of the disease with varied nodal presentations and extent of the disease in advance. Similarly, patients presented with N0 and N1 nodes show complete response while those with N2 nodes showed only 68% of complete response. This is arributed to increased size of the node and extracapsular extension by way of matted nodal presentation.

In view of histological differentiation, poorly differentiated carcinomas showed 100% complete response as expected. Moderately differentiated and well differentiated tumours showed reduction in complete response rate of 84% and 66% respectively. Well differentiated nature of the tumour is usually less responsive to radiation and it’s the reason behind the oral cavity tumours showing decreased complete response. But they have reduced local recurrences and distant metastasis.

As usually explained, stage III tumours show increased complete response of 93% whreas stage IV patients showed complete response rate of 75%. But these results are far better when compared to conventional radiation, concomitant boost radiation

alone, and concomitant boost with cisplatin alone. This explains the superiority of this study over the other similar studies.

Other factors such as age , gender , performance status were also analysed but this is not quite significant. Patients with performance status ECOG 0 had better outcome mainly due to the increased compliance of the treatment. Similarly patients were not distributed equally among all age groups so its very difficult to interpret among them. Also most of them were males due to their habits and only 3 were females of which 1 patient showed partial response due to large bulk and extent of the disease and the treatment break in between due to poor tolerance.

Regarding the treatment delay, 5 patients had 1 – 3 days of treatment delay and 4 patients had more than 4 days delay. Lesser the treatment delay, response is good. In treatment delays of 1 – 3 days, 60% had complete response. But in more than 4 days treatment delay, there is only 25% response and 75% had only partial response.

TOXICITY ASSESSMENT

Acute toxicities are assessed using RTOG morbidity scoring criteria. Skin toxicities are found in almost all patients and usually

occurs from the third week of treatment. Most of them had grade 1 reaction only and 30% patients had grade 2 and 3 reactions which were managed well with aloe vera and cansafe cream.

Mucositis was an important sideeffect that caused treatment delay during 4^{th} and 5^{th} week of treatment. 20% of the study population had grade 3 mucositis and 3% of them had Grade 4 mucositis for whom RT was suspended till mucositis heals. They were best managed with antibiotics, analgesics and low dose steroids.

Dry mouth was found in 72% of patients and managed with saliva supplements, artificial moth sprays. Pharyngitis and Laryngitis were found in 80%of patient in low grades and managed symptomatically.

Haematological toxicities were little more pronounced in this study. Only 10% of the patients needed blood transfusion during the treatment. 23% of patients had grade 1 and 2 leucopenia for which Inj G CSF was given subcutaneously for three days. RT was suspended for grade 3 leucopenia. There was no thrombocytopenia during this study.

Systemic toxicity were very less in this study. Only 16% of patients had grade 2 vomiting which were managed with IV fluids and antiemetics. There were no renal toxicity or cardiac toxicity in this study.

There were no treatment related deaths in this study.

Among the patients with partial response, 2 patients who had tumour in anterior 2/3rd tongue were taken up for surgery and other 3 patients who were not willing for morbid surgery was taken up for palliative chemotherapy.

This study showed an increased tumour control rates of complete response 83% when compared to study conducted by Ghoshal showing 71% complete response rate and another study from our institute showing 79% complete response rate. This may be attributed to the addition of weekly low dose chemotherapy in this study. At the same time grade 3 mucositis was only 23% when compared to 35% in the other two studies.

MERITS OF THE STUDY

- Concurrent chemoradiation is the ideal management of stage III and stage IV head and neck SCC and this study is based on it.

- It has shown improved local and regional control.
- The acute toxicities were manageable.
- There is no increase mortality or morbidity.
- Chemotherapy – cisplatin and paclitaxel given in low doses is acceptable by all patients.
- This study showed enhanced results in oropharyngeal, hypopharyngeal malignancies.

DEMERITS OF THE STUDY

- This is not a large randomozised control study and sample size is too small for statistical analysis.
- All patients were treated with theratron phoenix 2D technique.
- Long term followup is needed to calculate survival benefits.
- Double armed study is recommended to compare the results.

FUTURE PERSPECTIVE

Various concomitant boost trials are upcoming with conformal techniques also in the form of simulataneous integrated boost techniques. Many chemotherapy drugs are being used and evaluated along with radiation. Also many targetted agents such as EGFR inhibitors are also used along wirh radiation in the concurrent setting.

CONCLUSION

Most of the patients with biopsy proven head and neck squamous cell carcinoma report to our department in a locally advanced stage. This is mainly attributed to low socioeconomic status, poverty, illetracy. They have a fear of neglect by their own family and society which leads to delay in reporting to hospital at an advanced stage. Though many cancer awareness programmes are being conducted, the early case detection is still not achieved to a remarkable level in developing countries. Most of the patients present in younger age with good performance status. This becomes a great challenge in the management of such patients.

This study is designed for such patients with good performance status with advanced disease to achieve maximum tumour control without causing mortality or morbidity. This study is succeeded with a complete response rate of 83% and partial response rate of 17%.

But since there is no long term followup of this study, disease free survival and overall survival cannot be calculated. Large randomized trials with comparison to conventional RT has been planned for detailed analysis.

Though there is significant improvement in local and regional control of the tumour, there is enhanced acute toxicities which can be well managed with best symptomatic care. Therefore selection of patients is very important in this study in order to complete the treatment protocol within the stipulated time. The main advantage is the reduction of treatment duration to 5 weeks which is very essential in centers with patients overload.

Thus concomitant boost irradiation with weekly low dose chemotherapy is a feasible option with good locoregional control and manageable toxicities in patients with good performance status.

