COMPARISON OF LOW DOSE DAILY CISPLATIN VERSUS WEEKLY CISPLATIN ALONG WITH CONCURRENT ACCELERATED RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

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DEPARTMENT OF RADIOTHERAPY

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CERTIFICATE

This is to certify that **Dr.V.AMUTHA** has been a Post Graduate MD Student during the period from MAY 2015 to MAY 2018 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled "**COMPARISON OF LOW DOSE DAILY CISPLATIN VERSUS WEEKLY CISPLATIN ALONG WITH CONCURRENT ACCELERATED RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA**" is a bonafide work done by her during the 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.

DEAN,
Madras Medical College &
Rajiv Gandhi Government General Hospital,
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DECLARATION

I solemnly declare that the dissertation titled "**COMPARISON OF LOW DOSE DAILY CISPLATIN VERSUS WEEKLY CISPLATIN ALONG WITH CONCURRENT ACCELERATED RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA**" was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during **October 2016 to August 2017** under the guidance and supervision of **Prof. Dr.R.GIRIDHARAN.**

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Introduction

INTRODUCTION

Cancer is one of the most dreaded diseases in the world. As the life expectancy of the population rises, there is an increasing incidence in the trend of cancer in the world (1) . 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 is the most essential structure for physiological functions like respiration, nourishment, verbal communication and appearance, which are only one of its kind. Any kind of surgical procedure, reconstruction, radiation and chemotherapy induced toxicities has got a lot of difficulties over the normal physiological functions; causes disfigurement and decreases the quality of life.

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 para nasal sinuses.

The burden of head and neck cancer in the world is large and significant, being the 6th most common type of cancer overall. In India the incidence is even higher and is one of the most common type of cancer. The incidence also varies according to the geographic distribution and the local habits. Its incidence highly correlates with the abuse of tobacco in its various forms and the synergistic effect of its combination with its partner in crime, alcohol.

Majority of the patients present in the locally advanced stage where they are treated with a combination of all the three major modalities of oncology- surgery, chemotherapy and radiotherapy. However even with the best of therapy the overall 5 year survival amongst this group hovers around the 50% mark, and it is even less in a developing country like ours. And even with all the recent advances in therapeutics in all the three fields there has been no significant change in the survival.

EPIDEOMOLOGY:

Head and neck cancers in India accounts for about 30% of all cancers in the males, constitute 11 to 16% in females. Over 200,000 cases of head and neck cancers occur each year in India. Nearly 80,000 oral cancers are diagnosed every year in our country .

According to study published in Lancet in March 2012, the tobacco related cancers represented around 42% of male and 18% of female cancer

deaths in India. In men two most common fatal cancers are oral (including lip and pharynx) and lung (2).

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:

Among youth, there is some evidence of cancerous growth in use of other forms of tobacco (e.g., cigars, water pipes, electronic cigarettes) that may be displacing cigarette use.

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 (3). 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. In these analyses, the N-nitrosamines, benzene, 1,3-butadiene, aromatic amines, and cadmium often rank highly.

SMOKELESS TOBACCO:

Globally there is a 60% increase in alternative nicotine delivery systems like snuff, lozenges(5). 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 local preferences and are varyingly called as *gutkha, zarda, mawa, khaini (6).*

ALCOHOL:

Alcohol has synergistic effect with tobacco. Duration, intensity and concentration of alcohol consumption directly correlates with oral cavity cancer. A meta-analysis from 26 studies of oral and pharyngeal cancers found that consumption of 25, 50, or 100 g pure alcohol/day was associated with a pooled relative risk (RR) of 1.75, 2.85, and 6.01, respectively, of oral and pharyngeal cancer .Alcohol consumption also leads to immunosuppression, alcohol related diseases, altered behavior, unhealthy dietary pattern, and unstable emotional balance. All these factors have impact on cancer treatment and survival.

HUMAN PAPILLOMA VIRUS:

HPV infection is proved to be one of the causative factor in SCCHN. HPV prevalence is about 30-35% observed in head and neck cancers, with HPV-16 being detected in 60- 90% of infected cancer cases. HPV prevalence has been found to be highest in oropharynx tumors (palatine tonsil), less common in the oral cavity (7,8).

The oncogenesis of SCCHN by HPV is by transformation of epithelial cells by viral oncoproteins E6 and E7 which inactivate the tumor suppressor genes p53 and Rb in the host cell leading on to increased cell proliferation and inhibition of apoptosis.

HPV positive oropharyngeal cancers have characteristic features like

- Young patients,
- Nonsmokers

- Non alcoholics

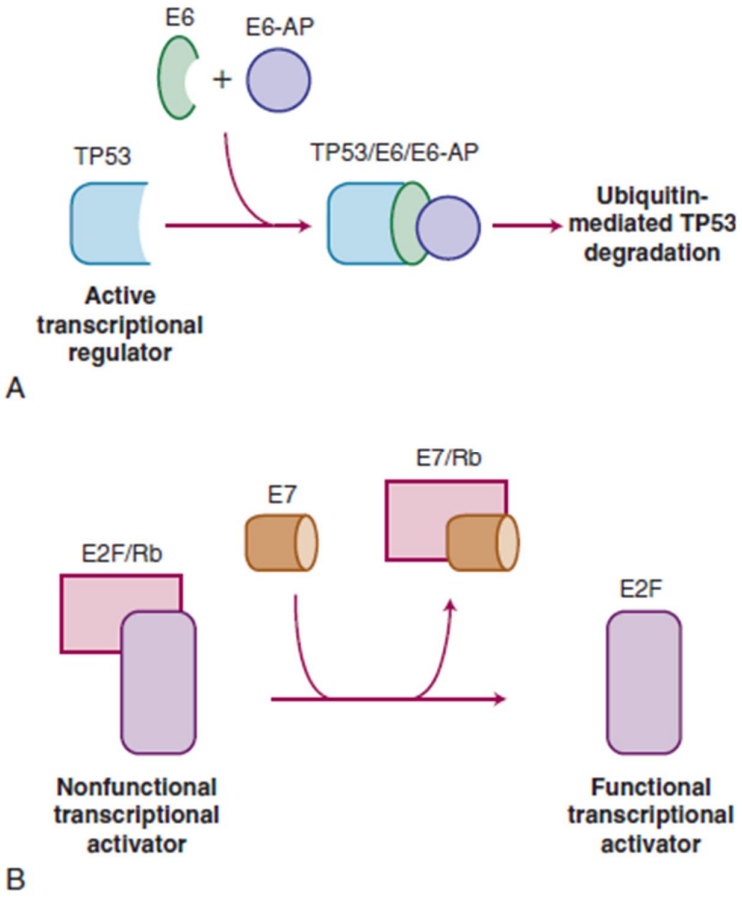
- Present with locally advanced disease with large T and N stage

- Often with basaloid histology

- Poorly differentiated

-Sexually transmitted cancer due to oral sexual activity

- Better prognosis due to sensitivity to radiotherapy and chemotherapy as compared HPV negative SCCHN



OTHER RISK FACTORS:

Diet deficient in antioxidants has been implicated to cause cancer in about 10% cases, spicy food consumption, sharp teeth, wood dust, heat fumes, heavy metal exposure (like asbestos, nickel, chromium), submucous fibrosis etc are also risk factors.

Plummer Vinson syndrome due to chronic iron deficiency and its association with post cricoid web can produce hypopharyngeal cancer.

Chronic actinic exposure can produce cancer of lip.

PRECANCEROUS CONDITIONS:

Leukoplakia, Erythroplakia, Submucous fibrosis, Lichenplanus, Epidermolysis bullosa, Discoid lupus erythematosus etc .

Leukoplakia:

A white mucosal patch or plaque, most common premalignant lesion of the oral cavity. It resolves with cessation of smoking.

Erythroplakia:

Reddish discolouration of the mucosa, 15-20% increased risk of cancer.

In a study done by Northern Ireland states that, only 15% of dysplastic lesions and 1% of non-dysplastic lesions(epithelial hyperplasia, lupus etc) turn to neoplasia (9).

INHERITED CONDITIONS like Fanconi Anemia (FA), Ataxia Telangiectasia, Blooms Syndrome, & Li-Fraumeni Syndrome has increased risk of head and neck cancer.

Inspite of all the aggressive campaign waged against tobacco, the rates of tobacco addiction, especially amongst the younger generation is increasing and as a result the incidence of tobacco related cancer in general and head and neck cancer in particular continues to show an increase. There is also an increasing number of cancers in the younger adults reflecting the widespread use of tobacco products amongst this group.

ANATOMY:

The **ORAL CAVITY** includes Mucosal Lip, Buccal Mucosa, Alveolar Ridge, Retromolar Trigone, Floor of the Mouth, Hard Palate and Oral Tongue

Lip: The lip begins at the junction of the vermilion border with the skin and includes only the vermilion surface. It is well defined into an upper and lower lip joined at the angle of mouth.

Buccal Mucosa: Includes the membranous lining of the inner surface of the cheeks and lips from the line of contact of the opposing lips to the line of attachment of mucosa of the alveolar ridge (upper and lower) and pterygomandibular raphe.

Alveolar Ridge: Mucosa overlying the alveolar process of the mandible or maxilla which extends from the line of attachment of mucosa in the gingivobuccal sulcus.

Retromolar Trigone: Mucosa overlying the ascending ramus of the mandible from the last molar tooth to the apex superiorly, adjacent to the tuberosity of the maxilla.

Floor of the Mouth: Semilunar space overlying the mylohyoid and hyoglossus muscles, extending up to the undersurface of the tongue. Its posterior boundary is the base of the anterior pillar of the tonsil. The ostia of the submandibular and sublingual salivary glands lie in the floor of mouth.

Hard Palate: Semilunar area between the upper alveolar ridge and the mucous membrane covering the palatine process of the maxillary palatine bones. It extends from the inner surface of the superior alveolar ridge to the posterior edge of the palatine bone.

Oral Tongue: The portion of the tongue which extends anteriorly from the line of circumvallate papillae to the under surface of the tongue at the junction of the floor of the mouth. It is divided into the tip, the lateral borders, the dorsum, and the undersurface of tongue.

PHARYNX: It is divided into Nasopharynx, Oropharynx and Hypopharynx.

Oropharynx: This part of pharynx extends from the soft palate to the superior surface of the hyoid bone / vallecula. Oropharynx includes base of tongue, vallecula, soft palate, uvula, tonsil with anterior and posterior tonsillar pillar, the glossotonsillar sulci and posterior pharyngeal walls.

Hypopharynx: Extends from the superior border of the hyoid bone to the lower border of the cricoid cartilage. It includes the pyriform sinuses (right and left), the lateral and posterior hypopharyngeal walls, and the postcricoid region.

The post cricoid area forms the anterior wall of the hypopharynx. It extends from the level of the arytenoid cartilages and to the plane of the inferior border of the cricoid cartilage.

The pyriform sinus extends from the pharyngoepiglottic fold to the cricopharynx and bounded laterally by the lateral pharyngeal wall, medially by aryepiglottic fold and the arytenoid and cricoid cartilages.

The posterior pharyngeal wall extends from the level of the superior surface of the hyoid bone to the inferior of the cricoid cartilage.

LARYNX: Composed of several cartilages connected by ligaments and muscles. It is divided anatomically into the Supraglottic, Glottic, and Subglottic regions.

The **Supraglottic** larynx consists of the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and arytenoids; the arytenoids are cartilages that articulate on the cricoid.

The **glottis** includes the true vocal cords and the anterior commissure.

The **subglottis** is 2 cm long and extends from 5 mm below the free edge of the true vocal cords to the upper margin of the first tracheal ring.

The preepiglottic space is bounded by the epiglottis posteriorly, the hyoepiglottic ligament and vallecula superiorly, and the thyroid cartilage and thyrohyoid membrane anteriorly and laterally.

HISTOLOGICAL CLASSIFICATION:

Squamous cell carcinoma constitutes 90 - 95% of the head and neck cancers. Remaining 5% are adenocarcinoma, verrucous carcinoma, minor salivary gland tumors, melanomas, adenoid cystic carcinoma, lymphoepitheliomas, and lymphoma (10).

With respect to grades of differentiation based on keratinization, squamous cell carcinoma as three types;

Well differentiated - >75% keratinized

Moderately differentiated -25_50% keratinized

Poorly differentiated- <25% keratinized.

SYMPTOMS:

Most common presenting symptom is ulcer (for ulceroprolifertive lesion) followed by pain, difficulty in swallowing (dysphagia), pain during swallowing (odynophagia), difficulty in breathing (dyspnea), change in voice, and neck swelling because of lymph nodal involvement. Other generalized symptoms are cough, weight loss, loss of appetite may cause further detoriation with treatment like concurrent chemoradiation. Nutritional status of the patient plays a major role in treatment outcome.

PROGNOSTIC FACTORS:

Most of our patients present with advanced T stage with Lymph node involvement in which case single modality treatment is not possible. Even with combined modality treatment, local recurrences occur in 40-50% of the patients.

TUMOR SIZE: T stage has major prognostic factor, advanced T stage have poor prognosis.

NODAL INVOVLMENT: reduces the survival by 50%.

TUMOUR SITE: Early Ca Larynx has good prognosis than oral cavity and hypopharynx. Other factors like perineural invasion, postoperative positive margins, extra capsular nodal extension, depth of invasion plays a major role.

MOLECULAR BIOMARKERS:

EGFR Mutation: Studies show that 80- 95% of the squamous cell carcinomas of the head and neck are associated with overexpression of EGFR receptors . Activated EGFR leads to cell proliferation, inhibits apoptosis, affects cell

differentiation, increases cell motility, stimulates angiogenesis and is known to induce metastasis. This gives a therapeutic target in manipulating receptor pathways in cancer cells with targeted agents, monoclonal antibodies, like cetuximab as shown benefit in the advanced stages(11).

P53 MUTATION:

Most common gene mutation observed in head and neck cancers. Associated with worse prognosis because this gene is involved in cell cycle regulation and apoptosis. It shows poor response to chemoradiotherapy.

HEAD AND NECK CANCER TREATMENT OVERVIEW:

Head and neck cancer has a multimodality treatment which includes Surgery, Chemotherapy, Radiotherapy and upcoming targeted therapy. The main outcome should be locoregional control with function preservation.

SURGERY:

Surgery was the primary modality used in the treatment of head and neck cancers. Primary is usually approached through a trans-oral, transcervical or, through mandibulectomy.

NECK NODES:

The anatomy of neck node levels should be known before lymph node dissection. There are no capillary lymphatics in head and neck epithelium so tumor must penetrate lamina propria before lymphatic invasion to occur. Thus

the involvement of lymph nodes in head and neck indicate that the tumor is locally advanced.

The lymph node levels of the neck are divided into seven levels.

Level I include Ia submental nodes and Ib submandibular nodes.

Level II upper jugular nodes , Level III middle jugular nodes

Level IV lower jugular nodes, Level V as posterior triangle lymphnodes.

Level VI pretracheal nodes, prelaryngeal and paratracheal nodes

Level VII mediastinal nodes.

Other regional nodes include

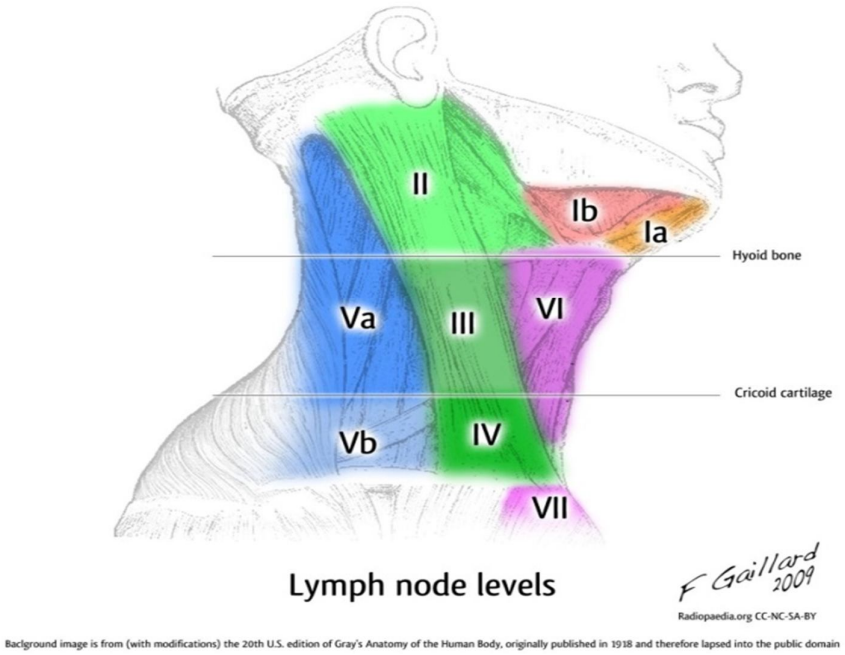
Suboccipital ,Retropharyngeal, Parapharyngeal, Buccinator (facial)

Preauricular, Periparotid and intraparotid depending upon the primary site.

Lymph node levels drain a particular site in head and neck. So surgery can be planned depending on the nodal region involvement. The primary site lip drains into Level I nodes with central part to submental nodes and angle of mouth to submandibular nodes. In case of oral cavity tumors mainly Level Ib submandibular and Level II nodes. Oral tongue as unique lymphatic drainage with Level Ib, II _IV; especially in lymphatics of tongue there is crossing over and thus bilateral nodal involvement is possible. Also tongue can have direct involvement of level IV node without Level Ib,II nodes involvement. Oropharynx will cause Level II and III involvement.

In case of Nasopharynx retropharyngeal lymph nodes are involved in 94% of cases or Level II in 90% of the patients. But it can involve Level II –V

group of nodes. In case of Hypopharynx bilaterality is common with involvement of Level II – IV group of nodes. Other areas like paranasal sinses, middle ear, vocal cords have fewer or no lymphatics.



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—cranial nerve XI is spared; type II—cranial nerve XI and the internal jugular vein are spared; type III (functional)—cranial nerve XI, the internal jugular vein, and the sternocleidomastoid muscle are spared. ***Selective*** **neck dissections** include the resection of lymph node levels that are at greatest risk for nodal metastatic spread. Types include the lateral, posterolateral, and supraomohyoid, which include resections of lymph node levels II–IV, II–V, and I-III, respectively (13).

A modified or selective neck dissection is recommended for the cN0 neck, for selected clinically positive necks (mobile, 1–3 cm lymph nodes), and for removing residual disease after RT when there has been excellent regression of N2 or N3 disease

INOPERABLE:

In a condition when adequate surgical clearance is not achievable , tumor spread to inaccessible areas like base of skull, infiltration into carotid artery,fixed nodes surgery is not an option. If the patient's general condition is poor surgery is not possible. Patients completed chemo radiotherapy with residual disease may be amenable to **Salvage surgery.**

RADIOTHERAPY:

Radiotherapy can be administered either Pre operatively, Post operatively or it can be definitive treatment with radiation alone in early stage tumors.

In case of postoperative Radiotherapy it should be administered after 4-6 weeks of surgery. Indications are advanced T stage, multiple node positivity and perineural or lymphovascular invasion. Post-operative chemo radiation is indicated in the case of positive margins and extracapsular extension(NCCN).

From 2D RT to 3D conformal RT to Intensity modulated RT, we are able to better spare the normal tissues from the deleterious effects of RT while at the same time delivering a substantial dose to the tumor.