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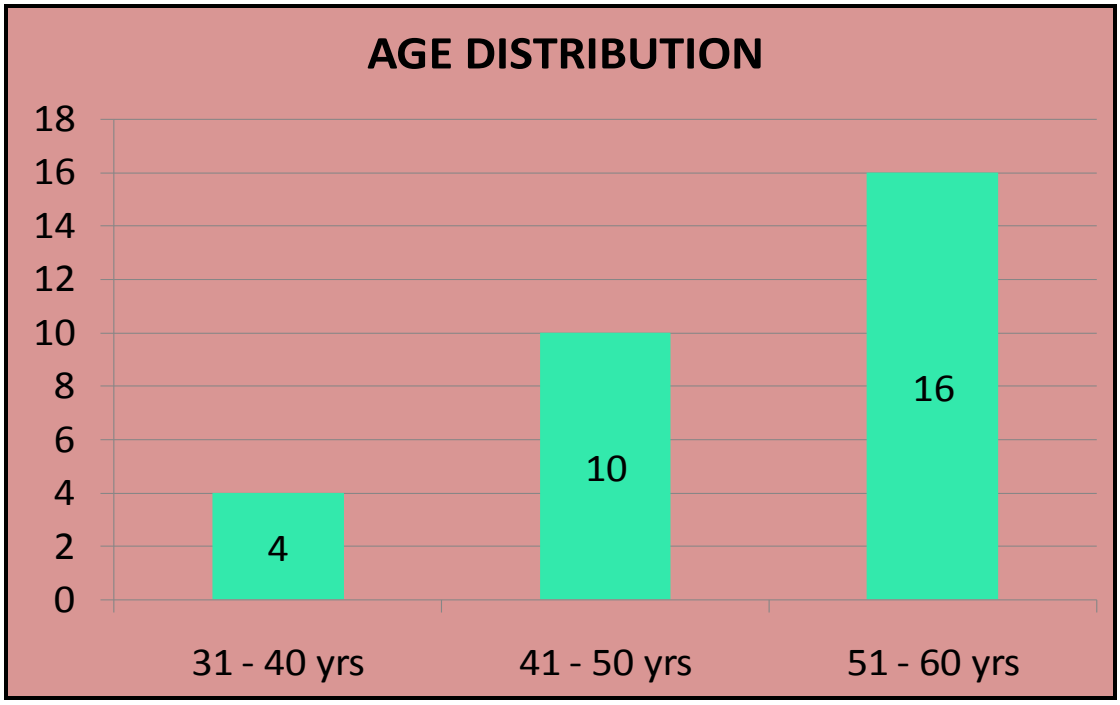
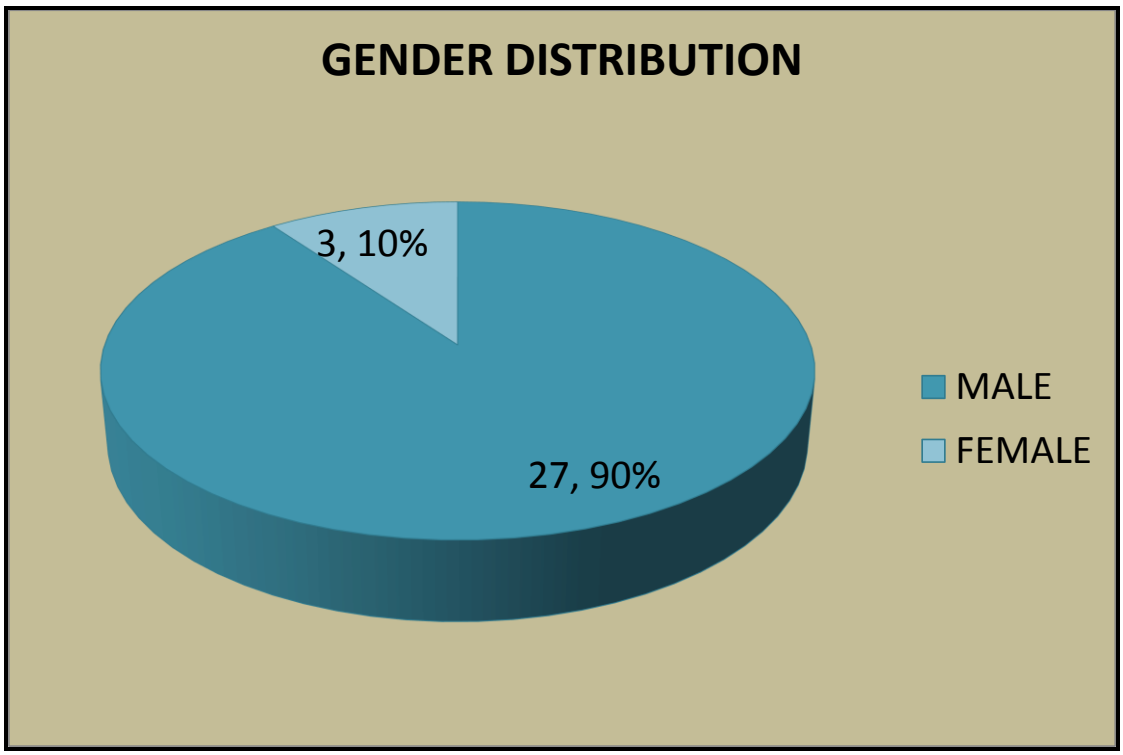
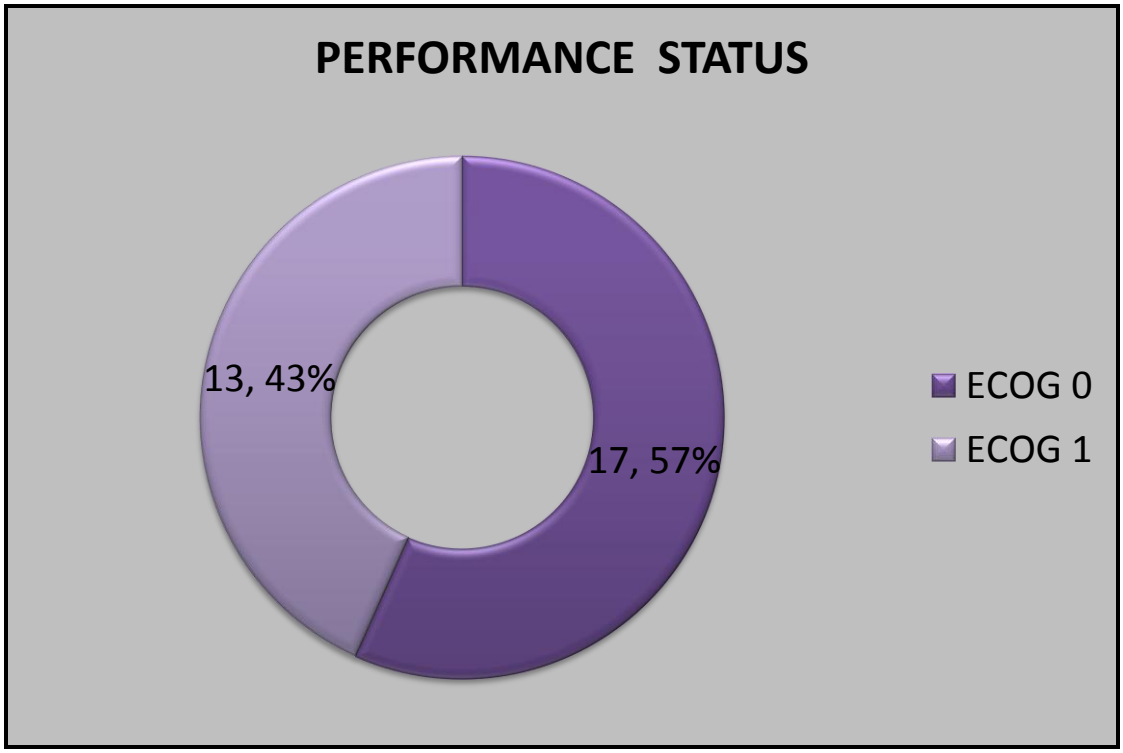
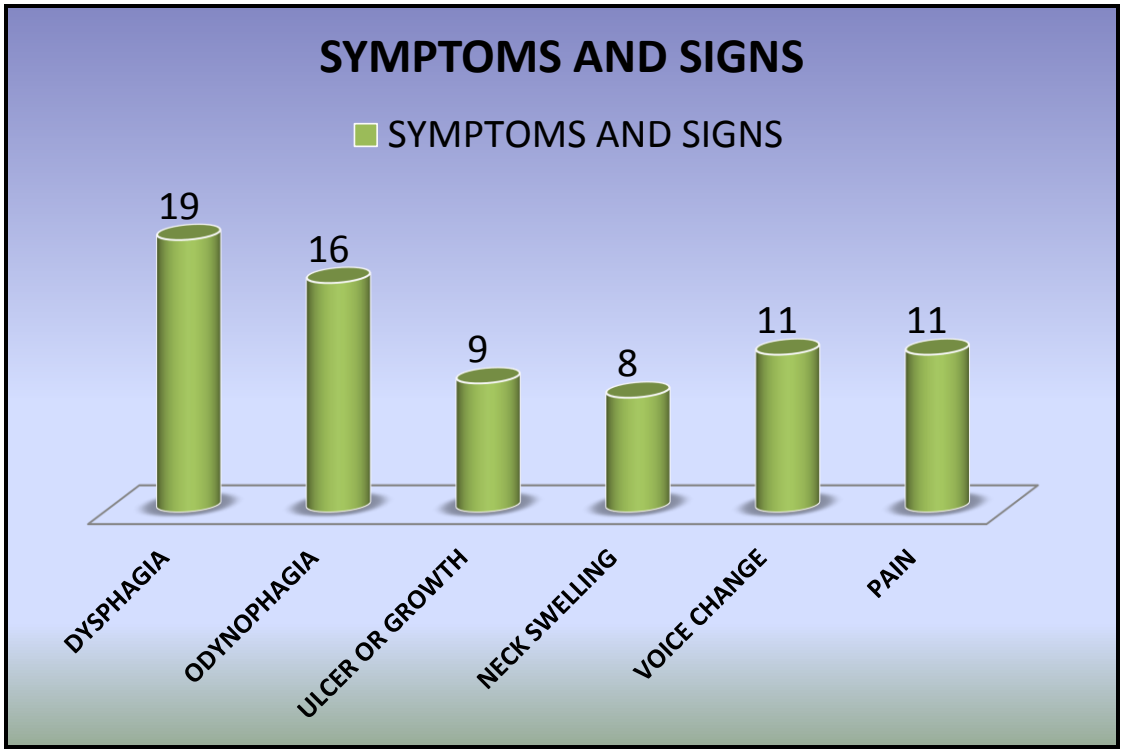
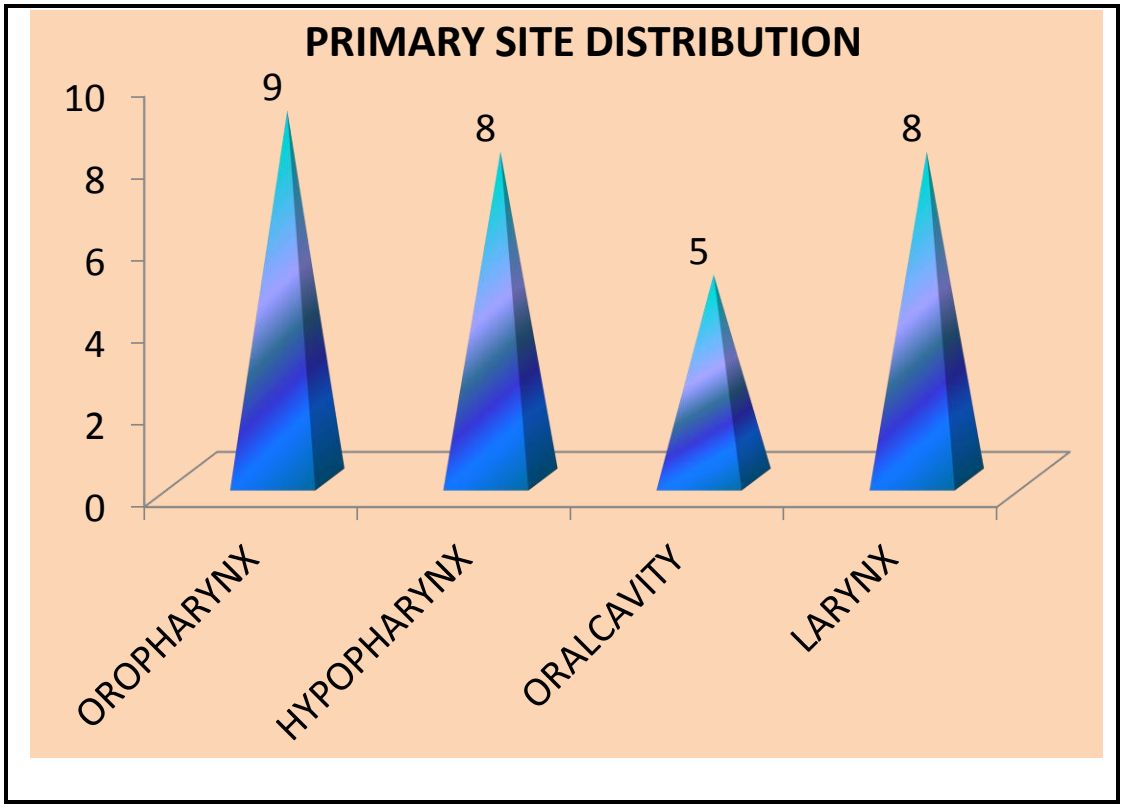
30) Hoffman W, Belkac, Schmidberger.N et al Radiotherapy and concomitant weekly one hour infusion of Paclitaxel in the treatment of head and neck cancer, Results from a phase I trial.Int.J. Radiat. Oncol Biol Phys. 1997; 38 : 691-696 doi : 10.1016