The fractionation of radiotherapy can be of different types as

CONVENTIONAL FRACTIONATION:

As definitive modality dose of 66-74 Gy is recommended to the gross disease and 44-64 Gy to the subclinical disease by the(NCCN). In a schedule of 2Gy per fraction 5 days a week.

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(67.2 Gy in 42 fractions of 1.6 Gy twice daily over 6 weeks, including a 2-week break).

Type C(Accelerated concomitant boost): Total dose is same; overall treatment time is reduced with concomitant boostregimen (72 Gy in 42 fractions over 6 weeks, with 1.8 Gy daily for the first 3.6 weeks and 1.8 Gy [large field] plus 1.5 Gy [boost field], 6 hours apart, for the last 2.4 weeks).

Hyper Fractionated Radiotherapy: Dose of radiation is increased, dose per fraction is significantly reduced, the numbers of fractions are increased and overalltreatment time is significantly unchanged (81.6 Gy in 68 fractions over 7 weeks, with 1.2 Gy given twice daily)..

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. In patients who presents with very advanced stage, such cases cure is not possible as effort to alleviate the symptoms.

BRACHYTHERAPY:

Brachytherapy is another way of therapy where the radiation source is kept in close proximity to the tumour. It can be used as a form of boost to the

tumour after initial EBRT or it can be used alone in small early stage disease. Its advantage is that the dose delivered is highly conformal and there is minimal damage to the adjacent normal tissue.

CHEMOTHERPY:

Role of chemotherapy with radiation is proved in various trials. The MACHNC trial has proved overall survival benefit of 4% with addition of chemotherapy in a patient treated with surgery or radiotherapy.

Chemotherapy can be administered either as Induction, Concurrent or Adjuvant setting.

INDUCTION CHEMOTHERAPY:

It proved that induction chemotherapy reduces distant metastates but no difference in overall survival.

The neoadjuvant setting has an organ preservation approach in laryngeal cancers-the Veterans Affairs trial used chemotherapy in the neo adjuvant setting compared to concurrent chemoradiation to achieve organ preservation (15,21) . The use of induction chemotherapy using standard doses of cisplatin and 5 FU in various trials has shown a response rate of 60 to 90 % including 25 – 30 % complete response. It also decreased the incidence of distant metastasis probably because of the effect on micro metastasis in the circulation. But it failed to demonstrate any improvement in the survival. The recent phase III randomised trial DeCIDE trial which uses induction chemotherapy using docetaxel, cisplatin and 5FU followed by concurrent chemo radiation also failed

to demonstrate any survival benefit from induction chemotherapy compared to concurrent chemo radiation(22).

ADJUVANT CHEMOTHERAPY:

In case of postoperative setting with positive margins and extracapsular extension(NCCN). Adjuvant chemo as a theoretical benefit of eradicating the sub clinical disease left behind after chemo radiation, also postulated that it sterilizes the micro metastasis present in the circulation and thereby prevent distal recurrence rate and improve overall survival rate. The increased sensitivity of minimal residual disease to anticancer drugs has been shown by cell cycle and growth fraction studies. Unfortunately these theoretical benefits are not proved by any randomised control trials and evidence to support the routine use of adjuvant chemotherapy is far from definitive.

CONCURRENT CHEMORADIATION:

In the path of concurrent chemo radiation, initially trials was done with Bleomycin, Mitomycin, Cisplatin etc. But as the results of Meta-analysis MACHNC has clearly proved that Cisplatin is the drug of choice in concurrent chemo radiation. This trial has shown an absolute benefit of 6.5% $\pm$1% at the end of 5 years in overall survival with concurrent chemo radiation as compared to 2 % benefit with Induction Chemotherapy.

Thus Cisplatin is used in various trials in different regimens. Cisplatin in three weekly or weekly regimens can be used in a way that the Cisplatin cumulative dose should be kept equal to or above 210mg.

TARGETED THERAPY:

As already stated that EGFR receptors is over expressed in 85-90% of head and neck cancers. Inhibitors of EGFR like monoclonal antibody Cetuximab was used in many trials. The EXTREME trial demonstrated that the addition of cetuximab to Cisplatin and 5 FU regimens in metastatic and recurrent head and neck cancer resulted in an improved overall survival (23). The landmark trial by **Bonner et a**l showed that addition of cetuximab concurrently to radiotherapy in locally advanced head and neck cancers resulted in a significant improvement in loco regional control and median overall survival (24).

OVERCOMING TUMOR HYPOXIA:

Radiotherapy and chemotherapy preferentially kill the actively proliferating cells in the oxygenated regions of the tumour. With each dose of radiosensitiser chemotherapeutic drug and radiation, the well oxygenated cells in the periphery of tumour die. There is a gross fall in the interstitial pressure within the tumour causing opening up of previously closed capillaries and redirection of blood flow to the hypoxic regions of the tumour.

PREVENTION OF HEAD AND NECK CANCER:

As there is a concept of Field Cancerization states that the entire upper aero digestive tract is subject to subcellular injury by exposure to carcinogens, hence susceptible to cancer formation. Thus a person with malignancy in upper

aerodigestive is prone for 20% increased lifetime risk of second primary tumor. This may be due to genetic alterations in time. This forms the basis of chemoprevention.

Many trials with different chemopreventive agents has been tried. Mainly with Cis-Retinoic acid; RTOG (The Radiation Therapy Oncology Group) trial with 13-*cis*-retinoic acid in a multi-institutional setting, consisting 1400 patients with stage I or II cancer were accrued. Unfortunately, this trial was negative and did not show any benefit to low dose isotretinoin in the prevention of second primary cancers.Other chemo preventive agents being investigated are green tea extracts, curcumin extracts, soybeans etc.

Other methods of prevention will include:

1. Awareness regarding tobacco products and regulations controlling the sale of tobacco products.
2. Awareness about sexual practices like oral sex resulting in HPV infection.
3. Abstinence from alcohol
4. Good oral hygiene
5. Good nutrient rich diet, fresh fruits and vegetables

RATIONALE OF THIS STUDY:

This study was based on the DAHANCA 6 .In this study patients were treated with 6 fractions per week to a total dose of 66Gy which reduced the

overall treatment time by 1week. Withers et al., and Bentzen and Thames showed that a dose of 0.48 Gy per day was recovered by tumour during fractionated radiotherapy of HNSCC. This was the reason why in our study in which overall treatment time was reduced by 1 week, produced higher response than conventional fractionation. By reducing overall treatment time by 1 week the 'Dose recovery factor' of 3.3Gy was avoided.

As the MACHNC trials clearly proved the benefit of adding chemotherapy concurrently with radiation shows improvement in overall survival of 8% at the end of 5yrs.Concurrent chemo radiation forms the treatment of choice in Locally Advanced Squamous cell carcinoma of Head and Neck .

CISPLATIN:

Cis-diaminedichloroplatinum is a platinum analogue that covalently binds to DNA analogue with preferential binding to the N-7 position of guanine and adenosine and causes the production of crosslinks either intrastrand (>90%) or interstrand (<5%) breaks that eventually lead to inhibition in DNA synthesis function as well as inhibition of transcription. It can also bind to nuclear cytoplasmic proteins resulting in cytotoxic effects. Apart from its cytotoxic effect it also acts as a radiosensitizer for radiation.

It is given parenterally and is widely distributed in plasma with less than 10% remaining in the plasma after 1 hour of infusion. Inside the cells it undergoes a reaction where a chloride molecule is replaced by a water molecule leading to the production of a highly reactive species which causes the cell damage. It is excreted mainly through the kidney.

The main toxicities of cisplatin include

- **Nephrotoxicity**: due to its activity on the renal microtubules, it causes renal damage. Dose limiting in upto 35-40% of patients. It is generally reversible however the effect is dose related and can lead to acute as well as chronic renal failure.
- **Myelosuppresion**: it is seen in 25-30% of patients with all the three cell lineages equally effected. As the dose is increased, leucopenia and thrombocytopenia are more pronounced.
- **Ototoxicity:** is also dose related resulting in high frequency hearing loss and tinnitus.
- **Neurotoxicity:** this is dose related most commonly resulting in in peripheral sensory neuropathy. Stocking and glove pattern of paresthesias and numbness are classically seen. Motor function defect, enceplhalopathy and seizures can also occur.

- **Nausea and vomiting:** it is also a common problem with the use of cisplatin. It can occur immediately- acute form or after 24 hours of infusion- delayed form.
- **Other toxicities** like alopecia, ocular toxicity hypersensitivity, azoospermia, sterility etc can also be seen.

Cisplatin forms the first line of chemotherapy in a number of cancers including head and neck cancer, lung cancer, bladder cancer, ovarian and testicular cancer, esophageal cancers, etc. the dose usually ranges from 75-100 mg/m^2 in a three weekly regimen to 30-40mg/m^2 with a weekly regimen.

Review of Literature

REVIEW OF LITERATURE

As the history of cancer and its treatment emerged in concept from the late 19th century, newer techniques and combination of chemotherapy with radiation has proved its importance in loco regional control and progression free survival.

BIOLOGICAL BASIS OF FRACTIONATION:

From experimental data it was evident that the benefits of fractionation were due to four factors, which are known as,

1. Repair
2. Reassortment
3. Repopulation
4. Reoxygenation

In general, repair and repopulation will tend to make the tissue more resistant wheras reassortment and reoxygenation tend to make it more sensitive. Tumor, Early responding tissue and Late responding tissues are having different cell kinetics, so they are affected by these 4 factors in different ways.

The **Strandquist plot** is the relation between the total dose and overall treatment time. The extra dose required to counteract tumor proliferation in a fractionated treatment is a sigmoidal function of time. The **Ellis NSD system**

made the important contribution of separating the effects of number of fractions and overall time.

THE LINEAR – QUADRATIC MODEL

The L.Q model explains that the radiation cell kill has 2 components. The initial linear component (αD) is due to single track events and quadratic component (βD^2) is due to two track events. (D-dose).

$$S=\exp(-\alpha D - \beta D^2)$$

S is the fraction of cells surviving a dose D.

This model explains why there are different responses between tumor, early responding tissues and late responding tissues; this is due to difference in repair capacity or shoulder shape of underlying dose-response curve. The dose response curve of late responding tissue is more curved than that of tumour and early responding tissue. In terms of linear quadratic relationship between effect and dose, this translates into a larger α/β ratio for early tissue, tumor tissue than for late tissue effects, α/β ratio is the dose at which linear and quadratic components are equal. So, by dividing total number of doses, preferentially reduces the late effects. The early responding tissue and tumor tissue, particularly, squamous cell carcinoma in head & neck are having a large α/β ratio. It is usual in radiotherapy to compare different fractionation regimens

using **BIOLOGICAL EFFECTIVE DOSE** or equivalent doses (BED). Using L.Q. Model, as suggested by Jack Fowler at ASTRO and ESTRO Tutorials,

$$E/\alpha = (nd) \times (1 + d /(\alpha/ß)$$

E/α - Biologically Effective Dose n - Number of fractions

d - Dose per fraction.

According to linear quadratic Model, Biological Effective Dose for a dose 66Gy, delivered in 5.3 weeks by 6 fractions/week is 72.4Gy and for 70 Gy in 5.5 weeks by 6 fractions/ week is 76.8 Gy.

ALTERED FRACTIONATION:

It has been well documented that a prolonged treatment time may reduce the chance of tumor control, and a substantial number of clinical reports indicate that a reduction in overall treatment time may result in improved tumor control.

Conventional fractionation was considered as the best balance between tumor kill and normal tissue toxicity. It refers to a radiation dose of 2 Gy per fraction, five days a week, up to a total dose of 66-70 Gy. This schedule was the first to be tried in the field of Radiotherapy and followed till date.

ACCELERATED REPOPULATION:

Treatment with any cytotoxic agent, including radiation, can trigger surviving cells (clonogens) in a tumor to divide faster than before. This is known as accelerated repopulation. During this time the tumor is overtly shrinking and regressing, the surviving clonogen are dividing and increasing in number more rapidly than ever.

Withers[34] and colleagues surveyed the literature on radiotherapy for head and neck and estimated the dose to achieve local control in 50% of cases as a function of overall duration of fractionated treatment. The analysis suggests that clonogen repopulation in this human cancer accelerated at about 28 days after the initiation of radiotherapy in a fractionated regime. A dose increment of about 0.6 Gy per day is required to compensate for this repopulation. Such a dose increment is consistent with a 4-day clonogen doubling rate, compared with a median of about 60 days for unperturbed growth.

The conclusion to be drawn from this is that radiotherapy, atleast for head and neck cancer, and probably in other instances also, should be started as soon after it has begun as practicable. It may be better to delay the initiation of treatment than to introduce delays during treatment. If overall treatment time is too long, the effectiveness of later dose fractions is compromised, because, the surviving clonogens in the tumour have been trigerred in to rapid repopulation. Late effects depend primarily on total dose and dose per fraction; overall

treatment time within the usual therapeutic range has little influence. Overall treatment time affects both acute effects and tumor control. It is now well documented for head and neck cancer, that, local control is reduced by about 0.4 -2.5% for each day that overall treatment time is prolonged.

To overcome these problems **altered fractionation** schedules have come.

ALTERED FRACTIONATION IN RADIOTHERAPY:

EORTC trial by Horriet et al in 1992 - this trial compared conventional fractionation, once daily fractionation of 70 Gy in 35-40 fractions in 7-8 weeks, to hyperfractionation of total 80.5 Gy in 70 fractions in 7 weeks as 2 fractions of 1.15Gy per day. Patients included were T2-T3 oropharyngeal carcinoma, N0, N1 disease. In the final analysis it was found that the local control was significantly higher in case of hyperfractionation. Also at 5 years, 59% of patients had local disease-free in this arm compared to 40% in the conventional fractionation arm. This trial showed that the treatment regimen is an independent significant prognostic factor for loco regional control which was responsible for a trend to an improved survival, without a significant difference in late toxicity.

DAHANCA 6 and 7 randomized controlled trial showed the benefit of short treatment time with six fractionation per week –due to the promising results of this trial, this schedule became the standard of management in Denmark. According to this trial the 5-year locoregional control rates were

70% vs 60% for the six fraction and five-fraction groups. The primary control was good but lymph nodes does not show any added benefit. This trial has increased acute toxicity but it was transient(35,36).

RTOG 9003 trial compared hyper fractionation and two forms of accelerated fractionation to standard fractionation radiotherapy. The hyperfractionation arm delivered 1. 2 Gy/fraction, twice daily, 5 days/week to 81.6 Gy/68 fractions/7 weeks; the accelerated fractionation included split at 1.6 Gy/fraction, twice daily, 5 days/week, to 67.2 Gy/42 fractions/6 weeks including a 2-week rest after 38.4 Gy and another form of acceleration with concomitant boost at 1.8 Gy/fraction/day, 5 days/week and 1.5 Gy/fraction/day to a boost field as a second treatment daily for the last 12 treatment days to 72Gy/42 fractions/6 weeks. Hyperfractionation and accelerated fractionation with concomitant boost showed significantly better local-regional control than standard fractionation(16) .

Although Hyper fractionation improves loco regional control, this occurs at the cost of increased acute toxicity which results in treatment breaks and increased hospital stay.

Sequencing Chemotherapy with Radiation:

The radiobiological basis of combining Chemotherapy with Radiation is to obtain maximum therapeutic benefit. Tumor cells have accelerated cell proliferation, hypoxia and acidity which are not present in normal cells. Similarly assessment of various mechanisms of resistance to

radiation and different chemotherapeutic agents are also important to be considered.

Spatial cooperation: in this case radiation acts loco regionally and chemotherapy at a distant site, without any overlap.

Independent toxicity: the chemotherapy drugs given may have a different toxicity profile and it does not increase radiation reactions.

Enhancement of tumor response: in this case the ability of chemotherapy to enhance the radiation response is exploited. This results in better tumor kill based on additive action. This however, does not include the cytotoxic action of the drug itself but only its radio sensitizing property, to prevent excess normal tissue toxicity.

If the overall cell killing in the combination treatment is contributed by individual cytotoxicity of the drug and individual effect of the radiation, then it is called **additive effect**.

If the cell killing in combined modality is greater than the cell killing by individual cytotoxic agents, then it is called as **supra additive effect.** This is possible when chemotherapeutic agents interact with radiation and potentiates the effect of later.

Inhibition of tumor repopulation: only in case of concomitant Chemoradiotherapy.

Protection of normal tissue: through administration of agents which selectively prevent normal tissue damage.

Improved tumor oxygenation: because of increased cell kill, leading to better local control.

There are numerous trials describing the time of Chemotherapy introduction with Radiation.

Induction chemotherapy:

The Department of **Veterans Affairs Laryngeal Cancer study Group** conducted a prospective randomised control study in locally advanced laryngeal cancer. The aim of this study was to compare the option of induction chemotherapy followed by radiotherapy with surgery reserved for residual or recurrent lesions is a feasible alternative to surgery followed by postoperative radiotherapy. Patients in the control arm received three cycles of induction chemotherapy using cisplatin and 5 fluorouracil. The patients were assessed after two cycles of chemotherapy. Any patient who failed to attain at least a partial response was taken up for immediate surgery followed by radiotherapy. Responding patients were allowed to complete three cycles of chemotherapy followed by definitive radiotherapy.

The results of the trial showed that overall survival was same in both arms. The 3 year survival rate was 53%. The loco regional recurrences were greater in the control arm (12% vs 2%), but since salvage surgery was done in recurrent cases the overall survival was not compromised. Another interesting result is distant relapses were decreased in the chemo arm (11 % vs 17 %). But despite decrease in distant relapses overall survival could not be improved. 64%

of the patients recruited in the chemotherapy arm retained functional larynx. The authors concluded that in view of the high rate of local recurrences in chemotherapy arm, more effective local therapy is needed to achieve larynx preservation(21).

EORTC/TAX 323 (Vermorken et al. 2007) in this study 358 patients with unresectable stage III–IV head and neck cancer were randomized toTPF (docetaxol/cisplatin/5-FU) vs. PF (cisplatin/5-FU) induction chemotherapy followed by RT alone, delivered with conventional(66 Gy) or hyperfractionated (74 Gy) RT. Induction TPF increased median survival (14.5→18.8 months), but increased hematological toxicity and chemo-related death (2.3 vs. 5.5%). 10 - 15% of patients after induction chemotherapy were unfit to receive Radiation in this study(25).

Thus role of Induction chemotherapy followed by Radiation is acceptable only in selected patients prone for distant recurrences. This benefit can be achieved with the compensation of loco regional recurrence.

ADJUVANT CHEMOTHERAPY:

Adjuvant chemotherapy in Head and Neck following surgery is less studied.

Intergroup study 0034 used postoperative cases were randomized in into two arms. Study arm had 3 days of Cisplatin (100mg/m2), 21 day cycle and infusional 5 fluorouracil(1000mg/m2/day for 5 days, followed by radiation dose of 50-60 Gy Vs control arm had radiation alone without chemotherapy. There

was no improvement in overall survival or locoregional control but the incidence of distant metastasis decreased significantly from 30% to 20%.

RTOG 95–01(Cooper et al. 2004): 459 patients with operable cancer of the oral cavity, oropharynx, larynx, or hypopharynx who had 2 involved lymph nodes, nodal extracapsular extension, or positive margin randomized to post-op RT (60–66Gy) vs post-op chemo-RT (60–66 Gy and cisplatin ×3cycles). Chemo-RT improved 2-year Disease Free Survival (43→54%), Loco Regional Control (72→82%), and had a trend for improved OS (57→63%), but increased grade 3–4 toxicity (34→77%). (28)

EORTC 22931(Bernier et al. 2004): 334 patients with operable stage III/IV oral cavity, oropharynx, larynx, and hypopharynx cancer randomized to post-op RT (66 Gy) vs. post-op chemo-RT (66 Gy and cisplatin 100 mg/m2 on days 1, 22, 43). Allpatients received 54 Gy to the low-risk neck. Chemo-RT improved 3/5-year Disease Free Survival (41/36→59/47%), 3/5-year Overall Survival (49/40→65/53%), and 5-year Loco Regional Control (69→82%), but increased grade 3–4 toxicity (21→41%)(27).

Trials conducted by **EORTC** and **RTOG,** both showed post-operative chemo radiotherapy as improved Disease free survival and loco regional control but with increased grade 3&4 toxicity.

CONCURRENT CHEMORADIATION:

Concurrent chemoradiation in locally advanced head and neck cancer, the history tracks down to the era when Inj. Mitomycin, Inj.Bleomycin were used

with Radiation. Initial trials done by NCOG, EORTC showed improvement in loco regional control and overall survival. Also there are trials with single agent Inj.methotrexate shows improve in loco regional control.

But with more understanding of the tumor radiobiology, radiosensitizers like 5- Fluorouracil and Cisplatin , either alone or together, have been tried in many studies and proved as effective & potent chemotherapy drugs to combine with radiation.

META-ANALYSIS OF CHEMOTHERAPY IN HEAD AND NECK CANCER (MACH-NC):

The first part of this landmark meta-analysis which was published in the year 2000 by Pignon et al. This analysis included 63 randomized trials. The initial report from 1965-1993, showed a significant absolute overall survival benefit of 4%, both at 2 and 5 years ($p<0·0001$) in favour of chemotherapy.

Concomitant chemotherapy showed an absolute survival benefit at 2 and 5 years of 8%. In adjuvant and neoadjuvant setting, there was no significant effect of chemotherapy seen on survival. The effect of multiagent concomitant chemotherapy was significantly greater than single-agent chemotherapy (hazard ratio 0·69 vs 0·87,$p<0.01$). For the effect of chemotherapy on survival by covariate values, the only significant observation was a decreasing effect of chemotherapy on survival with increasing age (trend test, $p=0·05$).As far as

timing of chemotherapy is concerned, there was a non-significant decrease in risk of death in the concomitant chemotherapy group. This meta-analysis included trials which were very heterogeneous and no solid conclusion could be drawn regarding the routine use of chemotherapy and the regimen to be used (17,18).

However, **the update** of this analysis, **published in 2009** which included 93 randomized trials and demonstrated an overall absolute benefit of chemotherapy to be 6.5% at 5 years and the hazard ratio was 0.81 ($p < 0.0001$). Whereas the absolute benefit of Induction Chemotherapy at 5yrs was 2.4% and that of Adjuvant Chemotherapy -1.0$\pm$ 2.2 % .This absolute benefit in the meta analysis proves that Concomitant Chemotherapy has superior results and shows advantage over induction or adjuvant chemotherapy.

There was no significant difference in the benefit of chemotherapy on survival ($p = 0.14$) between postoperative or curative radiotherapy with conventional or altered fractionation. Mono and poly-chemotherapy did not differ but the effect of chemotherapy was significantly higher ($p = 0.006$) with platinum than with other types of mono-chemotherapy agents. There was only one negative “cisplatin alone” trial in this meta-analysis which used a cumulative dose of 140 mg/m2 suggesting that the total dose of Cisplatin should be considered. It was also demonstrated that there is a statistically significant decreasing effect of chemotherapy on survival with increasing age.

This Meta-Analysis clearly states the benefit of concurrent Chemo radiotherapy in the Head and Neck Cancer beyond any doubt.

Latest trial Concurrent Vs Induction Chemo:

The **DeCIDE** (22), a phase III randomised trial using induction chemotherapy with Docetaxel, 5 fluorouracil and cisplatin in N2/N3 locally advanced head and neck cancers (2012 ASCO meeting). Patients were randomised to chemo radiation alone with five days of docetaxel 25 mg/m2, 5 fluorouracil 600 mg/m2 and hydroxyl urea 500 mg bid concurrently with radiation 150 cGy bid or with two cycles of induction chemotherapy using docetaxel 75 mg/m2, cisplatin 75 mg/m2 and 5 fluorouracil 750 mg/m2 for 5 days followed by the same chemo radiation. 280 patients were recruited to the study from 2004 to 2009 and the minimum follow up was two years. The primary end point was overall survival. From 142 patients randomized to induction, 91% received 2 cycles and 87% continued to chemoradiation. Grade 3-4 leukopenia and neutropenia rates were significantly higher in IC ($p=0.002$ and $p=0.02$). The authors demonstrated that induction chemotherapy was associated with lower distant failure (DF) rates but an improvement in overall survival (OS) could not been validated. This was a negative study, as there was no overall survival difference with trends favoring the experimental arm in terms of disease-free survival.

Another trial in ASCO 2012 **PARADIGM trial** (29) Induction chemotherapy followed by concurrent chemoradiotherapy (sequential

chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer : a randomised phase 3 trial-this study was conducted between 2004 to 2008, with a median follow up of 49 months 3-year overall survival was 73% in the induction therapy followed by chemoradiation group and 78%in the chemoradiation alone group (hazard ratio 1·09, p=0·77). Also, more patients had febrile neutropenia in the induction chemotherapy **.**Although survival results were shown to be good in both groups, there was no difference between those treated with induction chemotherapy followed by chemoradiation and those who received chemoradiation alone.

Both the DeCIDE and PARADIGM trial did not show a significant survival benefit with induction chemotherapy, but the toxicity were high in the induction arm. The option of induction Chemotherapy followed by chemoradiation still can be considered in selected patients.

PLATINUM BASED CHEMORADIATION:

Concurrent chemoradiation with cisplatin as become the standard of care with the standard land mark trials. Cisplatin acts as a radiosensitizer increases efficacy of radiation even at low doses.

WEEKLY CISPLATIN Vs THREE WEEKLY CISPLATIN:

Due to the benefit and effectiveness of Inj.Cisplatin concurrently with radiation in Squamous cell carcinoma of the Head and neck , it is used widely in the dose of 100mg/m^2 day 1,22,43 regimen. This regimen has become the

standard following many trials. But there are trials with smaller doses of Cisplatin which has proved to be quite effective. These nonstandard Cisplatin schedules have been preferred due to two main reasons – firstly, more frequent dosing may provide more radiosensitization during long course of radiation, and secondly, a smaller drug dose may have lesser chemotherapy related toxicity (32,33,34). With the three weekly regimen it was found that compliance to the schedule became a major issue, which is avoided in the case of smaller weekly doses. Based on trials like the Intergroup and RTOG – 0129, it has been suggested that the cumulative threshold dose of Cisplatin to achieve maximal benefit is 200 mg/m2. Also, as discussed in the MACH-NC analysis, a dose below 140 mg/m2 was found to have inferior results.

WEEKLY CISPLATIN TRIALS:

A study published from **TATA Memorial Hospital, Mumbai, by TejpalGupta in 2009 (30)**, compared high dose concurrent Cisplatin with weekly Cisplatin in a dose of 30 mg/m2 with radiation dose of 70Gy. Planned was seven cycles of weekly Cisplatin, two-thirds (65%) of patients in the study received ≥85% of planned Cisplatin dose. With a mean follow-up of 19 months, the 5-year local control was 57%, loco-regional control was 46% and the disease free survival was 43% respectively. Grade 3 or higher acute mucositis was seen in 29% cases and dermatitis in 35% cases respectively. This essentially manifested in patients receiving radiation dose ≥66 Gy and 6 or more cycles of chemotherapy.The conclusion drawn from the study was weekly

cisplatin has moderate efficacy with acceptable toxicity with the potential to become an optimal chemotherapeutic regimen especially in a limited resource setting .

Another study published by **Homma et al in 2011**, including 53 patients with locally advanced squamous cell carcinoma used weekly cisplatin 40 mg/m^2 on 7 weeks along with radiation of 70 Gy/2Gy per fraction in 35 fractions. The overall survival rate was 93.7% and disease free survival was 88%. The toxicity was manageable in all patients. The study demonstrated complete response rate of 98.1% This study showed that weekly cisplatin is a feasible alternative with less toxicity without compromising the results. Major benefit is that the patients can be monitored frequently and dose adjustments can be made if required (31).

Ho and his colleagues in 2008 showed that most of the patients in weekly Cisplatin arm received a higher cumulative dose of 240 mg/m2 or more as compared to the 3-weekly Cisplatin arm ($p = 0.04$). They also found that the 3-weekly regimen was associated with more delays (41% vs 29%) and omissions of chemotherapy (17.4% vs 5.6%) causing lesser patients to achieve a less cumulative cisplatin dose, potentially lowering dose-intensity(32).

A similar study was conducted at the University of Florida, presented at the ASTRO 2009 meet, later published in Cancer J 2010. This study demonstrated that weekly Cisplatin 30 mg/m^2 decreases the treatment toxicity without sacrificing efficacy in patients treated with concomitant chemo-radiation for locally advanced squamous cell carcinoma of the head and neck.

79% patients in the study were able to complete at least 6 cycles of chemotherapy and 95% patients received RT up to at least 72 Gy. The 5-year actuarial outcomes in this study were as follows: Loco regional control rate of 79%; Distant metastases, 12%; and overall survival of 59%. It was claimed by the authors that the toxicity rates of the study were lower than those reported for RTOG 9914 and 0129 (33).

At University of Wisconsin, Tray nor et al studied the feasibility of weekly cisplatin with Intensity modulated Radiotherapy (IMRT) in locally advanced squamous cell carcinomas.This study was conducted during a period of November 2001 to May 2007. A total of 57 patients were included and a weekly cisplatin dose of 30 mg/ m2 was used. The prescription dose to the GTV was 70 Gy.. The loco regional control was 85.5 % and median overall survival was 86.9%. The conclusion drawn from the study was weekly cisplatin 30 mg/m2 along with IMRT with a GTV dose of 70 Gy is well tolerated (34).

LOW DOSE DAILY CISPLATIN TRIALS:

Brainslav Jeremic et al- dept of otorhinolaryngology studied hyperfractionated radiotherapy with or without low dose cisplatin in advanced head and neck cancer. Hyperfractionation was given as 77 GY in 70 fractions over 7 weeks with or without low dose daily cisplatin 6 mg/m2 was given for five week daily . Patients with chemo radiation arm shows higher survival rates than radiation alone arm. Survival rate at 2 years were 68% vs 49%, survival rate at 5 years were 46% vs 25%. Locoregional progression free survival was

also high at 5 years which was 46 % vs 25 %. Distant metastasis free survival was also good at 5 years 86% vs 57 % respectively(39,40).

A randomised phase 2 trial **Bartelink et al** studied about conventional chemoradiation with low dose daily cisplatin 6 mg/m2 with 70 Gy RT in 2 GY per fraction over 7 weeks versus modified fractionated schedule giving 3 fractions / day of 1.6 GY each in weeks of 1,4,7. Both arm shows similar tumor response and also shows similar toxicities as that of conventional arm (38).

H.A.Wolff et al studied the toxicity of low dose daily cisplatin 6 mg/m2 inpost op patients of locally advanced head and neck cancers. Radiotherapy was conventionally given 70 GY of 2 GY each.3 year OS and locoregional control were 67% and 78% respectively.Grade 3 acute and chronic toxicities were less observed (41).

P.K.Gupta et al studied the comparison of low dose daily cisplatin 6mg/m2 with weekly cisplatin along with accelerated radiotherapy in locally advanced head and neck cancers. In this study ,low dose cisplatin was given on OP basis in 50 ml NS as bolus with 500ml NS prior hydration. Overall survival and disease free survival was somewhat superior than weekly schedule with insignificant P value. Toxicities like mucositis, dermatitis observed were less in low dose arm than in weekly arm(43).

Aims and Objectives

AIM & OBJECTIVES

The aim of this study was to evaluate and compare the use of daily low dose cisplatin versus weekly Cisplatin concurrently with accelerated radiation in locally advanced squamous cell carcinoma of head and neck.

Primary Objective:

To assess and compare the immediate loco regional response rates in locally advanced squamous cell carcinomas of the head and neck treated with low dose daily cisplatin versus weekly cisplatin concurrently with accelerated radiation.

Secondary Objective:

To assess and compare the acute toxicity to the treatment concurrent chemoradiation with low dose daily cisplatin versus weekly cisplatin.

Materials and methods

MATERIALS AND METHODS

STUDY DESIGN:

Double arm prospective study with a Phase II design.

STUDY DURATION: October 2016– August, 2017

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

SAMPLE SIZE: 30 consecutive patients in each arm with histopathologically proven squamous cell carcinoma of head and neck who fulfilled the 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 04.10.2016.

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 A locally advanced squamous cell carcinoma
- Previously not exposed to any chemo or radiotherapy
- ECOG 0-1
- No major life threatening comorbidities.

EXCLUSION CRITERIA:

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

PRE TREATMENT WORK UP:

1. Detailed history elucidation.

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 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 head and neck, plain and contrast, before initiating treatment and also after treatment for response assessment.

10. Chest X ray postero-anterior view.

11. Cardiac evaluation and fitness.

12. Naso-gastric tube insertion if indicated

13. Dental prophylaxis including scaling, dental filling and extraction if required.

14. Tumor stage, performance status and weight were recorded.

Staging was done based on American Joint Committee staging manual 7^{th} edition (for head and neck cancers).

15. Weekly CBC, RFT, LFT before each cycle of chemotherapy.

PATIENT PREPARATION DURING TREATMENT:

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

Quitting alcohol and tobacco

The harmful effects of tobacco, both in smoking and nonsmoking form, and alcohol were explained to the patient and their addictions as inferior

outcome after treatment and also has increased risk of second malignancy due to field cancerization effect.

Dental health:

Chemoradiotherapy to oral cavity poses an increased risk of dental caries. As the production of saliva is altered both in quality and quantity by concurrent chemoradiotherapy which leads to alteration of normal flora. Thus causes increased risk of caries formation due to mucositis and dryness. Oral discomfort due to mucositis can lead to decrease in brushing and flossing, also increases the risk of dental caries, which may lead to extraction, soft tissue necrosis, bone exposure, and osteoradionecrosis.

Dental care

Prior to irradiation all patients underwent dental evaluation; scaling and filling. Nonsalvageable teeth were extracted prior to radiotherapy to reduce the risk of osteoradionecrosis. A gap of two weeks was given after dental prophylaxis for proper healing of gums. Prophylactic antibiotic treatment was started following extractions if necessary.

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.Patients were advised to use soft brush and fluoride containing toothpaste daily during and after radiotherapy.

Mucositis

The major side effect of chemoradiotherapy is mucositis, a condition where patient perceives pain due to inflammation and ulceration of the mucosa. It occurs mainly due to disruption of normal mucosal barrier by chemoradiotherapy causes production of Reactive Oxygen Species resulting in increased production of proinflammatory cytokines (IL-1β, IL-6) which causes tissue injury and apoptosis of cells in the mucosa.

Retrospective review of over 200 head and neck cancer patients treated with radiotherapy at MD Anderson cancer centre, 66% of the patients had either grade 3 or 4 mucositis. According to various studies patients with oral cavity,nasopharynx, oropharynx cancer treated with concurrent chemotherapy or altered fractionation radiotherapy, had a higher rate of mucositis producing intense pain, weight loss, and treatment breaks which compromises loco regional control.

Studies shown that daily dose, cumulative dose and volume of irradiated tissue determine the severity of mucositis. This pain produced by mucositis can lead to nutrition compromise thereby lack of proper hydration and oral hygiene. The desquamated epithelium, fibrin, and polymorphonuclear leukocytes in a moist background provide a favorable environment for opportunistic infections such as candidiasis.

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

- Patient’s oral health were monitored daily during treatment.
- All patients were advised to gargle 20 to 25 mL of indigenously prepared mouthwash by dissolving three tablespoons of soda bicarbonate and three tablespoons of table salt (sodium chloride) in 200ml of distilled water, for every 4 to 6 hours.
- 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.

Other precaution:

Patients advised to restrain coarse and hot food items as they serve as irritant and exacerbate mucositis.

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

NUTRITIONAL CARE:

Most of the Head and neck cancer patients suffer from dysphagia and odynophagia either because of the tumor or due to treatment related effects like mucositis. This can affect the quality of life results in decreased food intake and they become nutritionally deprived resulting in weight loss.

All patients enrolled in this study were given dietary advice and encouraged to take easily available, nutritionally rich local foods, dairy products and fresh fruits and juices (avoid citrus fruits, acidic and spicy foods). Everyone

encouraged to take supplemental calories before treatment daily two raw eggs and milk.

Homemade preparation of health mix with milk which is rich in protein to regenerate tissue protein. Small soft meals in the form of bland diet at room temperature. All patients were monitored for weight loss every week and special meals were designed for individual patients.

Mostly during third or fourth week of radiation patients develop severe mucositis and need supplementary nutrition. Parenteral nutrition was also given if needed.Those patients who developed grade 3 or 4 dysphagia were inserted a naso-gastric tube so that nutrition was not compromised.

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

TREATMENT PROTOCOL:

60 locally advanced head and neck cancer patients were selected consecutively from the outpatient department, who then underwent the pre treatment work up as mentioned before. Following that they were randomized to treatment arm 1- low dose daily cisplatin 6 mg/m2 with accelerated radiation and treatment arm 2- weekly cisplatin 40 mg/m2 with accelerated radiation .

RADIATION THERAPY:

All patients were treated with a accelerated dose schedule of 2 Gy per fraction six days per week 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 with the patient in treatment position to verify the treatment field.

Radiation Dose:

Patients were treated with a dose of 2 Gy per fraction, with 6 fractions per week.

- **Phase I** to include the primary and the draining lymph node regions and a dose of 44 Gy / 22 fractions / 4.5 weeks was delivered 5 days in a week at 2 Gy / fraction (Monday to Friday).
- In **phase II-**off-cord reduction was done, and a dose of 16 Gy/8 Fractions / 1.5 weeks at 2 Gy / fraction was delivered 5 days in a week (Monday to Friday).
- **Phase III** will be delivered as a boost on all Saturdays, as limited volume portal including original GTV with a margin of 2 cm. A dose of 10

Gy / five fractions / over five Saturdays at 2 Gy / fraction was delivered. Radiotherapy was given same in both arms.

CHEMOTHERAPY SCHEDULE:

Arm 1-low dose daily cisplatin 6 mg/m2:

CDDP was given at 6 mg/m2 (capped at 10 mg) in 50 ml normal saline (NS) solution infused over ten minutes on all radiation treatment days after hydration with 500 ml of normal saline. Injection ondansetron 8 mg as antiemetics was given just before chemotherapy. This was given on all RT days one hour before radiation . Renal and hematologic parameters were assessed every week. Daily chemotherapy was given on outpatient basis.

Arm 2-weekly cisplatin 40 mg/m2:

Inj**.**Cisplatin 40mg/m^2 diluted in 500 ml normal saline, infused over 2 hours, every week on Mondays, during radiation to a total of 5-6 cycles. Renal and hematologic parameters were assessed prior to each cycle of chemotherapy.