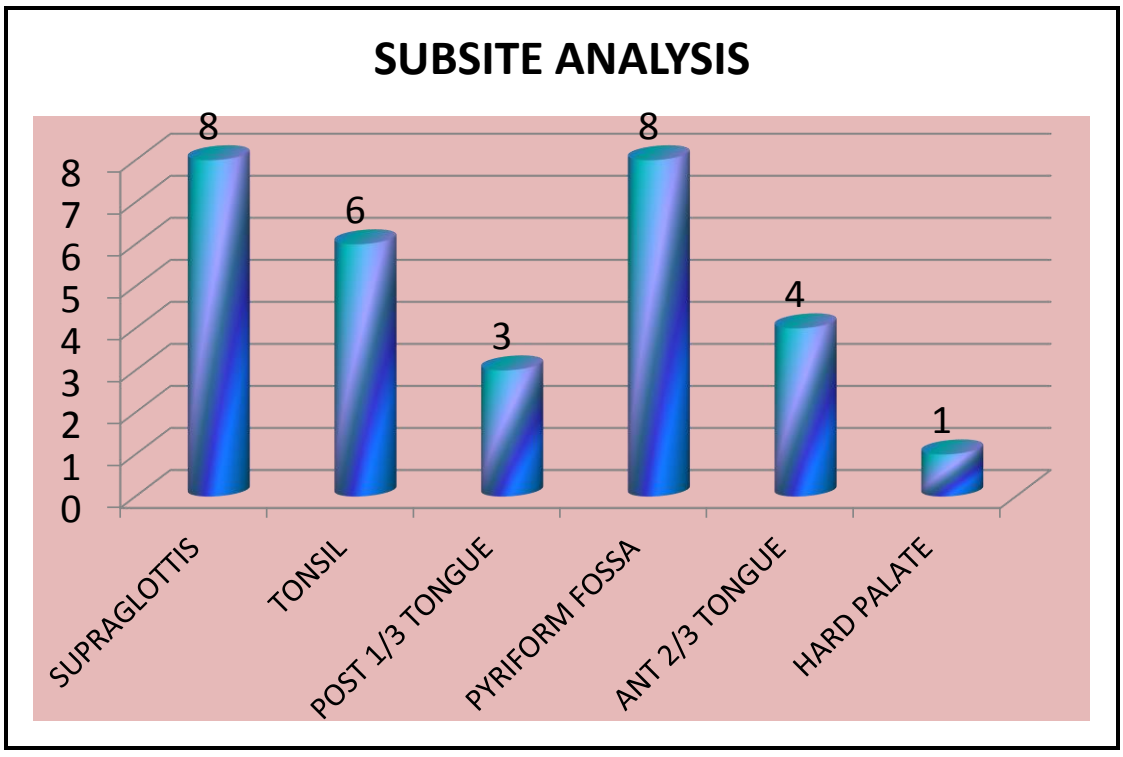

AGE DISTRIBUTION
18
16
14
12
10
8
6
4
2
0
4
10
16
31 - 40 yrs
41 - 50 yrs
51 - 60 yrs


GENDER DISTRIBUTION
3, 10%
27, 90%
MALE
FEMALE

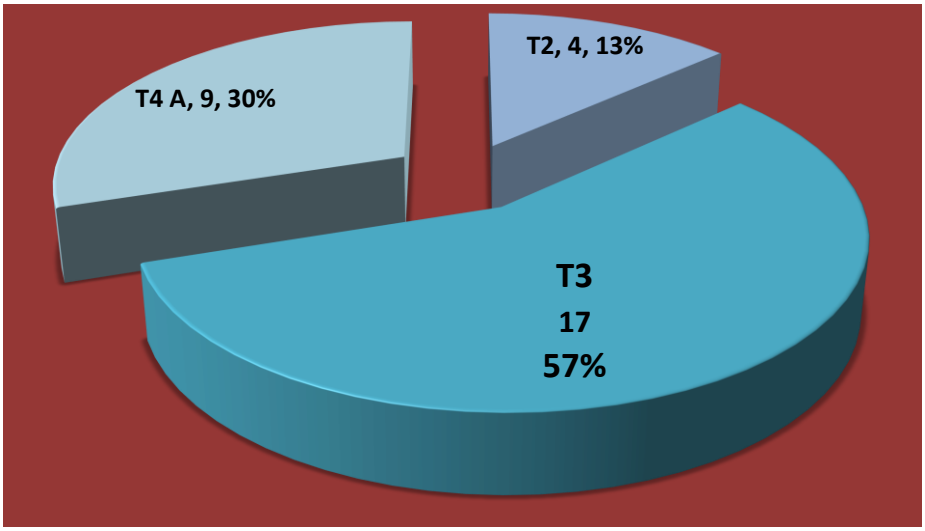

PERFORMANCE STATUS
13, 43%
17, 57%
ECOG 0
ECOG 1


SYMPTOMS AND SIGNS
SYMPTOMS AND SIGNS
19
16
9
8
11
11
DYSPHAGIA
ODYNOPHAGIA
ULCER OR GROWTH
NECK SWELLING
VOICE CHANGE
PAIN

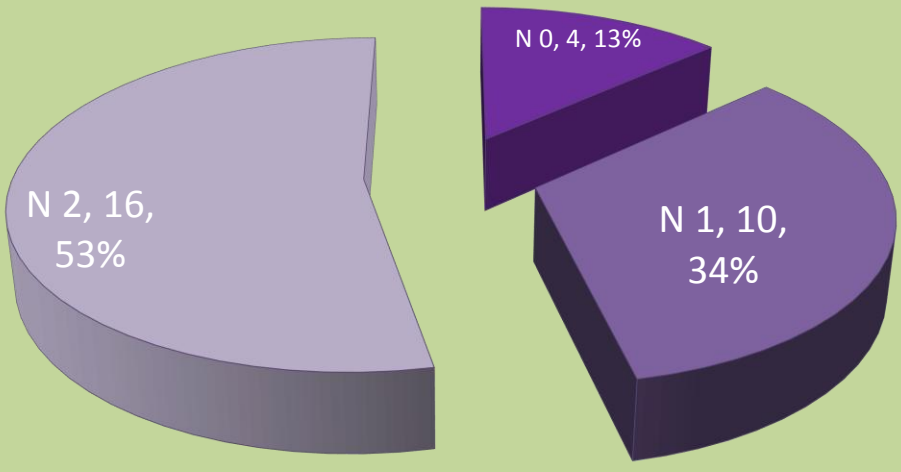

PRIMARY SITE DISTRIBUTION
10
8
6
4
2
0
9
8
5
8
OROPHARYNX
HYPOPHARYNX
ORALCAVITY
LARYNX

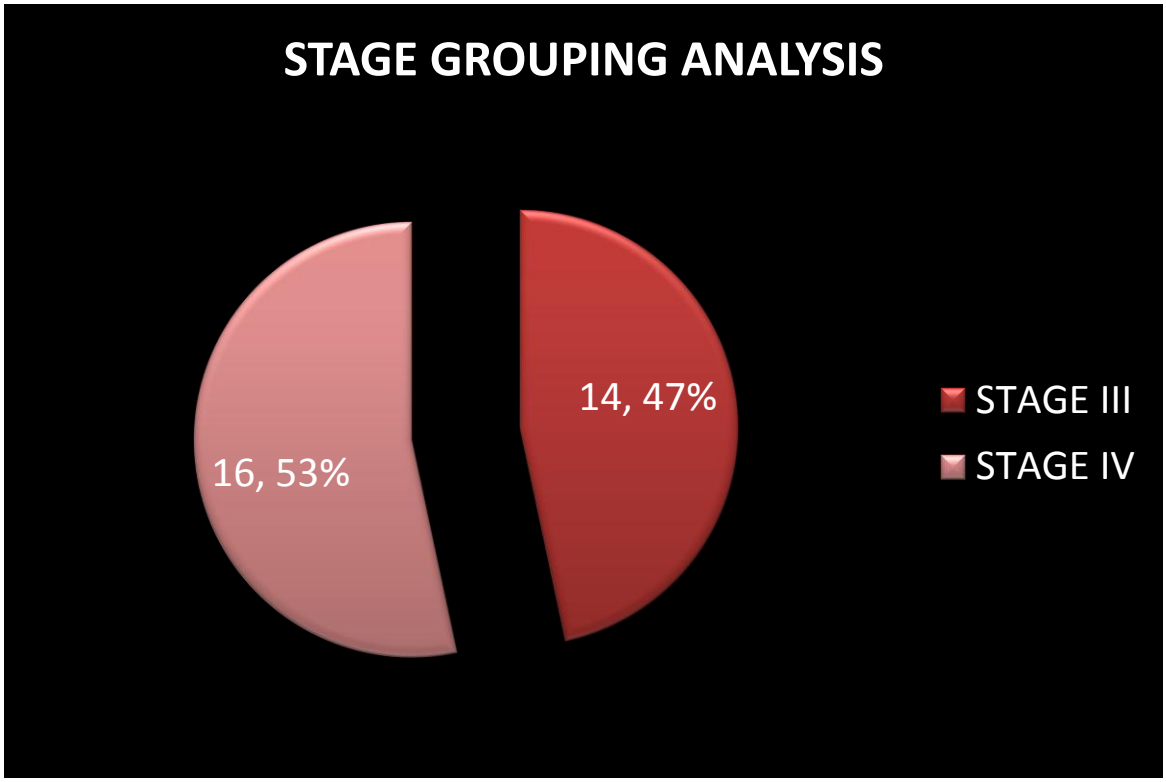

SUBSITE ANALYSIS
8
7
6
5
4
3
2
1
0
8
6
3
8
4
1
SUPRAGLOTTIS
TONSIL
POST 1/3 TONGUE
PYRIFORM FOSSA
ANT 2/3 TONGUE
HARD PALATE