PREMEDICATION: ARM 2:

All patients were pre hydrated with one pint of normal saline over one hour before starting chemotherapy.

Premedication given 30 minutes prior to chemotherapy included the following:

- Inj. Ondansetron 8 mg IV.
- Inj. Dexamethasone 8mg IV.

- Inj. Ranitidine 50 mg IV.
- Inj. Chlorpheniramine 1 vial.

All the above mentioned premedication was given on a bid basis.

Injection Cisplatin 40mg/m^2 mixed in 500 ml of normal saline and infused at 40 drops per minute in about 2 hours. Following this 500ml of normal saline was infused again over an hour.

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

ASSESSMENT DURING CHEMORADIATION:

Toxicity Assessment:

Patients were reviewed every day before radiation for any acute toxic reactions and infections. Reactions like skin desquamation, mucositis, laryngitis, dysphagia etc. were recorded and graded based on RTOG acute radiation morbidity criteria. If a patient developed grade 3 or higher reactions chemoradiation was suspended. Careful attention was given for maintenance of hydration, adequate dietary intake and good oral hygiene.

Hematological and renal parameters were assessed on a weekly basis . Hb less than 10 mg/dl was corrected by packed red cell transfusion. WBC and

platelet counts were kept under regular monitoring. If renal parameters are raised adequate hydration was done and nephrologist opinion obtained.

RESPONSE EVALUATION:

All patients were reassessed by clinical examination and with a CT Neck, 4 -6 weeks after completion of concurrent chemo radiation.

Response to treatment was described based 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:** At least 30% reduction in the sum of the longest diameter of target lesions, 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 4-6 weeks.
- Chest imaging, hearing evaluation, dental evaluation were done when indicated clinically. Continued smoking cessation, counseling to the patient and attender, rehabilitation, speech and swallowing therapy.

Results and analysis

RESULTS AND ANALYSIS

The total 60 patients recruited completed their entire treatment protocol and all of them were available for analysis of results.

PATIENT CHARACTERISTICS:

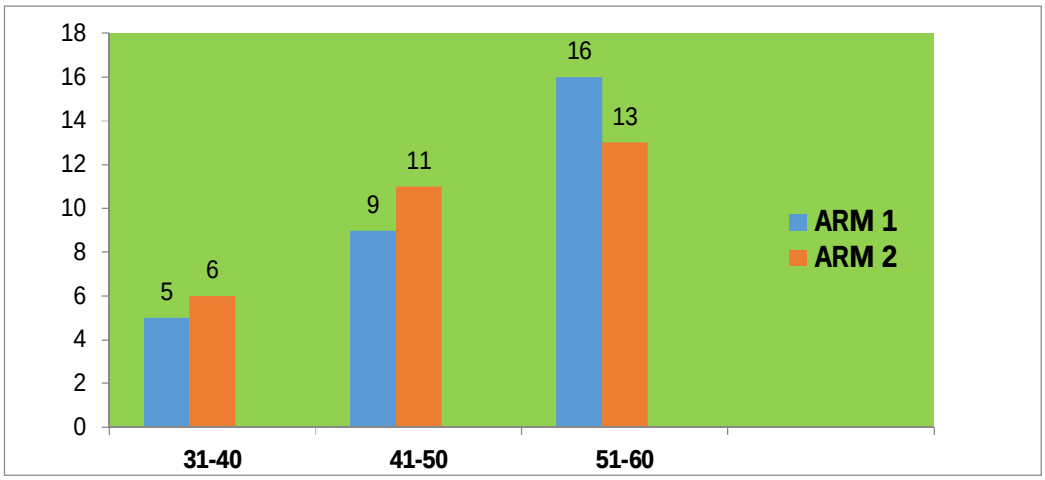
AGE DISTRIBUTION:

In this study, in both arms most of the patients belonged to the age group 51- 60yrs, followed by 41 -50yrs. Around 5% of the patients were in the age group of 31-40 years .

Table no: 1, AGE DISTRIBUTION OF THE STUDY POPULATION.

	ARM 1		ARM 2	
AGE group	NUMBER	%	NUMBER	%
31-40	5	17 %	6	20 %
41-50	9	30 %	11	37 %
51-60	16	53 %	13	43 %

FIGURE : AGE DISTRIBUTION OF THE STUDY POPULATION



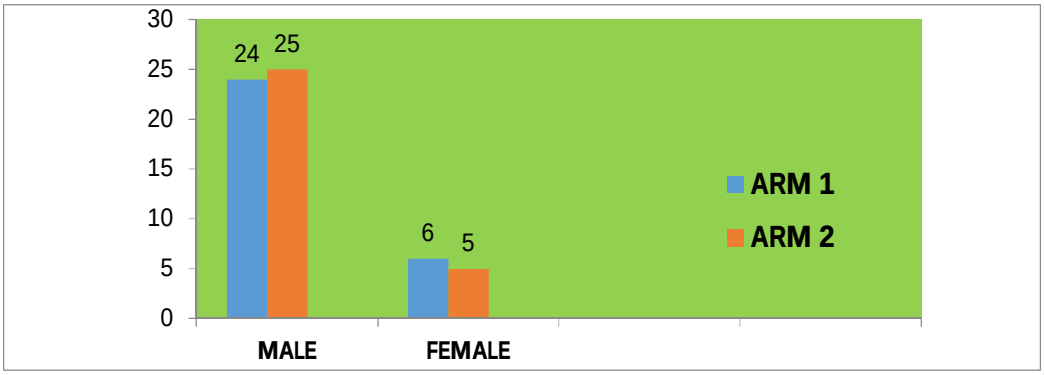
GENDER:

The gender distribution in the study population is dominated by the exposure of risk factors like tobacco, alcohol etc. Since male population are more frequent for exposure, this study has more male patients followed by less female patients in both arms.

Table no: 2, GENDER DISTRIBUTION OF THE STUDY POPULATION

	ARM 1		ARM 2	
SEX	**PATIENTS**	**%**	**PATIENTS**	**%**
MALE	24	80%	25	83 %
FEMALE	6	20%	5	17 %

FIGURE : GENDER DISTRIBUTION OF THE STUDY POPULATION .



PERFORMANCE STATUS:

All patients in this study had a general performance status of ECOG (Eastern Cooperative Oncology Group) grade 0 or 1.

Table no:3, ECOG : PERFORMANCE STATUS

	ARM 1		ARM 2	
ECOG	**NO.OF PATIENTS**	**%**	**NO.OF PATIENTS**	**%**
ECOG 0	19	63 %	18	60 %
ECOG 1	11	37 %	12	40 %

HABITS: In the natural history of head and neck cancer, habits /addictions of the patients to tobacco, alcohol plays a major role. In this study, as expected, majority of the patients had habit of both tobacco (smoking and smokeless) and alcohol .

Table no: 4; HABITS/ADDICTION OF THE STUDY POPULATION

	ARM 1		**ARM 2**	
HABITS	**PATIENTS**	**%**	**PATIENTS**	**%**
TOBACCO(SMOKING)	8	27 %	8	27 %
TOBACCO(SMOKELESS)	7	23 %	8	27 %
ALCOHOL	6	20 %	5	16 %
BOTH TOBACCO& ALCOHOL	5	17 %	6	20 %
NONE	4	13 %	3	10 %

FIGURE ; HABITS/ADDICTION OF THE STUDY POPULATION

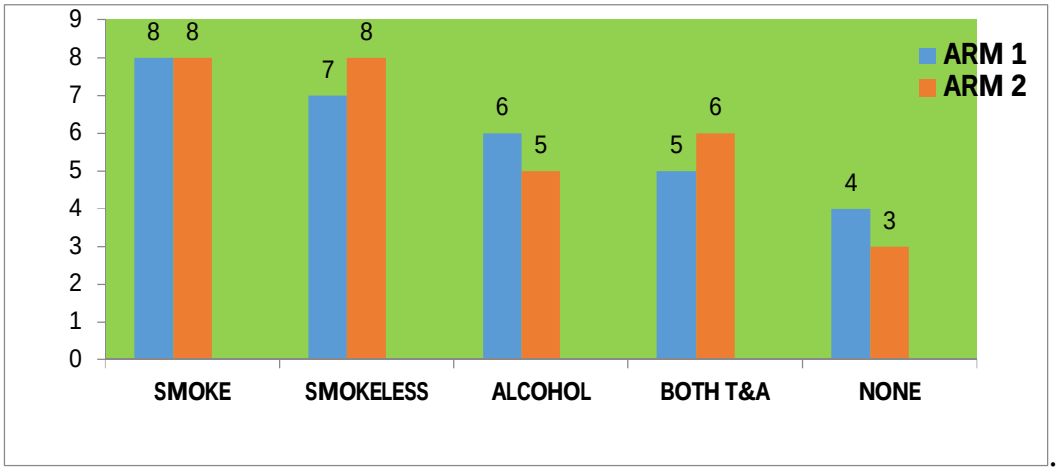
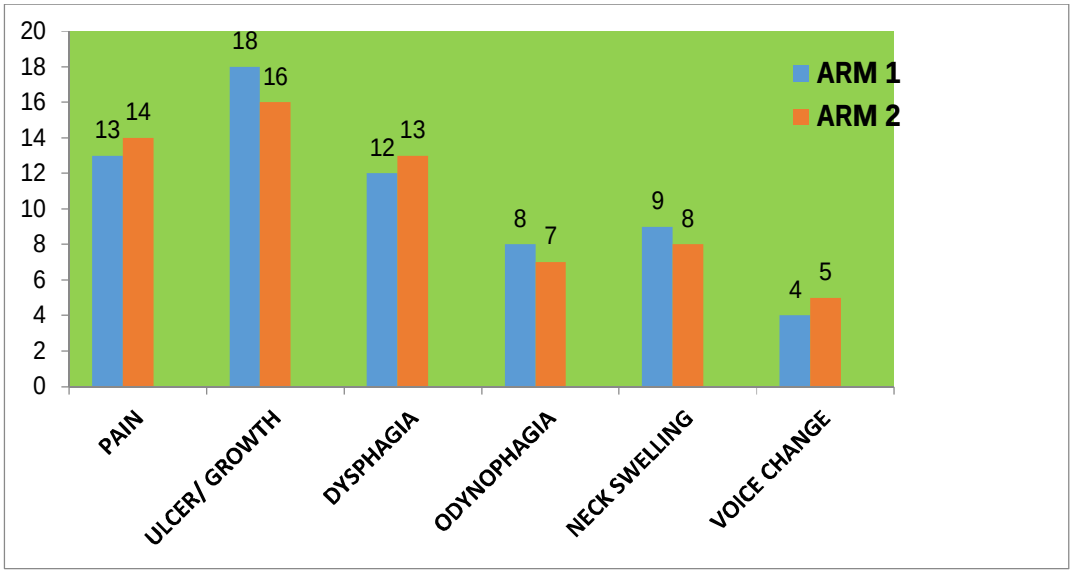


Table no: 5, SYMPTOMS AND SIGNS

	ARM 1		ARM 2	
PRESENTING SYMPTOMS/SIGNS	**NUMBER**	**%**	**NUMBER**	**%**
PAIN	13	43.3%	14	46.6 %
ULCER/GROWTH	18	60 %	16	53.3 %
DYSPHAGIA	12	40 %	13	43.3 %
ODYNOPHAGIA	8	26.6 %	7	23.3 %
NECK SWELLING	9	30 %	8	26.6 %
VOICE CHANGE	4	13.3 %	5	16.6 %

FIGURE : SYMPTOMS AND SIGNS



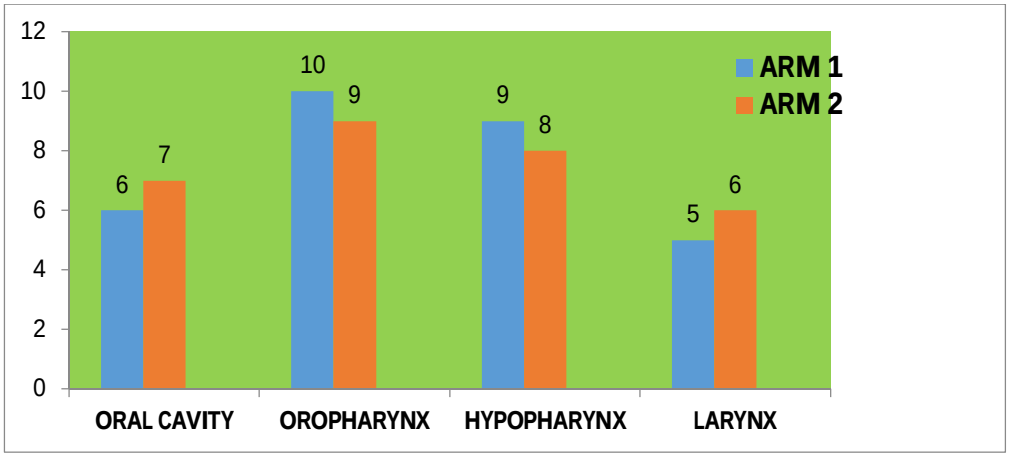
PRIMARY SITE:

In this study , arm 1 -Oropharynx were 10 patients, followed by Hypopharynx 9 patients then Oral cavity 6 patients and larynx 5 patients. Arm 2 –Oropharynx were7 patients, followed by Hypopharynx 8 patients then Oral cavity 7 patients and larynx 6 patients.

Table no : 6 PRIMARY GROWTH SITE:

	ARM 1		ARM 2	
PRIMARY SITE	**NUMBER**	**%**	**NUMBER**	**%**
ORAL CAVITY	6	20 %	7	23.3 %
OROPHARYNX	10	33.3 %	9	30 %
HYPOPHARYNX	9	30 %	8	26.7 %
LARYNX	5	16.7 %	6	20 %

FIGURE : PRIMARY GROWTH



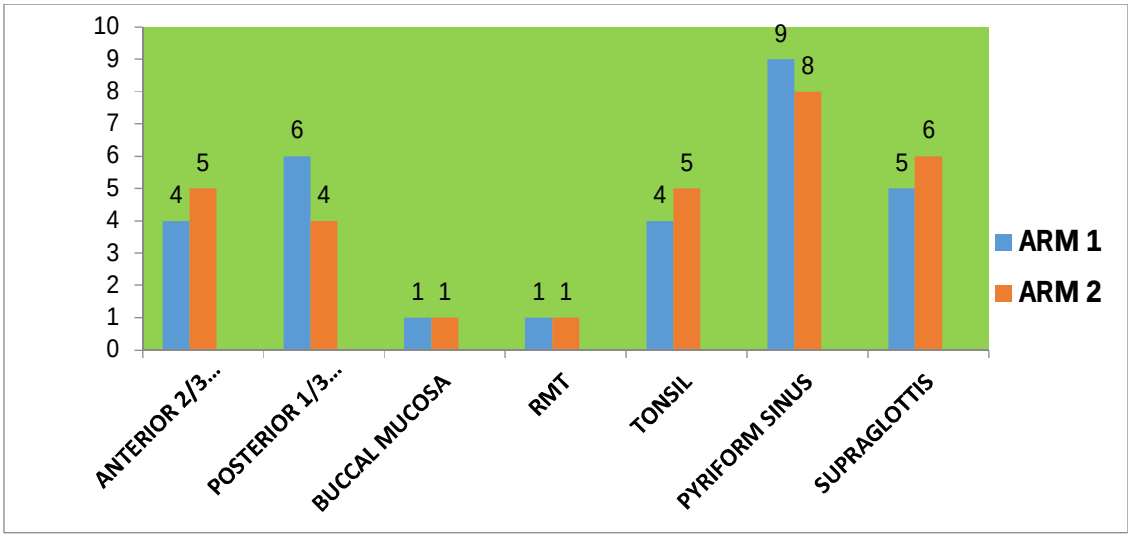
SUBSITE ANALYSIS:

In the subsite anaylsis , pyriform sinus were more in number in both arms..

Table no: 7, SUBSITE WISE DISTRIBUTION:

	ARM 1		ARM 2	
SUBSITE	**NUMBER**	**%**	**NUMBER**	**%**
ANT2/3TONGUE	4	13.3 %	5	16.6 %
POST 1/3TONGUE	6	20 %	4	13.3 %
BUCCALMUCOSA	1	3.3 %	1	3.3 %
RMT	1	3.3 %	1	3.3 %
TONSIL	4	13.3 %	5	16.6 %
PYRIFORMSINUS	9	30 %	8	26.6 %
SUPRAGLOTTIS	5	16.6 %	6	20 %

FIGURE : SUBSITE WISE DISTRIBUTION



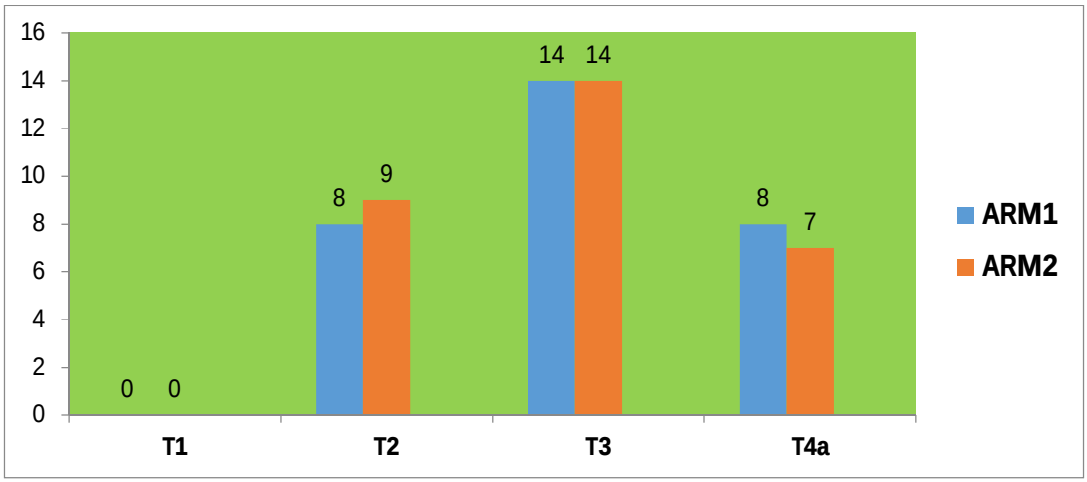
TUMOR STAGE:

This study included only locally advanced head and neck cancer ,T stage with T2 (with node positive), T3, T4a in both arms.

Table :8, TUMOR STAGE :

	ARM 1		ARM 2	
TUMOR STAGE	**NUMBER**	**%**	**NUMBER**	**%**
T 1	0	0	0	0
T 2	8	26.7 %	9	30 %
T 3	14	46.6 %	14	46.7 %
T 4a	8	26.7 %	7	23.3 %

FIGURE : TUMOR STAGE

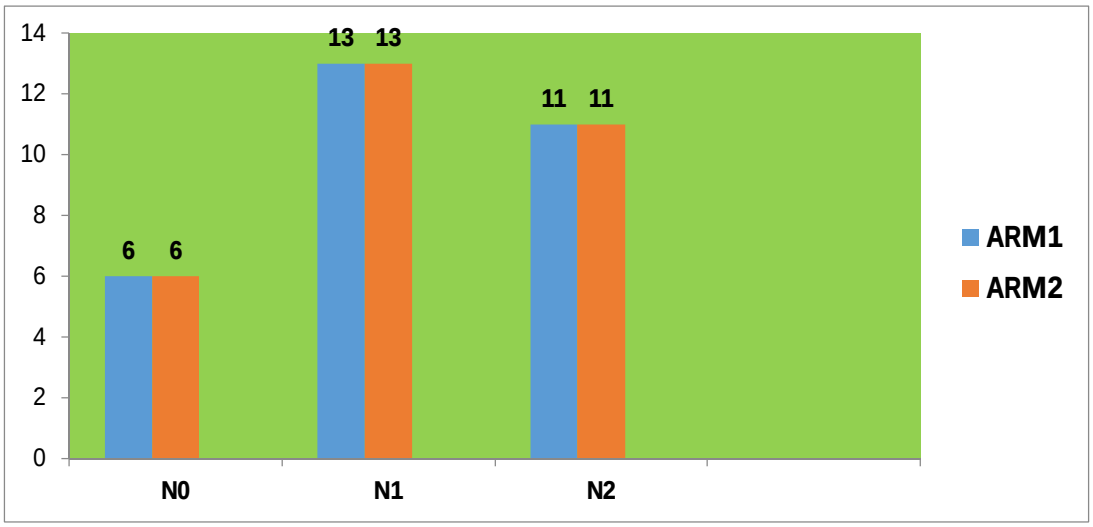


NODAL STAGE: Nodal staging 43% of the patients as N1, 37 % of the nodes are N2 in both arms.

Table no: 9, NODAL STAGE

	ARM 1		**ARM 2**	
NODAL STAGE	**NUMBER**	**%**	**NUMBER**	**%**
N 0	6	20 %	6	20 %
N 1	13	43.3 %	13	43.3 %
N 2	11	36.7 %	11	36.7 %

FIGURE: NODAL STAGE



STAGE GROUPING OF THE STUDY SAMPLE:

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

As our general population usually present late to the hospital most of our patients were in stage IVA .

Table no: 10, ARM 1 ,STAGE GROUPING

ARM 1 Tumor nodal stage	T2N1	T2N2	T3N0	T3N1	T3N2	T4aN0	T4aN1	T4aN2
ORAL CAVITY	0	0	1	1	1	1	1	1
OROPHARYNX	2	1	2	2	1	1	1	0
HYPOPHARYNX	1	2	1	1	1	0	1	0
LARYNX	1	1	0	1	1	0	1	0

FIGURE : ARM 1 ,STAGE GROUPING

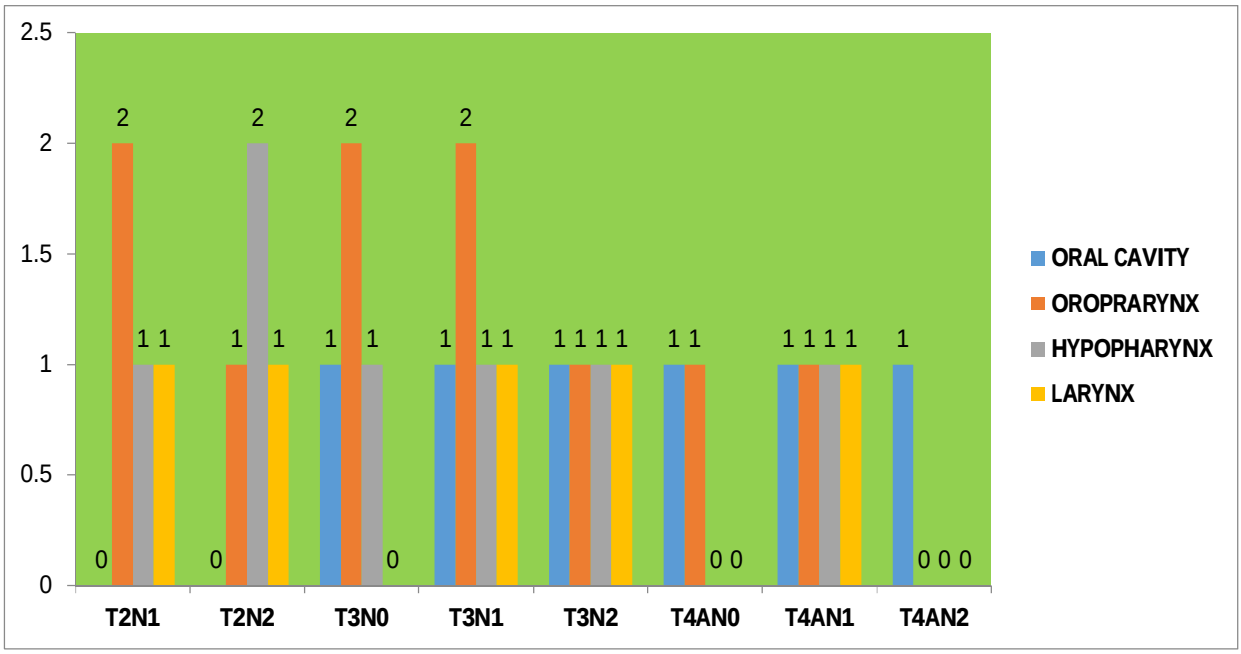
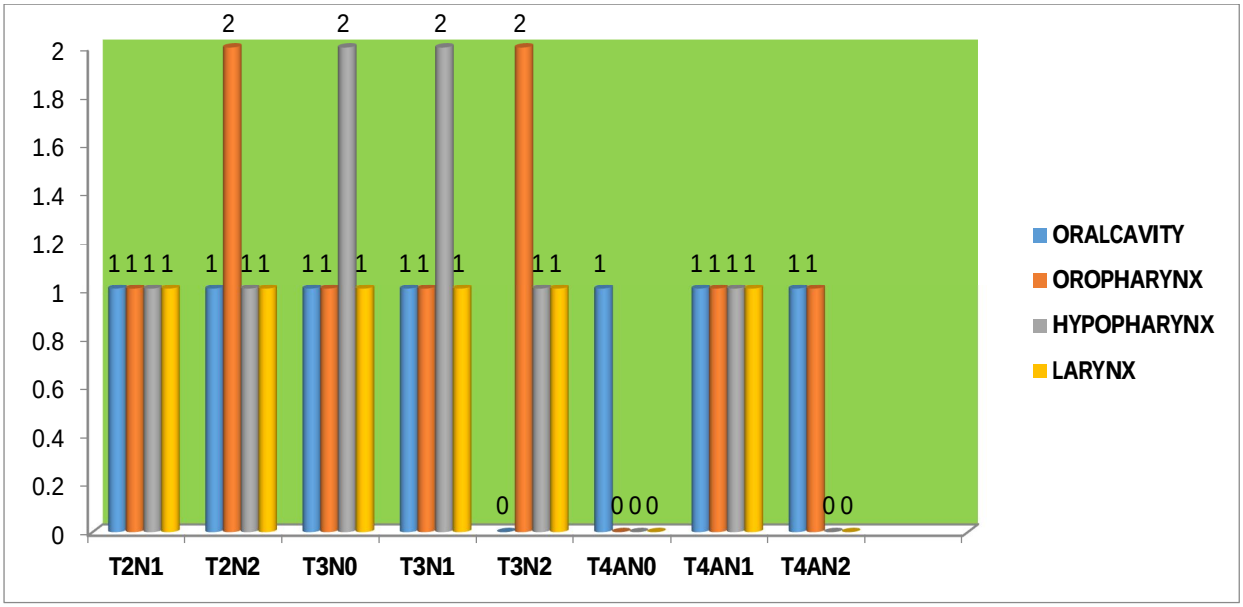


Table : 11 , ARM 2, STAGE GROUPING

ARM 2 Tumor nodal stage	T2N1	T2N2	T3N0	T3N1	T3N2	T4aN0	T4aN1	T4aN2
ORAL CAVITY	1	1	1	1	0	1	1	1
OROPHARYNX	1	2	1	1	2	0	1	1
HYPOPHARYNX	1	1	2	2	1	0	1	0
LARYNX	1	1	1	1	1	0	1	0

FIGURE : ARM 2, STAGE GROUPING



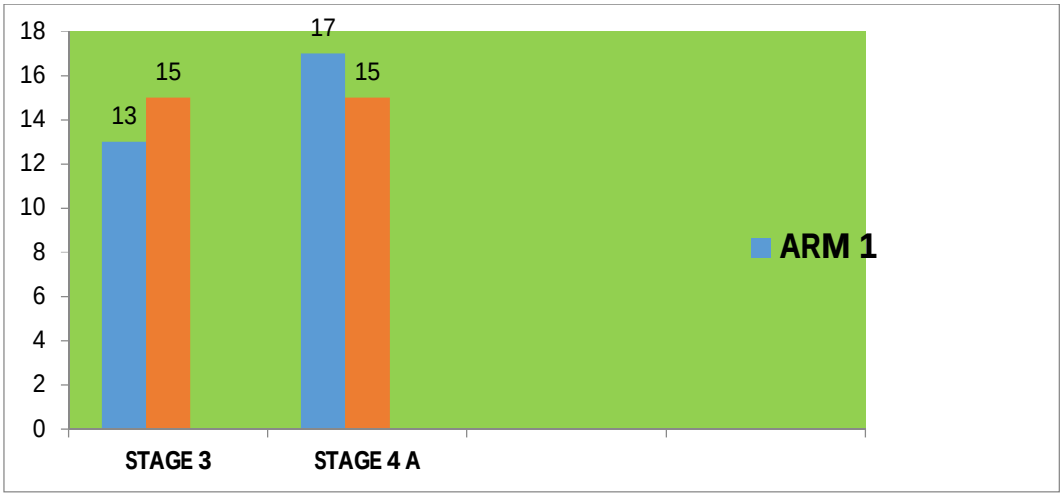
T3N0
T2N1
T3N1
} **-STAGE 3**

T4aN0
T4aN1
T4aN2
T2N2
T3N2
} **-STAGE 4 a**

Table :12, STAGE GROUPING

	ARM 1		**ARM 2**	
STAGE GROUPING	**NUMBER**	**%**	**NUMBER**	**%**
STAGE 3	13	43.3 %	15	50 %
STAGE 4a	17	56.7 %	15	50 %

FIGURE : STAGE GROUPING



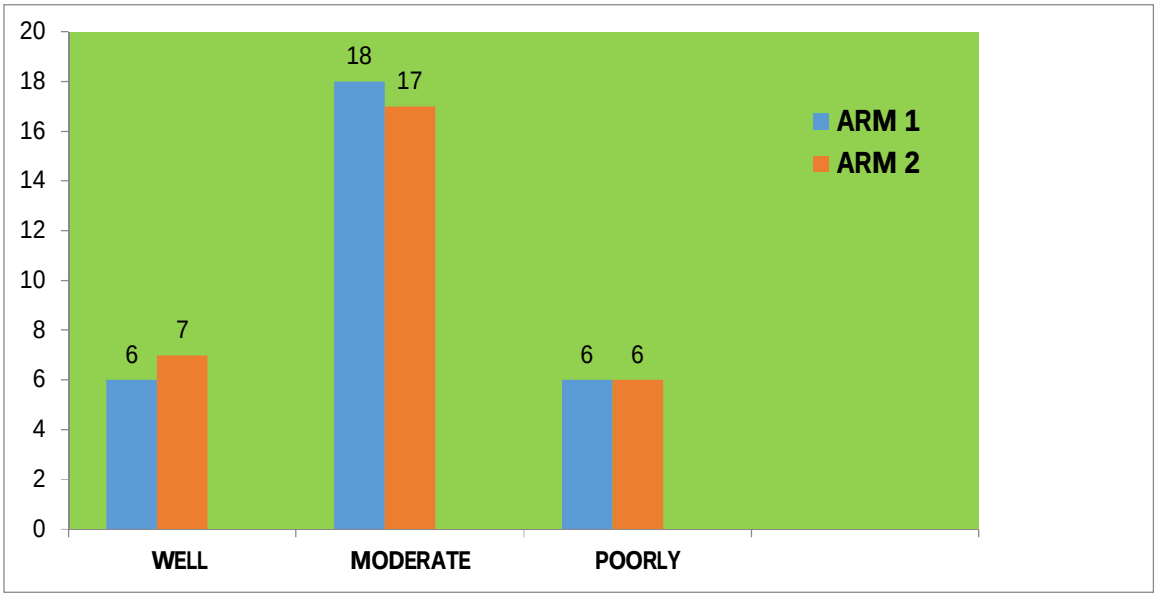
HISTOLOGICAL DIFFERENTIATION:

Most of the patients in the study belonged to moderately differentiated histology followed by poorly differentiated.

TABLE NO:13, : HISTOLOGIC DIFFERENTIATION

	ARM 1		ARM 2	
HISTOLOGICAL DIFFERENTIATION	**NUMBER**	**%**	**NUMBER**	**%**
WELL DIFFERENTIATED	6	20%	7	23.33%
MODERATELY DIFFERENTIATED	18	60%	17	56.66%
POORLY DIFFERENTIATED	6	20%	6	20%

FIGURE : HISTOLOGIC DIFFERENTIATION



TREATMENT RESULTS:

All 60 patients completed the treatment protocol and were assessed at the end of 4-6 weeks. 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.

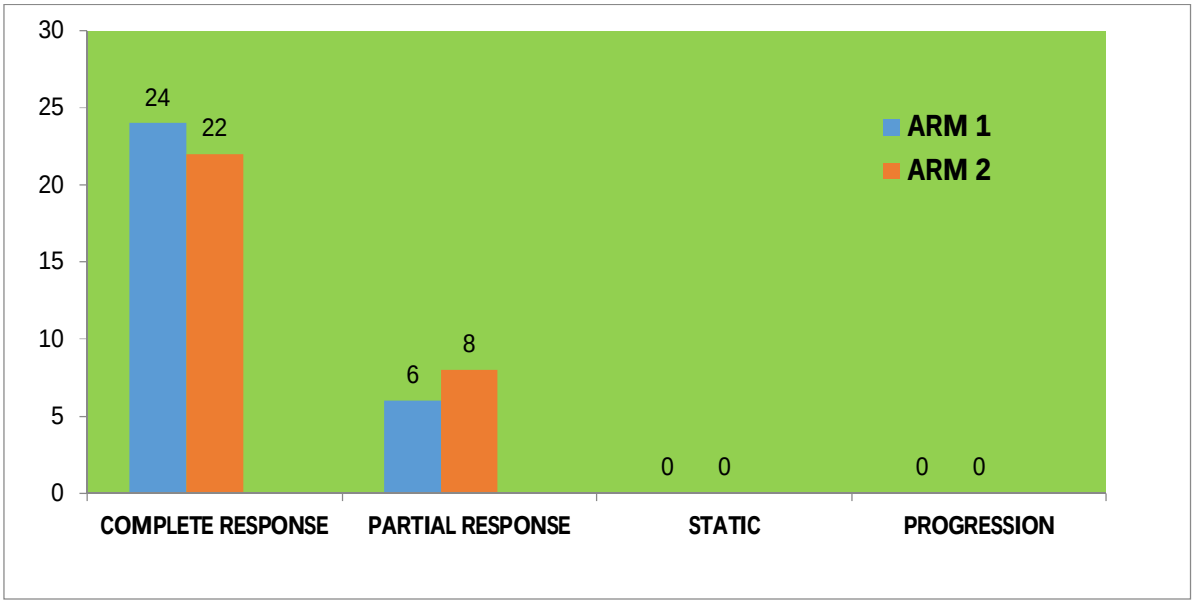
RESPONSE RESULTS:

In this study,80% had complete response and 20% had partial response in arm1 where as 73% of the patients had complete response and 27% had partial response in arm2. There was no static response or progression in the study.

Table no:14, RESPONSE RESULTS

	ARM 1		ARM 2		
RESPONSE	**NUMBER**	%	**NUMBER**	%	P value
COMPLETE RESPONSE	24	80%	22	73.33%	0.52
PARTIAL RESPONSE	6	20%	8	26.66%	0.60
STATIC RESPONSE	0	0	0	0	0
PROGRESSION	0	0	0	0	0

FIGURE : RESPONSE RESULTS



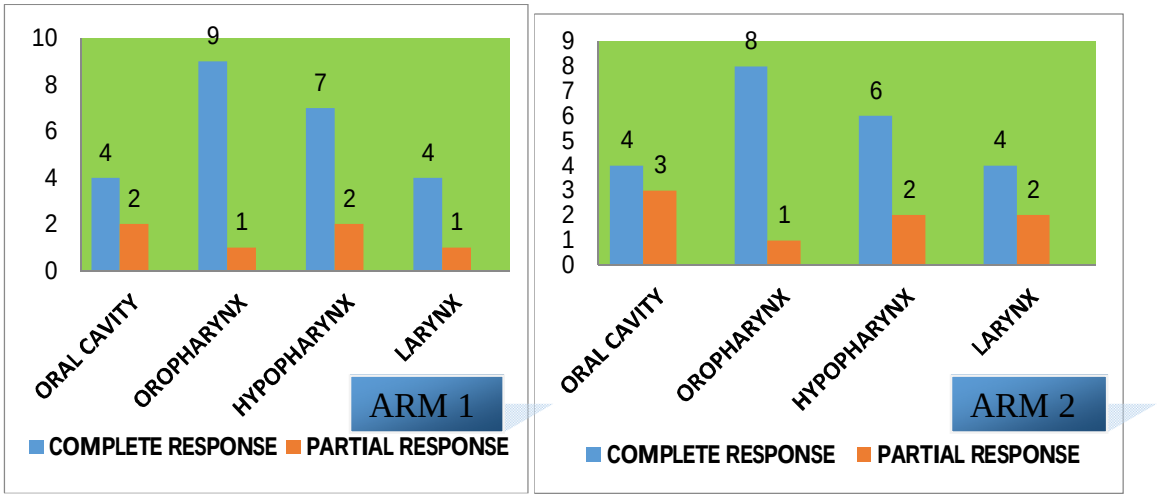
SITE Vs RESPONSE:

In both arms of this study , Oropharynx had highest complete response followed by hypopharynx and larynx and the least was oral cavity.

Table no:16, SITE VERSUS RESPONSE

	ARM 1		ARM 2	
SITE	**COMPLETE RESPONSE**	**PARTIAL RESPONSE**	**COMPLETE RESPONSE**	**PARTIAL RESPONSE**
ORALCAVITY	4 (66.6%)	2 (33.3%)	4(57%)	3(42.8%)
OROPHARYNX	9 (90%)	1(10%)	8(88.8%)	1(11.1%)
HYPOPHARYNX	7 (77.7%)	2(22.2%)	6(75%)	2(25%)
LARYNX	4 (80%)	1(20%)	4(66.6%)	2(33.3%)

FIGURE ; SITE VERSUS RESPONSE



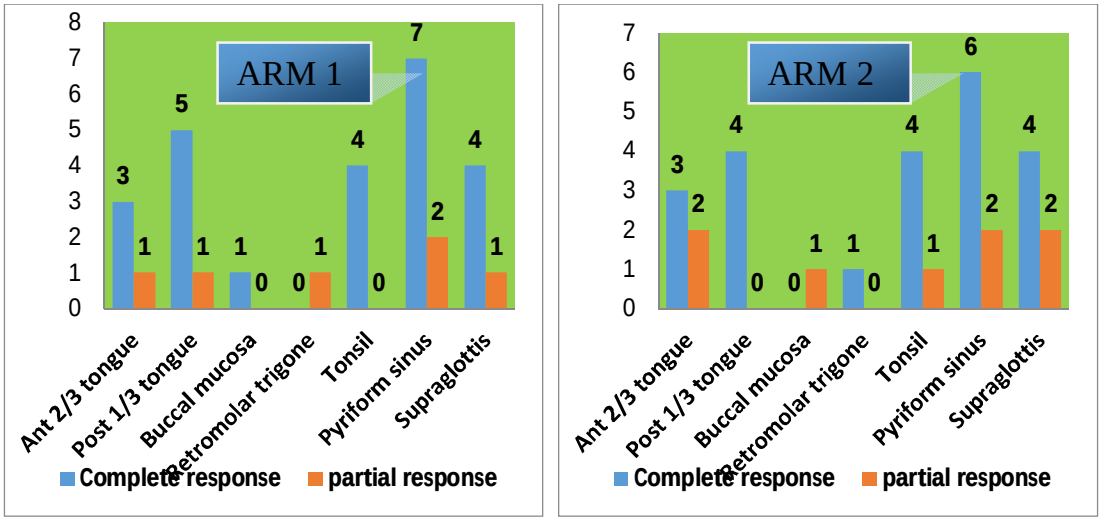
SUBSET ANALYSIS:

All the patient characteristics were analyzed for response at the end of the treatment. The subset wise analysis were done below.