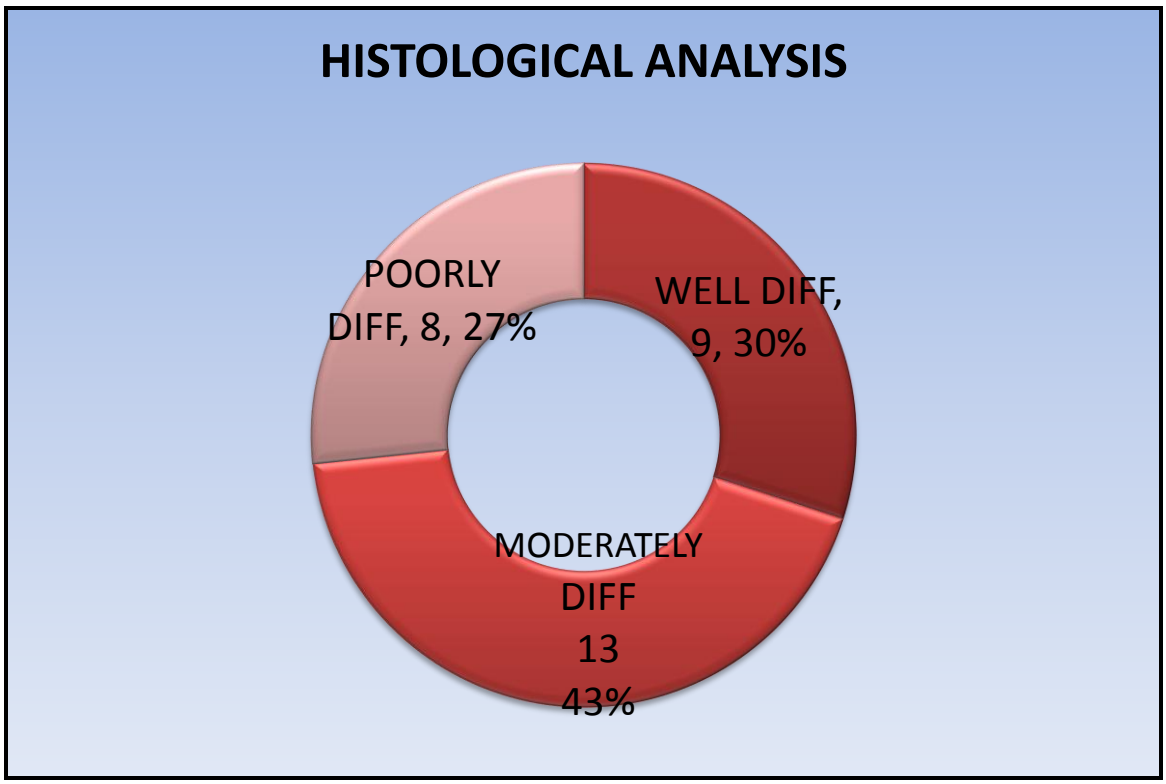
TUMOUR STAGE ANALYSIS

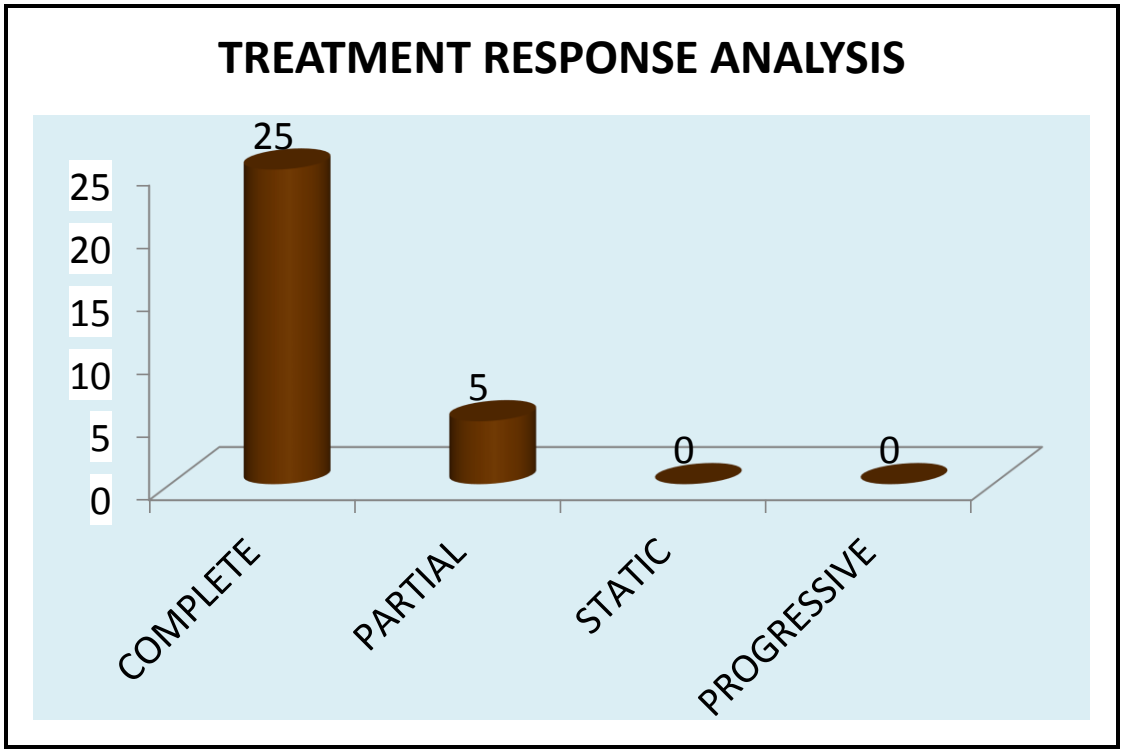


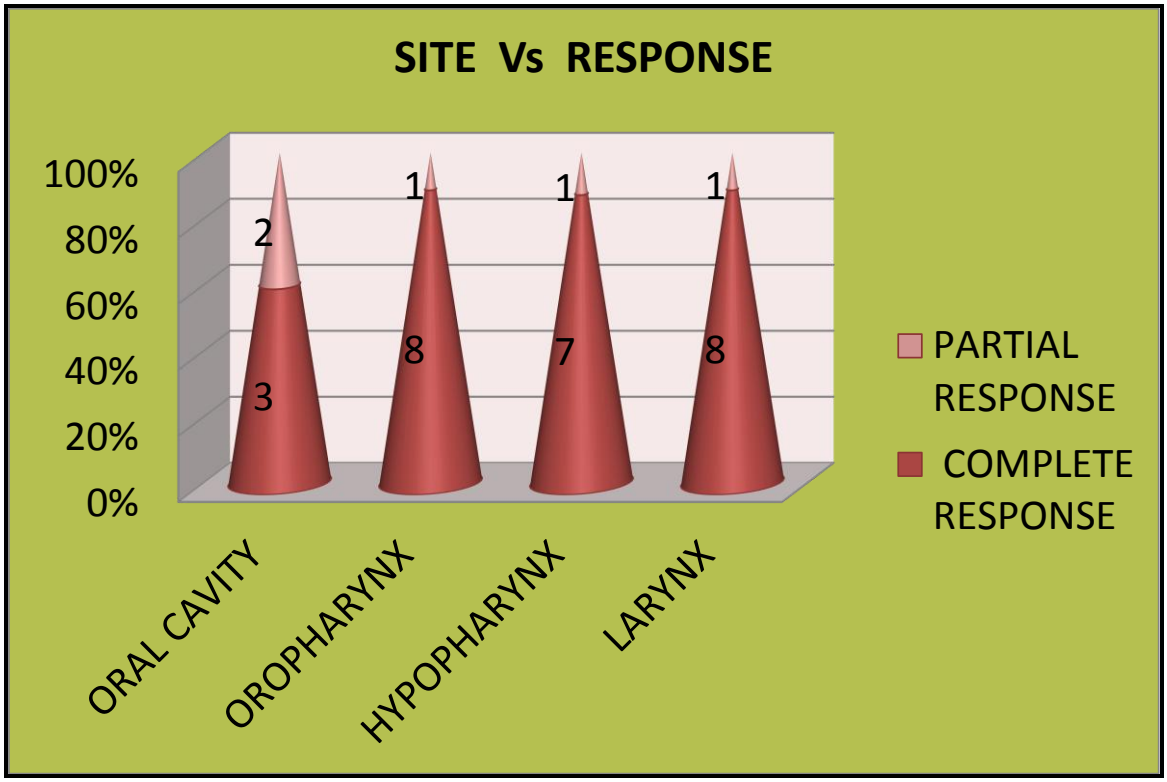
NODAL STAGE ANALYSIS



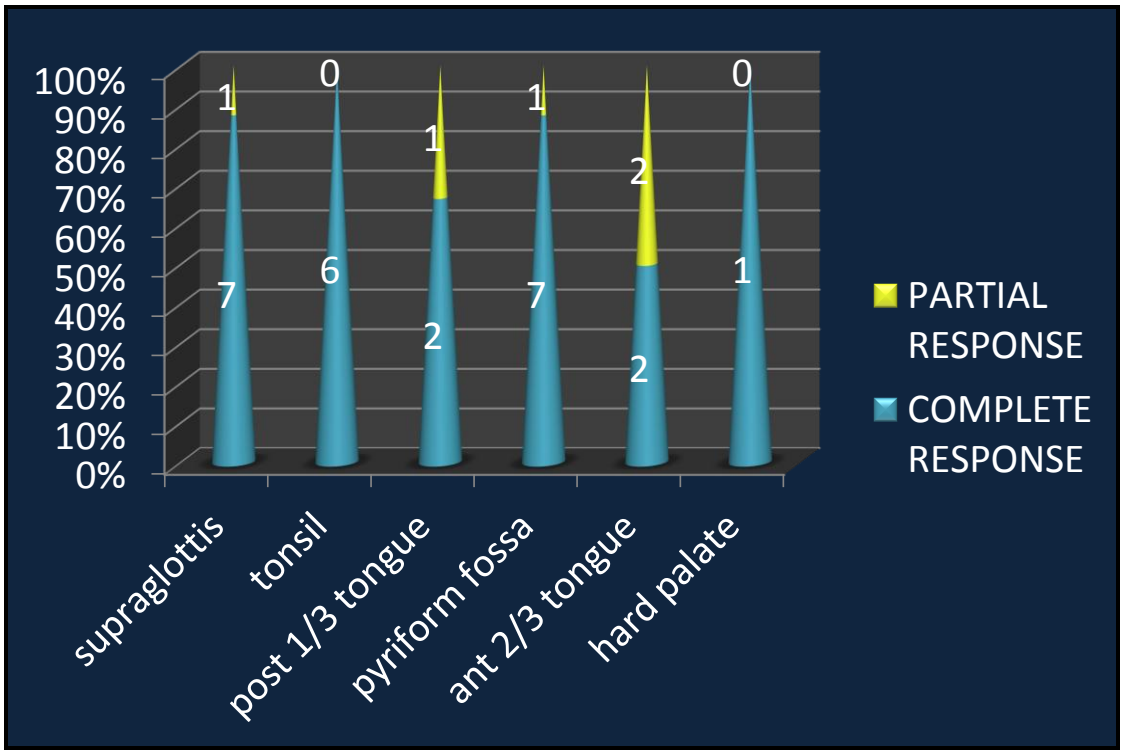

STAGE GROUPING ANALYSIS
14, 47%
16, 53%
STAGE III
STAGE IV


HISTOLOGICAL ANALYSIS
POORLY DIFF, 8, 27%
WELL DIFF, 9, 30%