Table: 15 , SUBSET ANALYSIS OF RESPONSE

	ARM 1		**ARM2**	
subsite	**Complete response**	**partial response**	**Complete response**	**partial response**
Ant 2/3 tongue	3	1	3	2
Post 1/3 tongue	5	1	4	0
Buccal mucosa	1	0	0	1
Retromolar trigone	0	1	1	0
Tonsil	4	0	4	1
Pyriform sinus	7	2	6	2
Supraglottis	4	1	4	2

FIGURE : SUBSET ANALYSIS OF RESPONSE



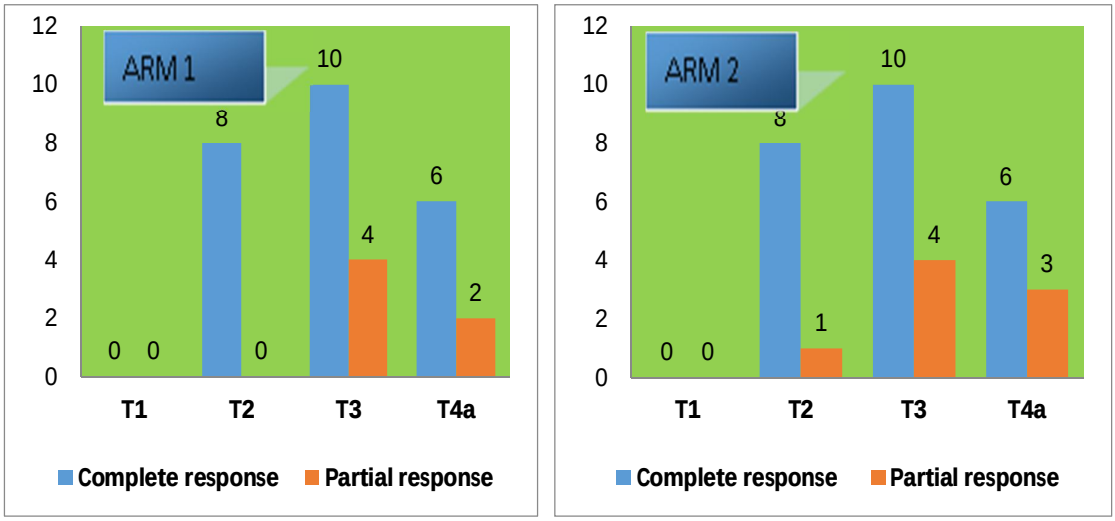
TUMOR STAGE Vs RESPONSE:

Among T3&T4 lesions,T4 had less complete response than T3 in both arms. This shows the advanced nature of the disease.

Table no: 16, TUMOR STAGE Vs RESPONSE

	ARM 1		**ARM 2**	
Tumor stage	**Complete response**	**Partial response**	**Complete response**	**Partial response**
T1	0	0	0	0
T2	8 (100%)	0	8 (88.9%)	1 (11.1%)
T3	10 (71.4%)	4 (28.6%)	10 (71.4%)	4 (28.6%)
T4a	6 (75%)	2 (25%)	4 (57.1%)	3 (42.9%)

FIGURE : TUMOR STAGE Vs RESPONSE



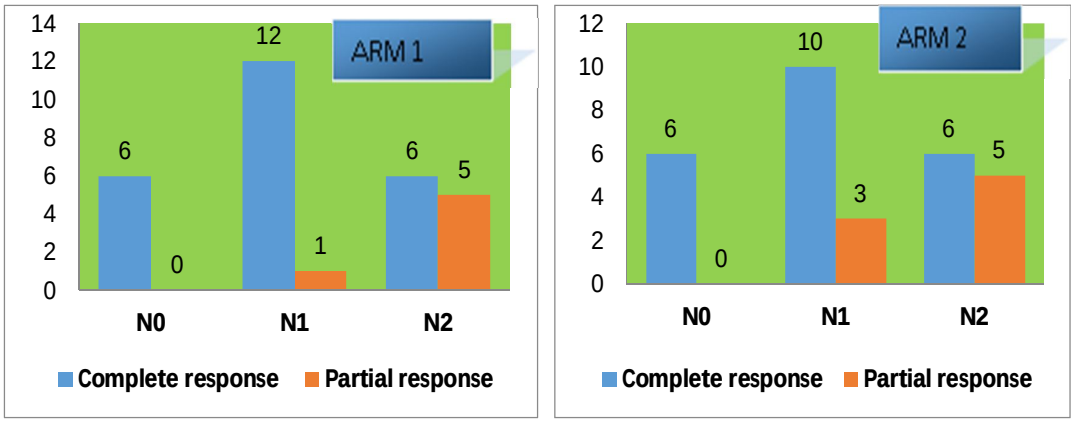
NODAL STAGE Vs RESPONSE:

All N0 patients had complete response , whereas N2 shows less complete response.

Table no:17, : NODAL STAGE Vs RESPONSE

	ARM 1		ARM 2	
NODAL STAGE	Complete response	Partial response	Complete response	Partial response
N0	6 (100%)	0	6 (100%)	0
N1	12 (92.3%)	1 (7.7%)	10 (76.9%)	3(23.1%)
N2	6 (54.6%)	5 (45.4%)	6 (54.6%)	5 (45.4%)

FIGURE : NODAL STAGE Vs RESPONSE



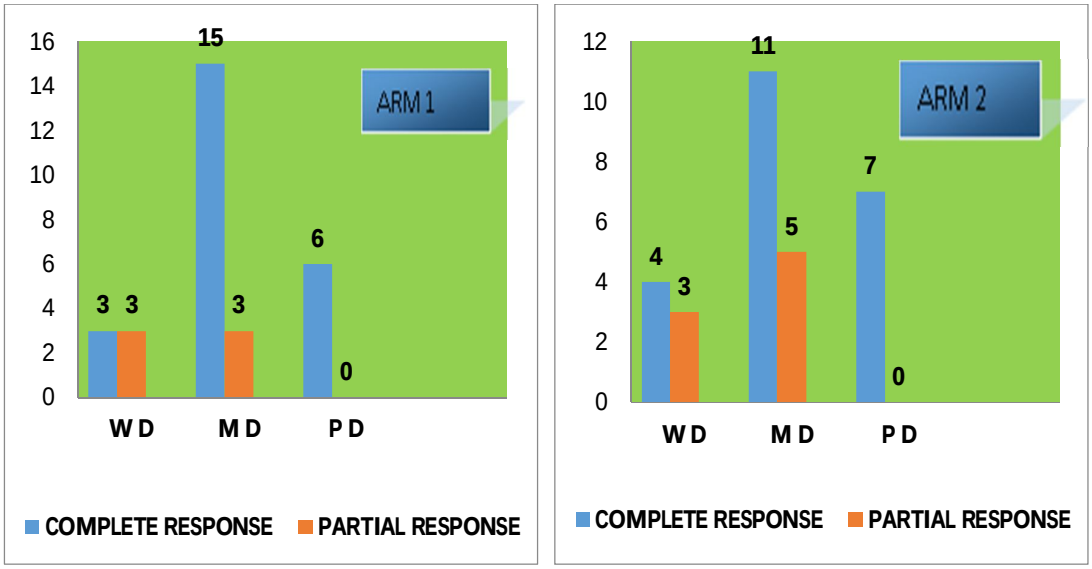
HISTOLOGICAL DIFFERENTIATION Vs RESPONSE:

As already mentioned maximum numbers of the patients in our study were moderately differentiated; in which maximum had complete response and less had partial response in both arms. All poorly differentiated cancer had complete response. In well differentiated tumors , half of them had partial response.

Table no: 18, HISTOLOGIC DIFFERENTIATION VS RESPONSE

	ARM 1		ARM 2	
HISTOLOGIC DIFFERENTIATION	**COMPLETE RESPONSE**	**PARTIAL RESPONSE**	**COMPLETE RESPONSE**	**PARTIAL RESPONSE**
WELL DIFFERENTIATED	3 (50%)	3 (50%)	4 (57.1%)	3(42.9%)
MODERATELY DIFFERENTIATED	15 (83.3%)	3 (16.6%)	11(68.8%)	5(31.2%)
POORLY DIFFERENTIATED	6 (100%)	0	7(100%)	0

FIGURE : HISTOLOGIC DIFFERENTIATION VS RESPONSE



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.

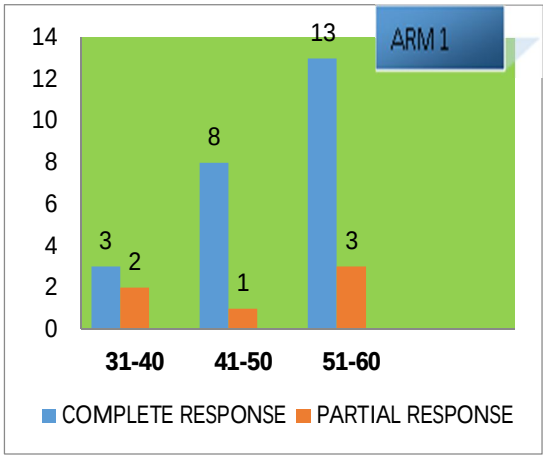
OTHER FACTORS AFFECTING RESPONSE:

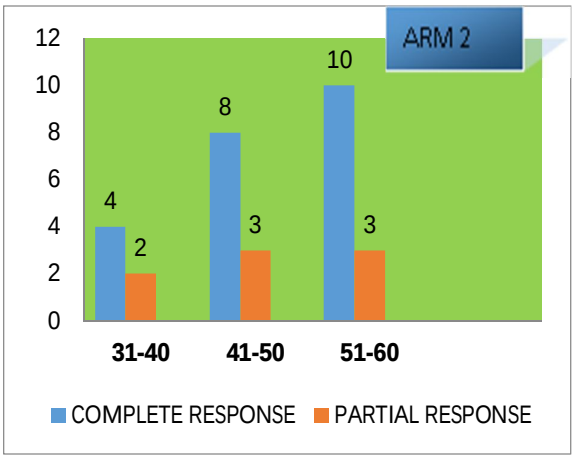
AGE: In this study ,people in both arms aged more than 50yrs were around 50% ,of which majority showed complete response than younger age group ie, below 40 years.

Table no: 19, AGE VS RESPONSE

	ARM 1		ARM 2	
AGE GROUP	**COMPLETE RESPONSE**	**PARTIAL RESPONSE**	**COMPLETE RESPONSE**	**PARTIAL RESPONSE**
31-40Yrs	3 (60 %)	2 (40 %)	4 (66.7%)	2 (33.3%)
41-50Yrs	8 (88.8%)	1 (11.2 %)	8 (72.7%)	3 (27.3%)
51-60Yrs	13 (81.2 %)	3 (18.8%)	10 (76.9%)	3 (23.1 %)

FIGURE: AGE VS RESPONSE





GENDER Vs RESPONSE: As the male population dominated the study 75% 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.

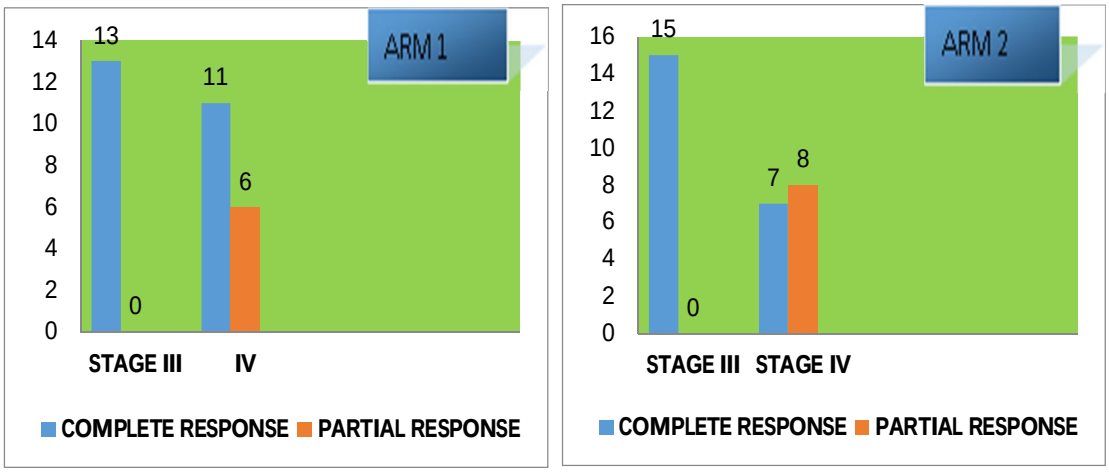
STAGE Vs RESPONSE:

The complete response in Stage IV was around 50 % in both arms but the partial response was more than 30% which is high compared to Stage III where they all had complete response. This is due to the fact that Stage IV disease is infiltrative and extensively spreading.

Table no :20, STAGE VS RESPONSE

	ARM 1		ARM 2	
STAGE	**COMPLETE RESPONSE**	**PARTIAL RESPONSE**	**COMPLETE RESPONSE**	**PARTIAL RESPONSE**
STAGE III	13 (100%)	0	15 (100%)	0
STAGE IV	11 (64.7%)	6 (35.3%)	7 (46.7%)	8 (53.3 %)

FIGURE: STAGE VS RESPONSE



TREATMENT BREAK Vs RESPONSE:

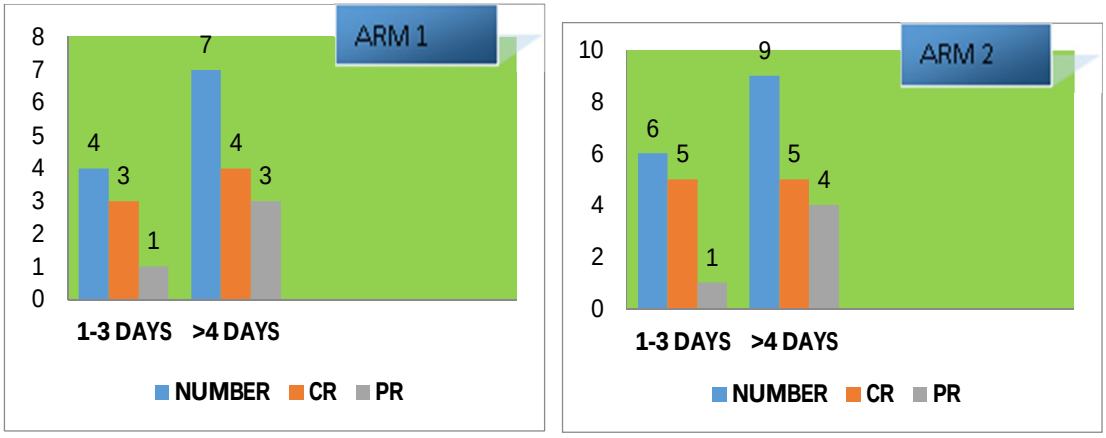
Treatment delay due to toxicities which caused prolongation of overall treatment time was analyzed for response. There was treatment delay in both the arms of around 50 %, another 50% who proceeded without delay in overall treatment time. Among the 50 % of the patients, who did 1-3 days treatment break had more than 75% complete response whereas only around 50% had complete response in case of treatment break for 4 days or more in both the arms.

Though there was treatment break all patient received chemo radiation to the prescribed schedule.

Table no: 21,TREATMENT BREAK VS RESPONSE

	ARM 1			**ARM 2**		
Treatment break	**number**	**CR**	**PR**	**Number**	**CR**	**PR**
1-3 days	4	3 (75%)	1 (25%)	6	5 (83%)	1 (17%)
>4 days	7	4 (57%)	3 (43%)	9	5 (56%)	4 (44%)

FIGURE: TREATMENT BREAK VS RESPONSE



TREATMENT RELATED ACUTE TOXICITIES:

ACUTE LOCAL TOXICITY: Acute local toxicity is done by RTOG Acute morbidity scoring Criteria.

SKIN REACTION: In this study ,arm 1 - 83 % of the patients had Grade 1 skin reactions in the form of dry desquamation, decreased sweating. Another 13% had patchy moist desquamation whereas only 3% of the patient had grade 3 confluent moist desquamation. Whereas, in arm 2-76 % of the patients had Grade 1 skin reactions in the form of dry desquamation, decreased sweating. Another 17% had patchy moist desquamation whereas only 6% of the patient had grade 3 confluent moist desquamation.

MUCOSITIS: As expected there was high incidence of mucositis in this study. Nearly 40% of the study population developed grade 2 reactions in the form of patchy mucositis which is more in arm 2. Around 13-16% had grade 3 confluent mucositis which was more in arm 2 , but there was grade 4 mucositis

in 3-6% of the patients which required treatment break and supportive measures with analgesics, strict oral hygiene, mouth wash with alcohol free antibacterial solution. Also Inj.Dexamethasone 8mg i.v. bid was given for 4-5 days.

SALIVARY GLAND /XEROSTOMIA:

The salivary gland toxicity in the form of xerostomia is usually managed with commercially available artificial salivary agents.In both arms, 73-80% of the patients had grade1 xerostomia with complaints like dry mouth and slightly altered taste sensation. Some 13-16% patients developed complete dryness, sticky saliva as grade 2 toxicity reaction in both arms.

PHARYNGITIS:

The patients with grade 2 and grade 3 dysphagia were given Ryles tube feeding and adequate nutrition was maintained. If needed intravenous fluids and parentral nutrition were given.

LARYNGITIS:

Grade 2 Laryngitis developed in 46% of the patients in arm 2 who had hoarseness of voice and constant cough requiring cough syrup. Grade 3 laryngitis developed in 26% of the patients in arm 2 they had only whispered speech. Remaining had grade 1 toxicity which subsided on its own. In arm 1, the same was present in less number of patients and less in severity.

Table no:22, ACUTE TOXICITY, ARM 1:

ACUTE TOXICITY	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
SKIN REACTIONS	0	25(83.3)	4(13.3%)	1 (3.3%)	0	0
MUCOSITIS	0	15(50%)	10(33.3%)	4(13.3%)	1 (3.4%)	0
SALIVARY GLAND	2	24(80%)	4(13.3%)	0	0	0
PHARYNGITIS/ DYSPHAGIA	0	13(43.3%)	9 (30%)	8(26.7%)	0	0
LARYNGITIS	0	16(53.3%)	8(26.7%)	6 (20%)	0	0

Table no:23, ACUTE TOXICITY, ARM 2:

ACUTE TOXICITY	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
SKIN REACTIONS	0	23(76.7%)	5(16.6%)	2 (6.7%)	0	0
MUCOSITIS	0	11(36.7%)	12(40%)	5(16.7%)	2 (6.6%)	0
SALIVARY GLAND	2(6.7	23(76.7%)	5(16.6%)	0	0	0
PHARYNGITIS/ DYSPHAGIA	0	8(26.6%)	11(36.7%)	11(36.7%)	0	0
LARYNGITIS	0	8(26.6%)	14(46.7%)	8 (26.7%)	0	0

FIGURE : SKIN REACTIONS :

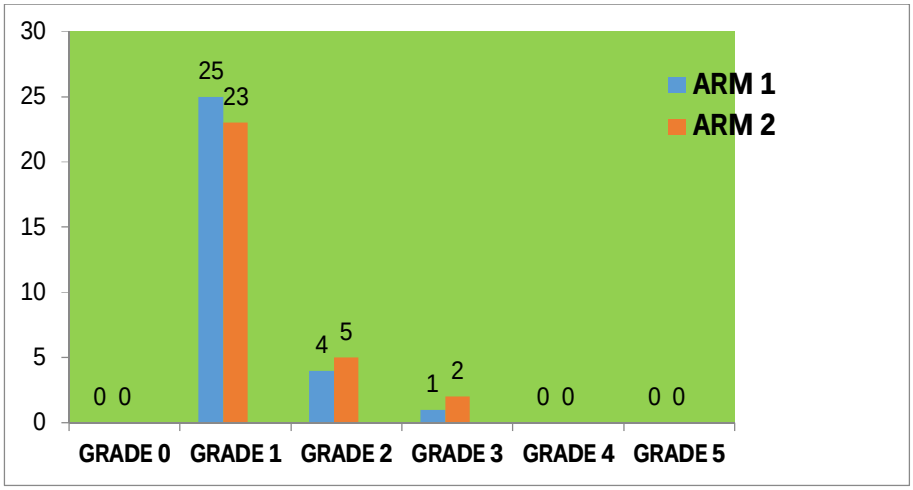


FIGURE: MUCOSITIS :

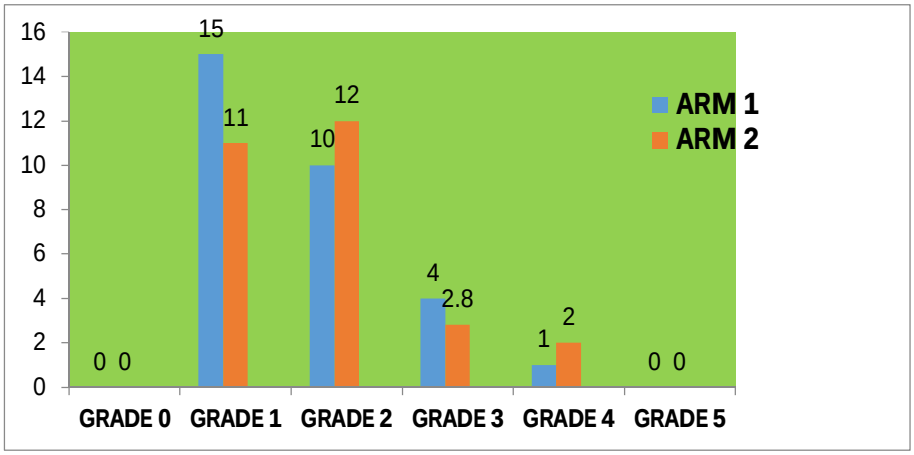


FIGURE: SALIVARY GLAND TOXICITY:

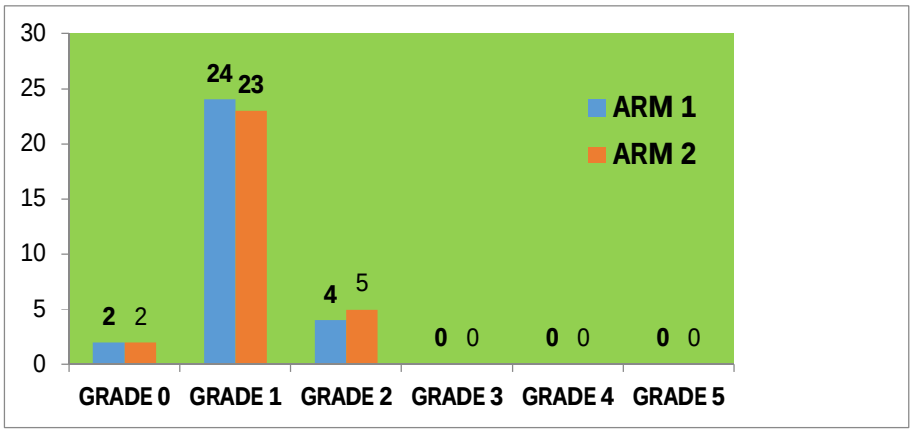


FIGURE: PHARYNGITIS/ DYSPHAGIA:

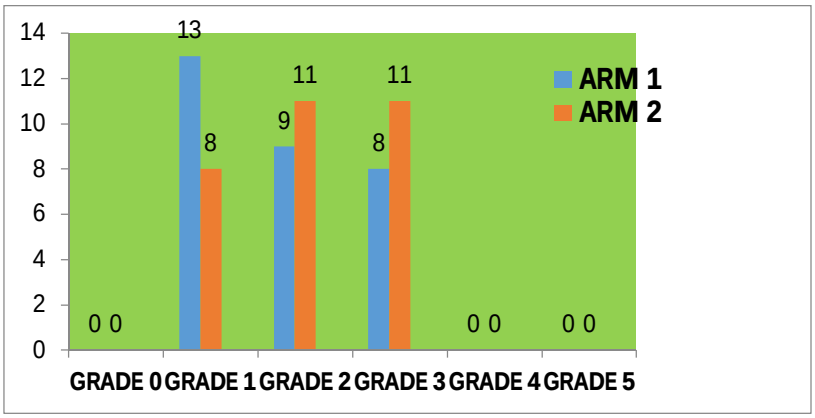
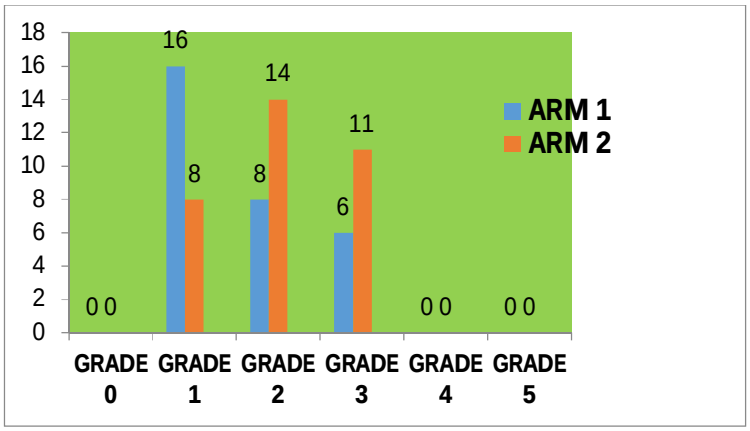


FIGURE:, LARYNGITIS :



SYSTEMIC TOXICITY: The treatment related systemic toxicity was assessed with CTCAE V 4.03 and presented .

NAUSEA: 86% of the study population developed loss of appetite grade1 nausea during their treatment course in arm 1 where as in arm 2 ,66%.but the patient who developed grade 2 nausea was more in arm 2.

VOMITING: In arm 2, 80% of the patients had grade 1(1 or 2 episode) of vomiting during chemotherapy mainly Cisplatin. 20% of the patients had grade

2(3or4episodes) of vomiting managed by Oral Rehydration Salt and Inj.Ondansetron iv bid for 3 -5 days. Intravenous fluids were given whenever necessary. In arm 1,only 6% had grade 2 vomiting which was very less than arm 2.

DIARRHOEA: Only 6% of the patients had grade 1 diarrhoea in both arms.Other than that none of the study patients had diarrhea. Mostly the grade 1 diarrhoea is self-limiting, anti-motility drugs like Tab. Loperamide was used when needed.

Table no: 24, SYSTEMIC TOXICITY ,ARM 1

TOXICITY	GRADE 1	GRADE 2	GRADE 3	GRADE 4
NAUSEA	26 (86.7%)	3 (10%)	1 (3.3%)	0
VOMITTING	28 (93.3%)	2(6.7%)	0	0
DIAHORREA	2 (6.66%)	0	0	0

FIGURE: , SYSTEMIC TOXICITY ,ARM 1

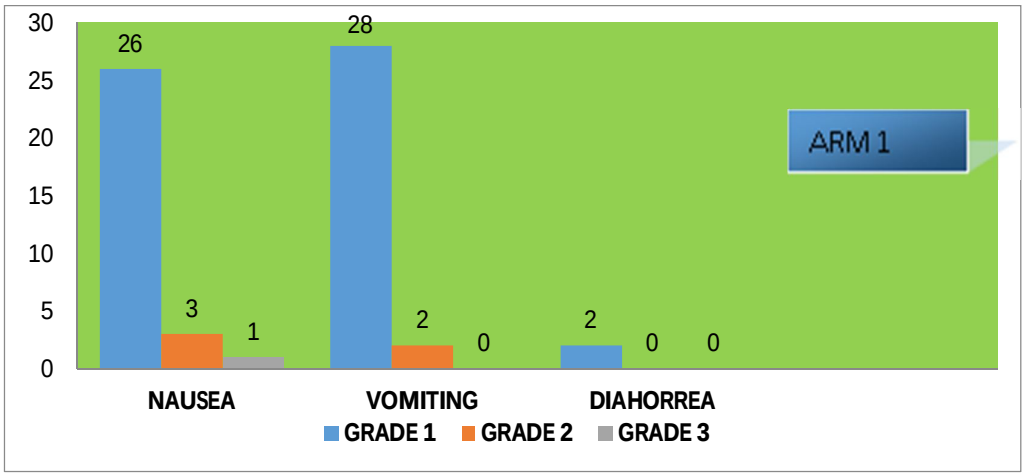
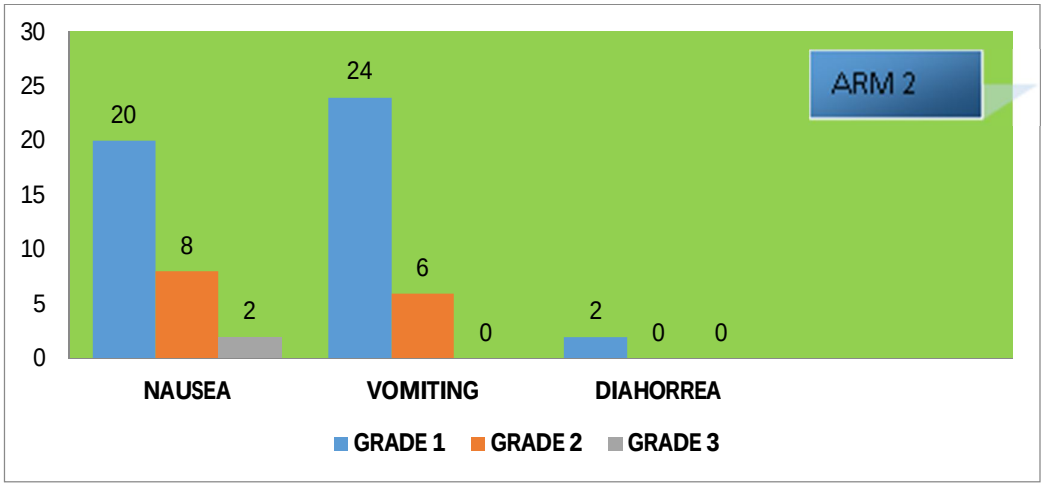


Table no: 25, SYSTEMIC TOXICITY , ARM 2:

TOXICITY	GRADE 1	GRADE 2	GRADE 3	GRADE 4
NAUSEA	20 (66.7%)	8 (26.7%)	2 (6.6%)	0
VOMITTING	24 (80%)	6(20%)	0	0
DIAHORREA	2(6.66%)	0	0	0

FIGURE:, SYSTEMIC TOXICITY ARM 2:



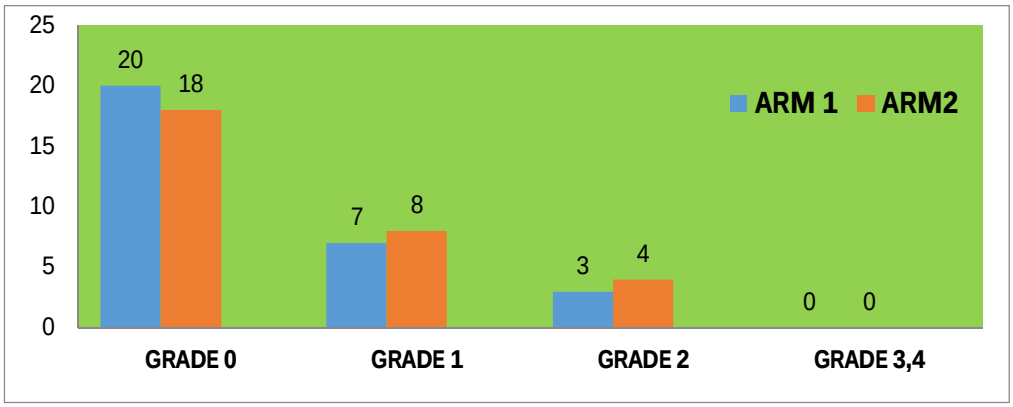
HEMATOLOGICAL TOXICITY:

ANAEMIA: In this study ,in both arms most of the patients completed their treatment without much reduction in their hemoglobin levels. However around 10 % of the patients developed reduction in Hb levels to below 9g% and required Packed cell transfusion.

Table no: 26, ANAEMIA

	ARM 1		ARM 2	
ANEMIA	**NUMBER**	**%**	**NUMBER**	**%**
GRADE 0 Hb >11 gm	20	66.7 %	18	60%
GRADE 1 9.5-11 gm	7	23.3 %	8	26.7%
GRADE 2 7.5-9.5 gm	3	10 %	4	13.3%
GRADE 3 5-7.5 gm	0	0	0	0
GRADE 4 < 5 gm	0	0	0	0

FIGURE :, ANAEMIA

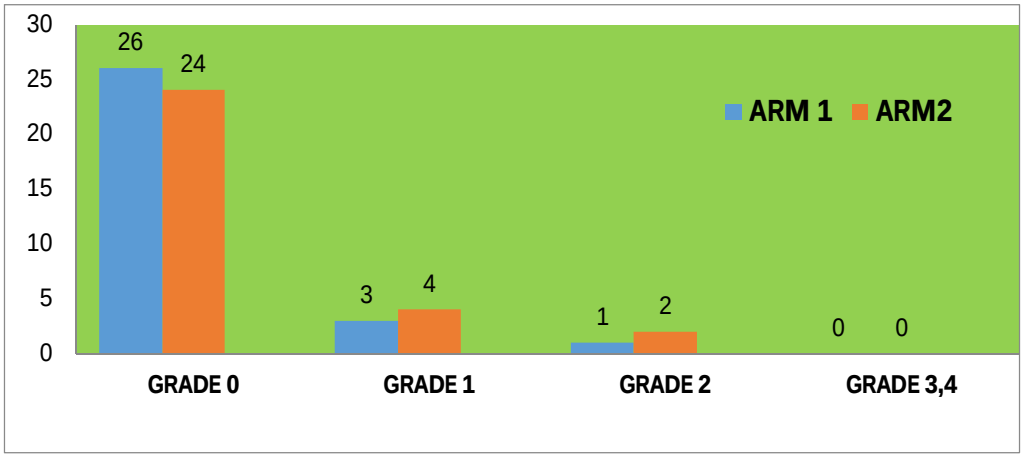


LEUCOPENIA: In both arms,majority of patients had WBC count >4000 completed their treatment without much reduction in WBC count . Only 1 patient in arm 1 and 2 patient in arm 2 had reduction in WBC count level during chemotherapy between 2000 – 3000 grade2 Leucopenia and they were given appropriate measures to regain their count and completed the treatment.

Table :27,LEUCOPENIA

	ARM 1		ARM 2	
WBC COUNT	NO	%	NO	%
GRADE 0>4000	26	86.7 %	24	80 %
GRADE 1 3000-4000	3	10 %	4	13.3 %
GRADE 2 2000-3000	1	3.3 %	2	6.7 %
GRADE 3 1000-2000	0	0	0	0
GRADE 4 <1000	0	0	0	0

FIGURE:,LEUCOPENIA



NEUTROPENIA: There was no neutrophil count reduction in the study.

THROMBOCYTOPENIA: None of the study patients developed thrombocytopenia.

RENAL TOXICITY: All patients had normal renal function tests. Hence none of the patient developed renal toxicity.

Discussion

DISCUSSION

Squamous cell carcinoma of the head and neck is one of the most prevalent cancers in India and has a high social and economic impact. Majority of the patients present in the locally advanced stage where surgical resection is either not possible or is associated with a lot of morbidity. Historically such patients were treated with local RT alone where the local control rates were between 50-70% and the 5 year survival was 10-20%.

There was a definite rationale for the combined use of chemotherapy and radiation in locally advanced head and neck cancer. Chemotherapy sensitizes tumors to radiotherapy by inhibiting tumor repopulation, it preferentially kills the hypoxic cells, inhibiting the repair of sublethal damage caused by radiation, it sterilizes the micrometastatic disease outside the radiation fields and also decreases the tumor mass which leads to improved blood supply and reoxygenation thus potentiating the effect of radiation.

Several trials investigating the feasibility as well the improvement of outcomes by using chemotherapy along with radiation were performed. In most of the trials cisplatin was the mainstay of chemotherapy and it was used alone or in combination with some other agents. The expected theoretical advantage of adding another cytotoxic agent in the form of chemotherapy to that of radiation was clearly demonstrated in these trials and was confirmed by a number of meta-analysis.

Many meta-analyses have been conducted to show whether chemo-radiotherapy association is better than radiotherapy alone in view of locoregional control or survival. Among these meta-analyses the most well known and important one is the Meta- Analysis on Chemotherapy in Head and Neck cancer (MACH-NC) published by Pignon et al. It showed that adding chemotherapy to radiation had the following advantages in locally advanced cancer of the head and neck:

1. The use of chemotherapy increased the overall survival at 5 years by 5% irrespective of the timing of association
2. The concurrent use of chemotherapy with radiation improved the overall survival by 8%
3. The use of neoadjuvant chemotherapy followed by radiation alone is less effective as compared to concurrent chemoradiation
4. The use of cisplatin as the chemotherapy has evident benefit
5. The use of combination chemotherapy does not seem to provide added advantage over the use of single agent.
6. And as the age of the patient increase over 70, the benefit of adding chemotherapy is less evident.

As of now the standard of care for all those locally advanced unresectable head and neck cancer is concurrent chemoradiation with a radiation dose of upto 70 Gy and three weekly cisplatin of 80-100mg/m^2. However the three weekly

regimen is associated with a number of toxicities and poor compliance. Literature wise evidence exists that the weekly regimen of cisplatin is as efficacious as the three weekly regimen as long as a minimum threshold cumulative dose of 200mg/m^2 is achieved. This comes with a significant lesser toxicity in the weekly arm. In a study conducted in our department, the weekly regimen was as efficacious as the three weekly regimen with lower toxicities.