MODERATELY DIFF 13 43%

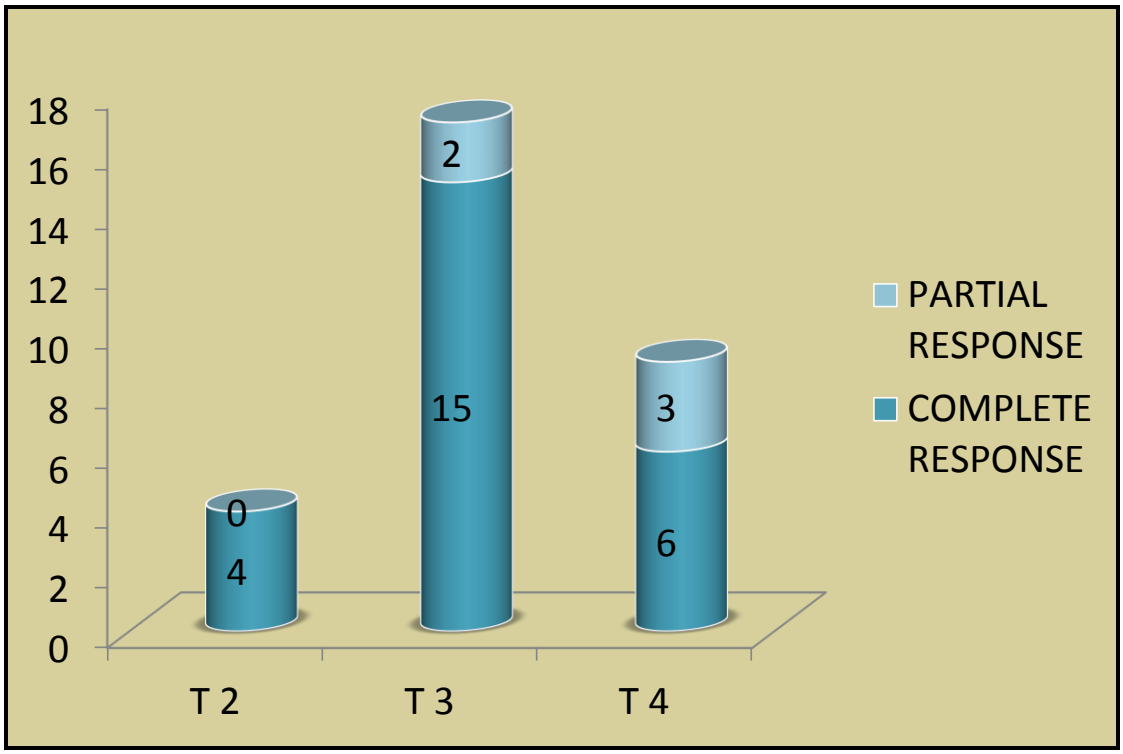

TREATMENT RESPONSE ANALYSIS
25
20
15
10
5
0
25
5
0
0
COMPLETE
PARTIAL
STATIC
PROGRESSIVE

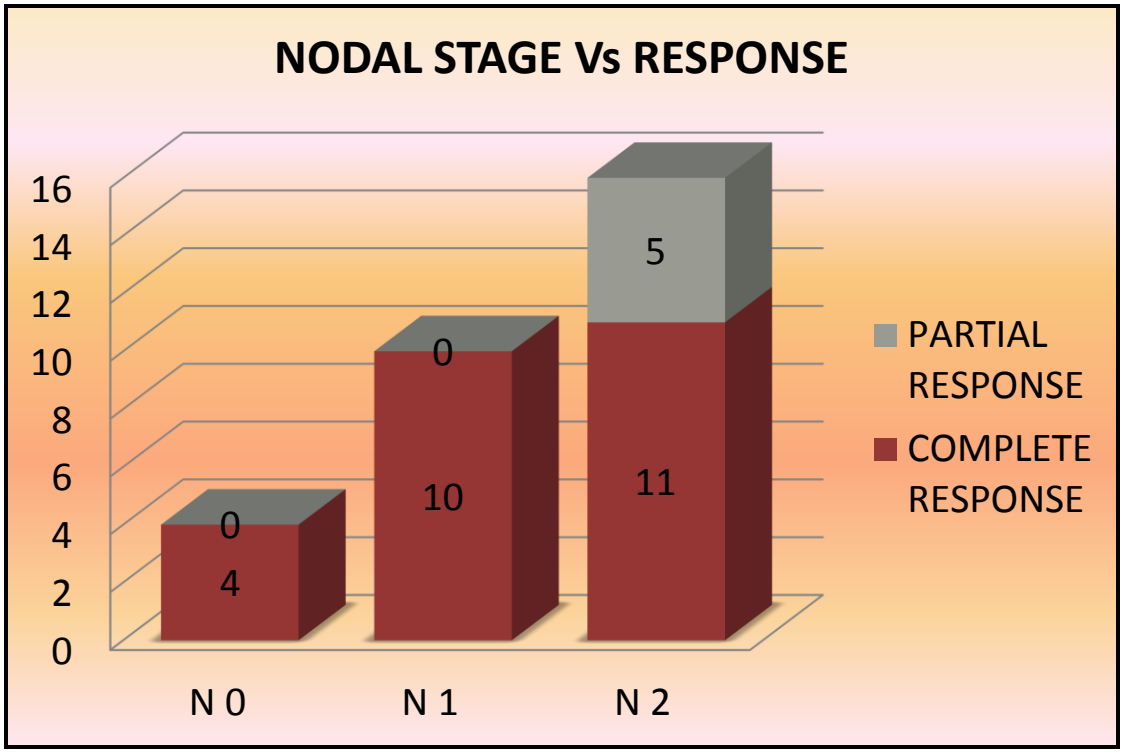

SITE Vs RESPONSE
100%
80%
60%
40%
20%
0%
2
3
1
8
1
7
1
8
ORAL CAVITY
OROPHARYNX
HYPOPHARYNX
LARYNX
PARTIAL RESPONSE
COMPLETE RESPONSE

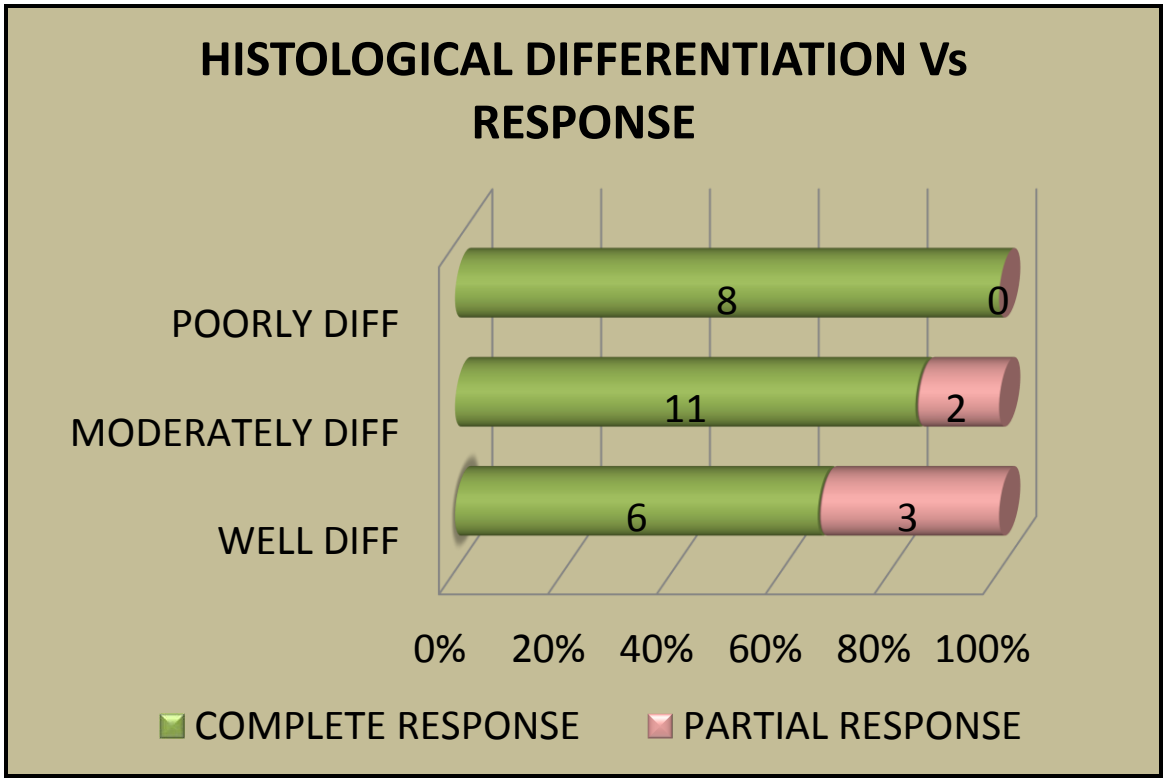
SUBSITE VS RESPONSE

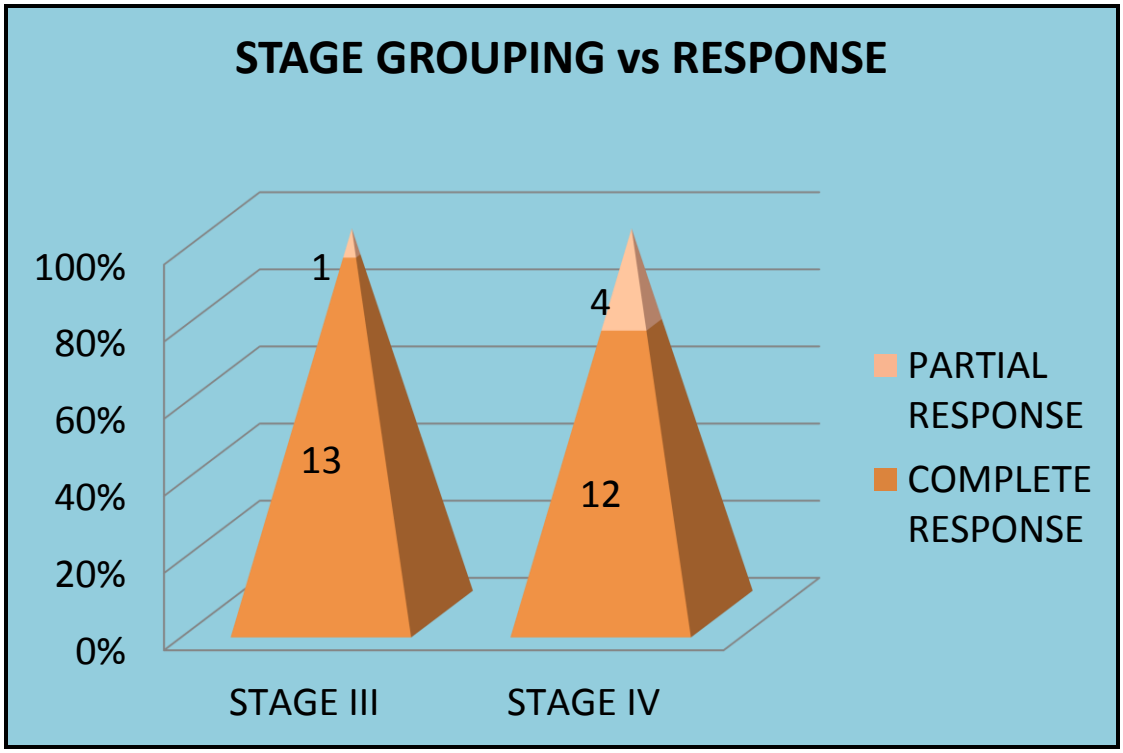


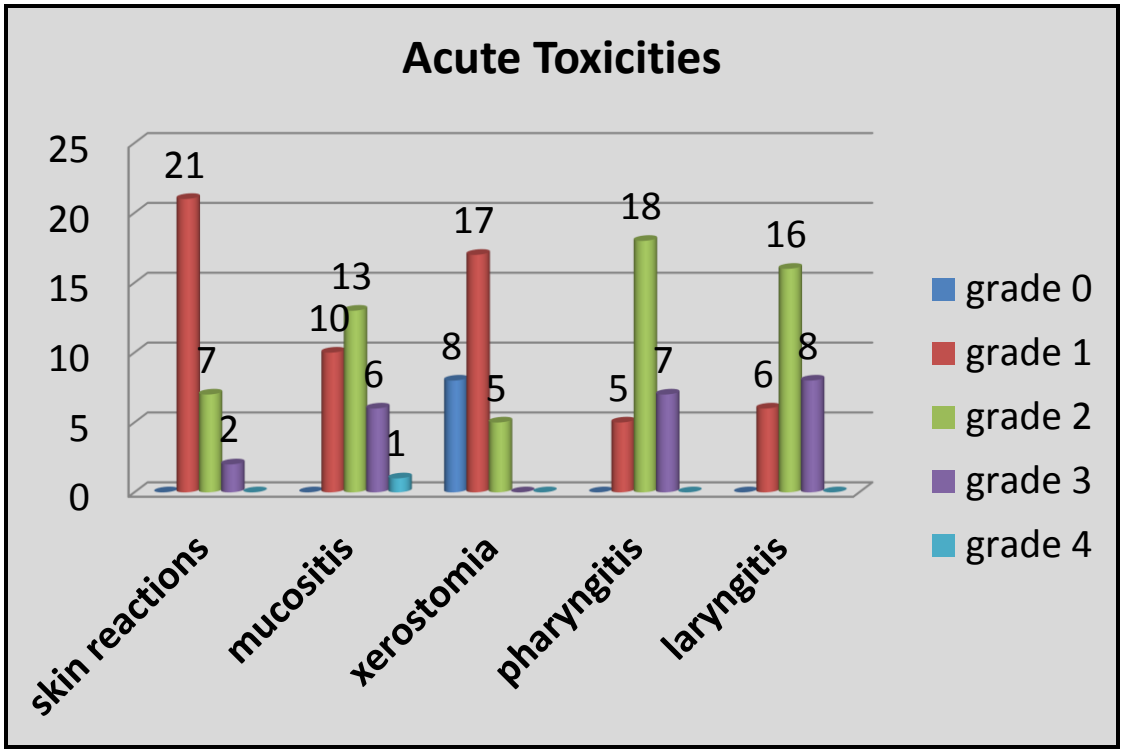
TUMOUR STAGE VS RESPONSE

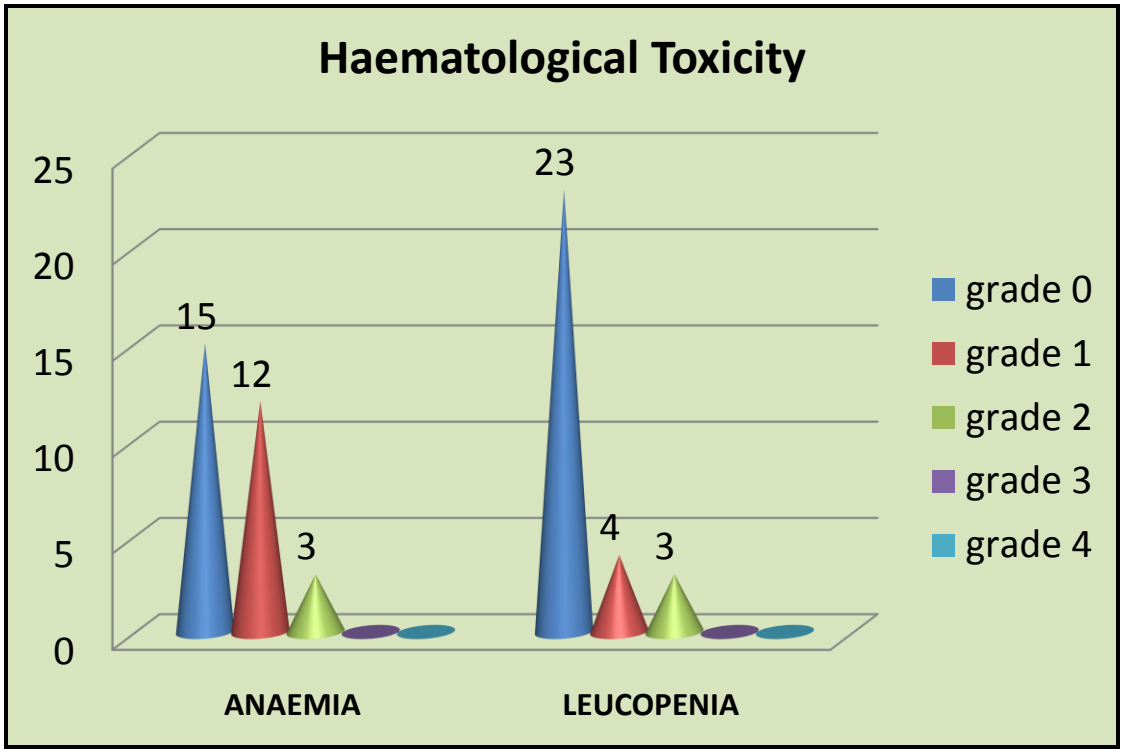


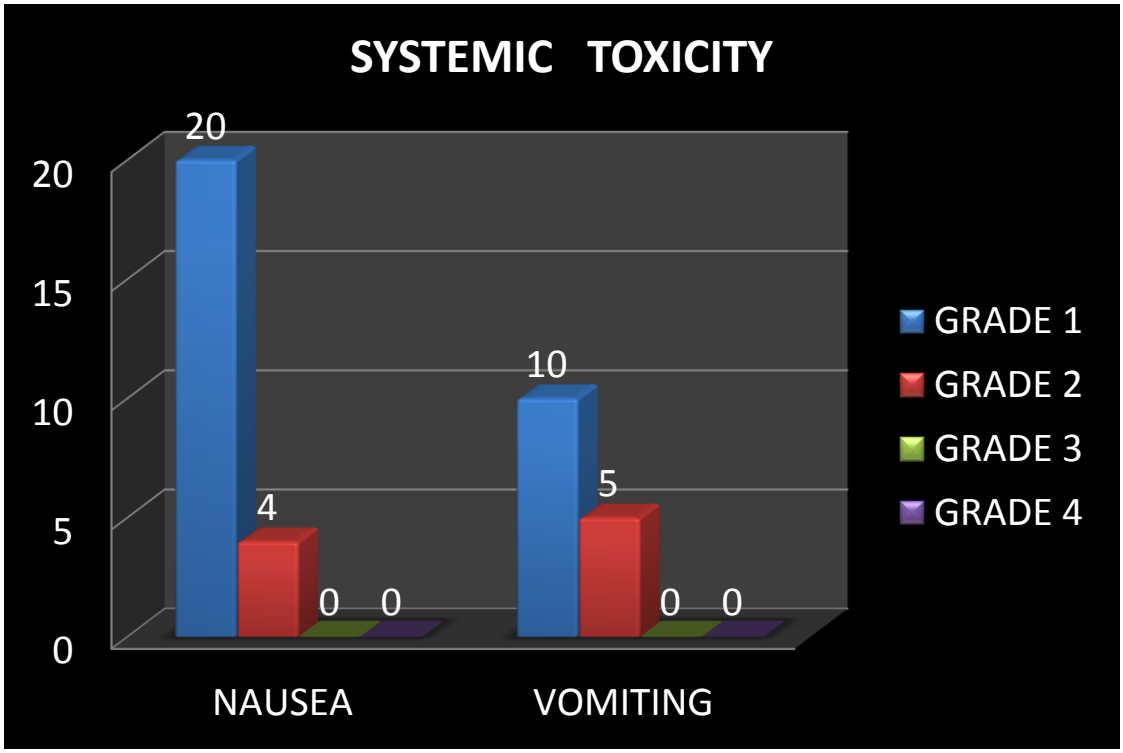

NODAL STAGE Vs RESPONSE
16
14
12
10
8
6
4
2
0
0
4
0
10
5
11
N 0
N 1
N 2
PARTIAL RESPONSE
COMPLETE RESPONSE


HISTOLOGICAL DIFFERENTIATION Vs RESPONSE
POORLY DIFF
MODERATELY DIFF
WELL DIFF
8
0
11
2
6
3
0%
20%
40%
60%
80%
100%
COMPLETE RESPONSE
PARTIAL RESPONSE


STAGE GROUPING vs RESPONSE
100%
80%
60%
40%
20%
0%
1
13
4
12
STAGE III
STAGE IV
PARTIAL RESPONSE
COMPLETE RESPONSE


Acute Toxicities
25
20
15
10
5
0
21
7
2
10
13
6
1
8
17
5
5
18
7
6
16
8
skin reactions
mucositis
xerostomia
pharyngitis
laryngitis
grade 0
grade 1
grade 2
grade 3
grade 4


Haematological Toxicity
25
20
15
10
5
0
15
12
3
23
4
3
ANAEMIA
LEUCOPENIA
grade 0
grade 1
grade 2
grade 3
grade 4


SYSTEMIC TOXICITY
20
15
10
5
0
20
4
0
0
10
5
0
0
NAUSEA
VOMITING
GRADE 1
GRADE 2
GRADE 3
GRADE 4

APPENDIX - I

LIST OF TABLES

APPENDIX – II
LIST OF FIGURES

APPENDIX – III
RTOG ACUTE RADIATION MORBIDITY CRITERIA

Site	Grade0	Grade1	Grade2	Grade3	Grade 4
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous Membrane	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Salivary Gland	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste		Acute salivary gland necrosis

Site	Grade0	Grade1	Grade2	Grade3	Grade 4
Pharynx & Esophagus	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyper alimentation	Complete obstruction, ulceration, perforation, fistula
Laryngitis	No change over baseline	Mild or intermittent hoarseness/cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

APPENDIX – IV
HEMATOLOGIC TOXICITY

Grade	0	1	2	3	4
HEMATOLOGIC WBC (X 1000)	>=4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
PLATELETS (X 1000)	>=100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
NEUTROPHILS	>=1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
HEMOGLOBIN (GM %)	>11	11- 9.5	<9.5 - 7.5	<7.5 - 5.0	-

APPENDIX - V
COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS CTCAE VERSION 4

GRADE	1	2	3	4
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake, tube feeding, TPN, or hospitalization indicated	-
Vomiting	1-2 episodes (separated by 5 minutes) in 24 hrs	3-5 episodes (separated by 5 minutes) in 24 hrs	>/=6 episodes (separated by 5 minutes) in 24 hrs,tubefeeding,TPN or hospitalization indicated	Life-threatening consequences, urgent intervention indicated
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 -6 stools per da over baseline; moderate increase in ostomy output compared to baseline	Increase of =7 stools per day over baseline; incontinence; hospitalization indicated;severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

ANNEXURE – 1

INFORMATION TO PARTICIPANTS

Title: **"CONCOMITANT BOOST IRRADIATION WITH WEEKLY LOW DOSE CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK"**

Name of Participant:
Name of the Principal(co – investigator) :DR.S.SELVALAKSHMI
Name of the institution : Department of radiotherapy, 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?

- 65% patients with head and neck tumors present with locally advanced disease. Concurrent chemoradiotherapy is a treatment program for locoregionally advanced squamous cell carcinomas of the head and neck (SCCHN), with established benefits in both organ preservation and survival. Concomitant Boost means delivering two fractions of radiation daily either in the beginning or in the end of treatment in order to prevent accelerated repopulation in head and neck cancers. The boost is given only to the primary tumour site and the involved nodes. Weekly cisplatin is a more acceptable regimen than three weekly cisplatin. Paclitaxel causes cell cycle arrest at G2M phase which is a radiosensitive phase and thereby potentiating radiation. Radiotherapy will be delivered by opposing lateral fields with a telecobalt machine using concomitant boost technique of 45gy/1.8gyper# /25# - 5 weeks and 22.5gy/ 1.5gy per# /15# given as a boost only to small field including primary and involved node at an interval of 6 hrs during last 3 weeks of treatment. Patients are given a break on Saturday and Sunday. Weekly Cisplatin and Weekly Paclitaxel chemotherapy is given every Monday before radiation. Entire treatment is to be completed in 5 weeks time .Primary and gross adenopathy receive 67.5GY.

- We want to test the efficacy and safety of "concomitant boost radiotherapy with weekly low dose chemotherapy " .We have obtained permission from the Institutional Ethics Committee.

The study design

Single arm prospective study

Study Procedures

The study involves evaluation of Locally advanced squamous cell carcinoma of the head and neck with concomitant radiotherapy and chemo in the form of low dose weekly inj.cisplatin and inj paclitaxel. Every week before 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 – II

INFORMED CONSENT FORM

TITLE OF THE STUDY **"CONCOMITANT BOOST IRRADIATION WITH WEEKLY LOW DOSE CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK"**

NAME OF THE PARTICIPANT:
NAME OF THE PRINCIPAL (Co – Investigator) : DR.S.SELVALAKSHMI.,
NAME OF THE INSTITUTION: 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 "CONCOMITANT BOOST IRRADIATION WITH WEEKLY LOW DOSE CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK"

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 undergo 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 understand 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)

Signature of Investigator Signature of participant

Date : Date:

ANNEXURE - III

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு

தலை மற்றும் கழுத்து பகுதியில் உள்ள முற்றிய ச்கோமெளஸ் செல் வகை புற்றுநோய்க்கு மாற்று கதிர்வீச்சு சிகிட்சையும் (இணைந்த ஊக்க கதிர்வீச்சு சிகிட்சை முறை) அதனுடன் வாரம் ஒரு முறை அளவு குறைக்கப்பட்ட வேதி சிகிட்சையும் கொடுத்தல்

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்துக்கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனக்கு புற்றுநோய் இருக்கும் பகுதியில் கதிர்வீச்சு சிகிச்சையும் அதனுடன் வாரம் ஒரு முறை சிஸ்பிளாடின் மற்றும் பேக்லிடேக்ஸல் மருந்தும் எடுத்துக் கொள்ள சம்மதம்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் நான் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் தலை மற்றும் கழுத்து பகுதியில் முற்றிய புற்றுநோய் குறித்த இந்த ஆய்வுக்கான விவரங்கள் கொண்ட தகவல் தாளைப் பெற்றுக்கொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியின்படி கதிர்வீச்சு சிகிச்சை மற்றும் புற்றுநோய் மருந்துகள் பெற்றுக்கொள்ள சம்மதம். இந்த ஆராய்ச்சிக்கு தேவையான பிற பரிசோதனைகள் செய்துக்கொள்ள சம்மதம்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம் தெரிவிக்கிறேன்.

நாள் :

இடம் : கையொப்பம்

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு

தலை மற்றும் கழுத்துப்பகுதியில் உள்ள முற்றிய ஸ்குவாமஸ் செல் வகை புற்றுநோய்க்கு மாற்று கதிர்வீச்சு சிகிச்சையும் (இணைந்த ஊக்க கதிர்வீச்சு சிகிச்சை முறை) அதனுடன் வாரம் ஒருமுறை அளவு குறைக்கப்பட்ட வேதி சிகிச்சையும் கொடுத்தல்

ஆய்வாளர் :

பங்கேற்பாளர் :

இந்த ஆய்வு ராஜீவ் காந்தி அரசு பொது மருத்துவமனையில் நடைபெற உள்ளது. நீங்களும் இந்த ஆய்வில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதிலுள்ள தகவலின் அடிப்படையில் இந்த ஆய்வில் பங்கேற்பதா அல்லது வேண்டாமா என்று நீங்கள் முடிவு செய்து கொள்ளலாம். உங்களது சந்தேகங்களை எங்களிடம் கேட்டு நிவர்த்தி செய்து கொள்ளலாம்.

இந்த ஆய்வின் நோக்கம்:

மாறிவரும் பொருளாதார காரணிகள் மற்றும் வாழ்க்கைமுறையின் காரணமாக தலை மற்றும் கழுத்துப்பகுதி புற்றுநோயினால் பாதிக்கப்பட்டவர்களின் எண்ணிக்கை சமீபகாலமாக அதிகரித்துக்கொண்டே வருகிறது.

பெரும்பாலானோர் இந்த நோய் முற்றிய நிலையிலேயே மருத்துவமனைக்கு வருகின்றனர். அதனால் முழுவதும் குணப்படுத்தக்கூடிய வைத்திய முறைகளை பயன்படுத்தும் வாய்ப்பை இழக்கின்றனர். அதனால் நோய்க்குறி தனிப்பு வைத்திய முறைகளை மட்டுமே பயன்படுத்தும் நிலைக்கு ஆளாகின்றனர். இவ்வகையான வைத்தியத்தில் பலவகை உள்ளன. இந்த ஆய்வில் பயன்படுத்தும் வைத்திய முறையின் மூலம் சிறந்த நோய்க்குறி தனிப்பையும் குறைவான பின்விளைவுகளையும் பெரும் வகையில் வழி செய்வதே எங்கள் நோக்கமாகும்.

ஆய்வின் செயல்முறை:

நோயாளிகள் இரத்தப் பரிசோதனை, முகம் மற்றும் கழுத்துப்பகுதி சி.டி.ஸ்கேன், நெஞ்சுப்பகுதி எக்ஸ்-ரே, பல் சுத்தம் மற்றும் பாதுகாப்பு, புகைப்பழக்கத்தை கைவிட ஆலோசனை முதலியவற்றை மேற்கொள்ள வேண்டும். இவை அனைத்தும் வழக்கமாக எல்லா புற்றுநோயாளிகளிடமும் நோயின் நிலையை அறிய மேற்கொள்பவையே. நோயாளிகளுக்கு தினமும் இருமுறை 5 நாட்கள் 6 வாரங்களுக்கு நோய்குறி தனிப்பு கதிர்வீச்சுடன் வாரம் ஒருமுறை சிஸ்பிளாட்டின், பாக்லிடாக்சில் எனும் மருந்துகள் செலுத்தப்படும்.

ஆறு வாரங்கள் கழித்து நோயின் நிலையை அறிய சி.டி.ஸ்கேன் மற்றும் உடல் பரிசோதனை செய்யப்படும். இந்த பரிசோதனைகள் இவ்வகையான வைத்தியத்தின் விளைவுகள் மற்றும் பயன்களை அறிய அவசியம்.

ஆய்வினால் ஏற்படும் நன்மைகள்

சிறந்த நோய்க்குறி தனிப்பும், குறைவான பின்விளைவுகளும் கிடைக்க அதிக வாய்ப்புகள் உள்ளன.

ஆய்வினால் ஏற்படும் தீமைகள்

வழக்கமான கதிர்வீச்சுகளில் வரும் விளைவுகளைவிட அதிகம் ஏதுமில்லை.

ஆய்வினால் பிறருக்கு ஏற்படும் நன்மைகள்:

இந்த ஆய்வில் கலந்துகொள்வதன் மூலமாக நீங்கள் நோயின் தன்மையில் முன்னேற்றம் பெறலாம். மேலும் வருங்காலத்தில் பிற நோயாளிகளும் பயன்பெற இந்த ஆய்வு உதவியாக அமையும்.

மருத்துவ சிகிச்சையின் தகவல்கள் குறித்த விவரங்கள்:

உங்கள் மருத்துவ சிகிச்சை குறித்த தகவல்கள் ரகசியமாக பாதுகாக்கப்படும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுக்கு பரிசோதனைகள் செய்து அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

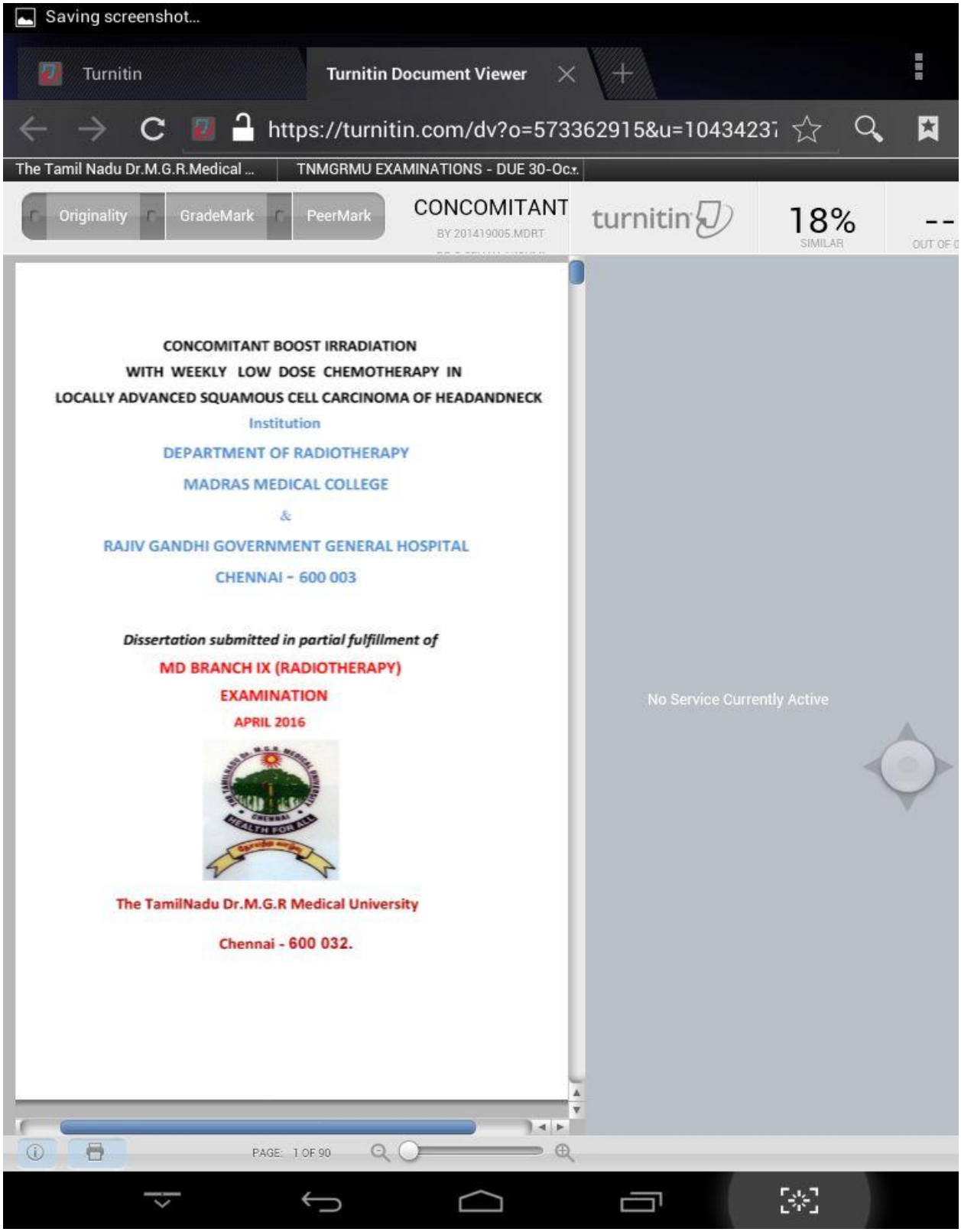
இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

ANEXURE V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OUT OF
CONCOMITANT BOOST IRRADIATION
WITH WEEKLY LOW DOSE CHEMOTHERAPY IN
LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEADANDNECK
Institution
DEPARTMENT OF RADIOTHERAPY
MADRAS MEDICAL COLLEGE
&
RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL
CHENNAI - 600 003
Dissertation submitted in partial fulfillment of
MD BRANCH IX (RADIOTHERAPY)
EXAMINATION
APRIL 2016
The TamilNadu Dr.M.G.R Medical University
Chennai - 600 032.
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PAGE: 1 OF 90

ANNEXURE – VI

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

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

CERTIFICATE OF APPROVAL

To
Dr.S.Selvalakshmi
Postgraduate in M.D.(Radio-Therapy)
Madras Medical College
Chennai – 600 003.

Dear Dr. S.Selvalakshmi,

The Institutional Ethics Committee has considered your request and approved your study titled **"Concomitant Boost Irradiation with Weekly Low Dose Chemotherapy in Locally Advanced Squamous Cell Carcinoma of Head and Neck" No.27012015.**

The following members of Ethics Committee were present in the meeting held on 20.01.2015 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6. Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7. Prof.K.Ramadevi, Director , Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.S.G.Sivachidambaram, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
10. Thiru S.Rameshkumar, Administrative Officer	: Lay Person
11. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

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.

22/1/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

CONCOMITANT BOOST RADIATION

ORIGINALITY REPORT

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3	Kasibhatla, M.. "How Much Radiation is the Chemotherapy Worth in Advanced Head and Neck Cancer?", International Journal of Radiation Oncology, Biology, Physics, 20070801 Publication	1%
4	Heather E. Newlin. "Concomitant weekly cisplatin and altered fractionation radiotherapy in locally advanced head and neck cancer", Cancer, 06/22/2010 Publication	1%
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