Cisplatin with radiation	**Complete response**	**Partial response**
Three weekly	**64**	**36**
weekly	**62**	**38**

Theoretically, daily administration of low-dose cisplatin may derive the maximum benefit from fractionated administration of concurrent chemoradiation. With each fraction of radiation, cisplatin acts as a radiosensitiser. Added to that, pharmacokinetics indicate that increased exposure to active platinum compound is more effective i.e. continuous exposure , (practically low dose CDDP) is superior to bolus administration of chemotherapy.

The choice of daily cisplatin instead of weekly schedule was based on the experience reported by Jeremic *et al* and Bartelink *et al* . Jeremic *et al* have reported superior outcomes with concurrent use of daily cisplatin as compared to RT alone. They observed the benefit appeared to be of

the order of the benefit reported by 3 weekly schedule. It also highlights on practical benefits of such a protocol ie., no need for excess hydration while giving low dose daily. This may especially relevant from a tropical countries point of view where dehydration is a common occurrence. It also suggests no requirement for elective hospitalization for chemotherapy delivery and lastly such a schedule offer more control over delivery or stoppage of chemotherapy as and when required.

Regarding the optimal dose of low dose cisplatin many studies have used 6 mg/m ^{2} upto the maximum of10 mg daily. Homma *et al* used low dose daily cisplatin at 4 mg/m ^{2} and compared it with weekly carboplatin and found results to be inferior. This could have been due to use of ineffectively low dose schedule of cisplatin daily.

Alteration of fractionation by either hyperfractionation or acceleration has improved the loco regional control. DAHANCA 6 and 7 was the accelerated fractionation schedule followed as standard of care in Denmark. They studied two independent risk factors of radiation resistance known as hypoxia and repopulation. The benefit of acceleration was in addition to the effect achieved by the use of hypoxic modification. Therefore moderately accelerated RT in head and neck cancers with one week reduction in overall treatment time was found to be superior to a conventional regimen. The applicability of this protocol has also been tested by International Atomic Energy Agency (IAEA) in Asian and African countries. They reported a similar benefit of 10%

improvement in local control as the DAHANCA study. In IAEA conducted trial significant proportion of patient were treated by a Telecobalt machine. In the present study, we too adopted 6 fractions a week radiotherapy using Telecobalt machine by reducing the overall treatment time by 1 week.

Glicksman *et al* combined low dose cisplatin with late intensification hyperfractionated radiation in stage III, IV cases. 95% of the patients who initiated, completed the treatment. The disease-specific survival was 78% at 3 years and the combination was well-tolerated .

In the present study ,we compared the overall response rate and toxicity occurred while using low dose daily cisplatin as outpatient infusion with accelerated radiation versus weekly cisplatin as inpatient infusion with accelerated radiation.

In both arms the complete and partial response was 100% with no static or progressive disease. Low dose arm shows slightly higher complete response ie., 80% compared to weekly arm which shows 73% and the remaining had partial response. P value was 0.52 for complete response and 0.60 for partial response which was statistically insignificant due to inadequate sample size. There was no significant association of the response to therapy when compared with the gender of the patient, the age of diagnosis, performance status of the patient.

In this study, primary tumors in the oropharynx, hypopharynx and the larynx had a better response to treatment in both arms as compared to those in

the oral cavity. This may be due to the fact that most of the oral cavity tumors were well differentiated and had a poor response to treatment. This also corroborated with the finding where poorly differentiated tumors had better treatment response rates as compared with the well differentiated histologies.

Tumors with lesser volume of disease i.e. T3 diseases had better response rates as compared with the T4 diseases which had extensive infiltration and the same findings were seen in the nodal disease where N0 and N1 tumors responded better than the N 2 and N3 tumors. Also the response rates in the nodal region was better than that in the primary in both arms.

Also those patients who had a break in the continuity of the treatment had a inferior outcome as compared with those who had no breaks. This reflects the importance of completing the treatment without any break as the problem of accelerated repopulation can lead to treatment failure.

The primary objective of this study was to determine the loco regional control as discussed above. As the sample size was small, statistical analysis is questionable for its significance.

The secondary objective of this study is the toxicity assessment. Even though all of the patients developed some form of acute toxicity to chemoradiation, the rates of grade 3 and 4 toxicities were low in both arms. Around 6% of the patients had grade 3 skin reaction in arm1 and 3% in arm2,P value is 0.6 and no grade 4 reactions. Also the rate of grade 4 mucositis were also low in both arms 3% and 6% with P value is 0.7 but it needs treatment to

resolve and again proceeded with complete treatment. This is attributed to the additional effect of radiotherapy that too patients are treated with 2D Cobalt 60 and not in 3DCRT, IMRT.

The incidence of grade 3 pharyngitis with P value -0.2 were 26% and 36% respectively and the incidence of grade 3 laryngitis with P value - 0.5 were 20% and 26% respectively in both arms. There were no grade 4 reactions in two arms.

Other systemic toxicities like nausea (P value-0.4), vomiting (P value-0.6), diarrhea(Pvalue-0.5) were also seen in the patients but all were manageable with routine anti emetic measures. None of the patients had grade 3 diarrhoea or vomiting in both arms.

The hematological toxicity was also minimal with no incidence of grade 3 or 4 toxicity. 10% in arm1 and 13% in arm2 patients had grade 2 anaemia which was corrected with blood transfusion. Most of our patients are from low socioeconomic status, anemia may be explained due to nutritional deprivation. There were 3% in arm1 and 6% in arm 2 patients had grade 2 leucopenia and managed accordingly. There was no incidence of any febrile neutropenia or thrombocytopenia in the patients.

All patients were hydrated properly during chemoradiation and thus none of the patients had renal toxicity There was no incidence of any liver toxicity in any of the patients in both arms.

There wasn't any treatment related deaths in this study.

MERITS OF THE STUDY:

- All patients had locally advanced head and neck squamous cell caracinoma, the treatment of choice is concurrent chemoradiation which was given.
- Maximum tumoricidal dose of 70Gy was administrated.
- Optimal dose of weekly cisplatin > 200mg/m^2 and daily cisplatin 210 mg/m^2 were achieved in all patients.
- The chemotherapy schedule in both arms assisted to strict regular monitoring of toxicity reactions.

- Toxicities were manageable. No treatment related death occurred in both arms of this study. Toxicity were graded with RTOG Acute radiation morbidity scoring criteria and CTCAE version 4.03
- Response assessment was done after 4-6weeks of completion of chemoradiation, RECIST 1.1 criteria was used for assessment.

DEMERITS OF THIS STUDY:

- There wasn't long term follow up of this study, so progression free survival, overall survival could not be assessed.
- Radiation delivery was given through 2D technique.
- This is a phase two trial, hence randomized control trial must follow to determine prognostic significance and survival rates.

Future perspective:

This study further established the feasibility and efficacy of concurrent low dose Cisplatin as outpatient infusion with accelerated radiation in locally advanced head and neck cancers. Randomized trial using the same protocol is recommended.

Conclusion

CONCLUSION

The head and neck cancer burden is a distressing problem in the developing countries like India. Most of our people are in low socioeconomic status, illiterate and lack of awareness of medical attention; makes people to present in locally advanced stage.

The aim of this study was to evaluate the response of locoregional control and acute toxicity in locally advanced cases by comparing the low dose daily cisplatin versus weekly cisplatin concurrently with accelerated radiation. The dose of daily cisplatin 6 mg/m^2 has shown effective locoregional control with a complete response of 80% and partial response of 20% and the dose of weekly cisplatin 40mg/m^2 has shown locoregional control with a complete response of 73% and partial response was 27% with slightly higher toxicity than low dose which was manageable. This showed that low dose arm was not inferior to weekly arm.

Though there is lack of long term follow up of this study, locoregional control was effective. Large scale randomized study are recommended in near future for Progression free survival and Overall Survival.

In our institution which are overburdened with patients , low dose cisplatin with accelerated radiation schedule appears feasible and logistically suitable out-patient option with good locoregional control and with manageable toxicity in locally advanced head and neck cancer.

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Annexures

APPENDIX

RTOG ACUTE RADIATION MORBIDITY CRITERIA

SITE	GRADE 0	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
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 pretreatment 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

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

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, tube feeding, 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 day 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

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

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

CERTIFICATE OF APPROVAL

To,
Dr.V.Amutha
Post Graduate in MD Radiotherapy
Madras Medical College
Chennai 600 003

Dear Dr.V.Amutha,

The Institutional Ethics Committee has considered your request and approved your study **titled "COMPARISON OF LOW DOSE DAILY CISPLATIN VERSUS WEEKLY CISPLATIN ALONG WITH CONCURRENT ACCELERATED RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA" NO. 09102016.**

The following members of the Ethics Committee were present in the meeting hold on **04.10.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.K.Ramasubramanian,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
8.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,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.

20/10/16

Member Secretary – Ethics Committee

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

URKUND

Urkund Analysis Result

Analysed Document: amutha thesis.docx (D30979644)
Submitted: 10/3/2017 1:53:00 PM
Submitted By: dramutha84@gmail.com
Significance: 4 %

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https://en.wikibooks.org/wiki/Radiation_Oncology/Head_%2526_Neck/Post-op

Instances where selected sources appear:

39

CERTIFICATE – II

This is to certify that this Dissertation work titled **"COMPARISON OF LOW DOSE DAILY CISPLATIN VERSUS WEEKLY CISPLATIN ALONG WITH CONCURRENT ACCELERATED RADIOTHERAPY IN LOCALLY ADVANCED HEAD & NECK SQUAMOUS CELL CARCINOMA"** of the candidate **Dr.V.AMUTHA** with registration Number **201519001** for the award of **M.D. Degree** in the branch of **RADIOTHERAPY**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded Thesis file contains from introduction to conclusion pages and result shows **4 Percentage** of Plagiarism in the dissertation.

Guide & Supervisor sign with seal.

INFORMATION TO PARTICIPANTS

Title :Comparison of low-dose daily cisplatin versus weekly cisplatin along with concurrent accelerated radiotherapy in locally advanced head & neck cancer

Name of Participant:

Name of the Principal(co – investigator) :DR.V. AMUTHA

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. Accelerated radiation means Reduction in overall treatment time by increasing the weekly number of fractions

decreases the opportunity for tumor cell regeneration during treatment and therefore, increases the probability of tumor control for a given total dose.

daily administration of low‑dose cisplatin may derive maximum benefit from fractionated administration of both treatment modalities concurrently. With each fraction of RT, cisplatin acts as a radiosensitizer

- Weekly cisplatin is a more acceptable regimen than three weekly cisplatin.
- Radiotherapy will be delivered by opposing lateral fields with a telecobalt machine using Thermoplastic immobilization devicein the form of

  Phase I to include the primary and the draining lymph node regions and a dose of 44 Gy/22 fractions/4.5 weeks was delivered 5 days in a week at 2 Gy/fraction (Monday to Friday).

  In **phase II-**off-cord reduction to be done, and a dose of 16 Gy/8 fractions/1.5 weeks at 2 Gy/fraction was delivered 5 days in a week (Monday to Friday).

  Phase III will be delivered as a boost on Saturday, as limited volume portal including original GTV with a margin of 2 cm. A dose of 10 Gy/five fractions/over five Saturdays at 2 Gy/fraction was delivered.

- **Weekly Cisplatin arm**:

CDDP (35 mg/m2) weekly (maximum 50 mg) along with proper premedication will be given.

- **Daily cisplatin arm:**

CDDP will be given at 6 mg/m2 (capped at 10 mg) in 500 ml normal saline (NS) solution for all 6 weeks of treatment.

injectionondansetron 8 mg will be given just before chemotherapy

Entire treatment is to be completed in 6 weeks time .Primary and gross adenopathy receive70 Gy.

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

The study design: double arm prospective study

Study Procedures:

The study involves evaluation of Locally advanced squamous cell carcinoma of the head and neck with accelerated radiotherapy and chemo in the form of weeklyinj.cisplatin or low dose daily cisplatin. 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

INFORMED CONSENT FORM

TITLE OF THE STUDY:**Comparison of low-dose daily cisplatin versus weekly cisplatin along with concurrent accelerated radiotherapy in locally advanced head & neck cancer**

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL (Co – Investigator) : **DR.V.AMUTHA**

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 myfree power of choice, hereby give my consent to be included as a participant in" :**Comparison of low-dose daily cisplatin versus weekly cisplatin using concurrently with six fractions per week radiotherapy in locally advanced head & neck cancer".**

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 12month(s).

9. I agree to under go complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck

10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.

11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have 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)

Name _____ Signature_____ Date_____

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

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent

Name _____ Signature_____ Date_____

கதிர்வீச்சு சிகிச்சை அளிக்கபடும் இடத்திலுள்ள தோல் பராமரிப்பு

செய்	செய்யாதே
• சிகிச்சை அளிக்கப்படும் முந்தைய நாள் மட்டும் முகச்சவரம் செய்யலாம்.	• சிகிச்சையின் போதோ ,சிகிச்சை இடைவெளியின் போதோ (சனி,ஞாயிறு) முகச்சவரம் செய்யக்கூடாது.
• தோல் உரின்தலோ சிவந்தாலோ மருத்துவரை அணுக வேண்டும்.	• சிகிச்சை கிடைக்கும் இடத்தில் தண்ணீரோ வியர்வையோ படக்கூடாது. • அதன் மேல் தேங்காய் எண்ணெய்,வாசலின் ,முகபவுடர், மஞ்சள் தடவகூடது . • துணி வைத்து தோலை தேக்கக்கூடாது.
வாய் பராமரிப்பு • மருத்துவர் கூறிய அளவில் சமையல் உப்பு மற்றும் ஆப்ப சோடா உப்பு ஆகியவற்றை தண்ணீரில் கலந்து நாலு -ஆறு முறை வாயை கொபளிக்க வேண்டும் . • குழந்தைகள் பிரஷ் கொண்டு பல் துலக்கலாம் . • மருத்துவர் கூறிய மருந்தை மட்டும் உபயோகிக்கவும் .	• அதிக அளவு வெயிலோ குளிரோ அதன் மேல் படக்கூடாது.

செய்	
• அதிக காரம் எண்ணெய் சேர்க்ககூடாது (ஊறுகாய்) • டீ காபி தவிர்க்கவும்.	• புகை பிடிக்கக்கூடாது, மது அருந்தக்கூடாது .
• ஆப்பில் வாழை பழம் சிறிய துண்டுகளாகவோ பழச்சரகவோ குடிக்கலாம். • தினம் ஒரு வேகவைத்த முட்டை சாப்பிடலாம். • வேக வாய்த்த காய்கறிகளை மட்டும் சாப்பிடுங்கள் .	• சிப்ஸ் மிச்சர் காரசேவ் போன்றவற்றை தவிர்க்கவும்.
• பழங்களில் திராட்சை ,எலுமிச்சை தக்காளி தவிர்க்கவும். • தினம் இரண்டு கப் பால் (பூஸ்ட் ஹார்லிக்ஸ்)குடிக்கவும். • வேக வைத்த துவரம் பருப்பு,பாசி பயறு ,சுண்டல், உருளை கிழங்கு சாப்பிடலாம் . • பாலில் தோய்த்த ரொட்டிதுண்டுகள் சாப்பிடலாம் . • எளிதில் ஜீரணம் ஆகக்கூடிய உணவை மட்டும் சாப்பிடுங்கள் . • காய்கறி சூப் ,மட்டன்,சிக்கன் சூப் குடிக்கலாம் .	• வெற்றிலை பாக்கு மூக்குப்பொடி பான்பராக், ஹான்ஸ் ,மாவா கண்டிப்பாக பயன் படுத்தக்கூடாது .

ஒப்புதல் படிவம்

தலை மற்றும் கழுத்துப்பகுதி முற்றிய புற்று நோய்க்கு வாரத்தில் ஆறு நாட்கள் கதிர் வீச்சு சிகிச்சையுடன் சேர்த்து குறைந்த அளவு தினசரி கீமோதெரப்பிக்கு எதிராக வாராந்திர கீமோ தெரப்பியுடன் ஒப்பீடு பற்றிய ஆராய்ச்சி.

பங்கேற்பாளர் பெயர் :

ஆராய்ச்சியாளர் பெயர் :

நிறுவனத்தின் பெயர் :

_____ என்ற நான் இப்படிவத்திலுள்ள விவரங்கள் அனைத்தும் படித்தேன் (அல்லது எனக்கு படித்துக் காட்டினார்கள்) நான் இது சம்மந்தமாக கேட்ட கேள்விகளுக்கு முறையாக பதிலளிக்கப்பட்டது. நான் பதினெட்டு வயது நிரம்பியவர், மேலும் என் முழுமனதோடும், சுயநினைவோடும் இந்த மேற்குறிப்பிட்ட மருத்துவ சிகிச்சைக்கு பங்கு பெற சம்மதிக்கிறேன்.

1) நான் எடுத்துக்கொண்டிருக்கும் சிகிச்சை முறைகள் அல்லது கடந்த ஒரு வருடமாக நான் எடுத்துக்கொண்ட சிகிச்சை முறைகள் பற்றியும் (நாட்டு வைத்தியம் உட்பட) எனது ஆராய்ச்சியாளருக்கு தெரிவித்துள்ளேன்.
2) எனக்கு பின்வரும் ஆறு வாரங்கள் கதிர்வீச்சு சிகிச்சை குறித்த விளக்கமும், கீமோதெரப்பி எவ்வாறு கொடுக்கப்படும் என்பதன் விவரமும் எனக்கு முழுமையாக விளக்கப்பட்டது.
3) எனக்கு என்னுடைய உரிமைகளையும், பொறுப்புகளையும், ஆராய்ச்சியின் தன்மை பற்றியும் ஆராய்ச்சியாளர் மூலம் விளக்கப்பட்டது.
4) எனக்கு இந்த ஆய்வினால் ஏற்படும் பின் விளைவுகள் பற்றி எடுத்துரைக்கப்பட்டது.
5) நான் எனது ஆராய்ச்சியாளருக்கு முழு ஒத்துழைப்பு தருவேன். மேலும் எனக்கு அசாதாரணமான அறிகுறிகள் ஏதேனும் தென்பட்டால் உடனடியாக தெரிவிப்பேன்.
6) கடந்த ஒரு வருடமாக எந்த ஆராய்ச்சியிலும் பங்கேற்கவில்லை என்பதை உறுதி கூறுகிறேன்.

7) நான் முழு இரத்த பரிசோதனை சிறுநீரகம் மற்றும் கல்லீரல் பரிசோதனை, நெஞ்சு ஊடுகதிர் தலை மற்றும் கழுத்து பகுதியில் கணினி வழி உடலுறுப்பு ஊடுகதிர் படம் செய்ய சம்மதிக்கிறேன்.

8) என்னால் எந்த நேரத்திலும் எக்காரணமும் இன்றி இந்த ஆராய்ச்சியிலிருந்து விடுவித்துக் கொள்ள முடியும் என்பதையும் இதனால் இந்த மருத்துவமனையில் மேற்படி எனக்கு அளிக்கப்படும் சிகிச்சையில் எந்த தடங்கலும் இருக்காது என்பதை அறிவேன்.

9) மேலும் ஆய்வாளர் எந்த நேரத்திலும், எக்காரணத்திற்காகவும் என்னை இந்த ஆராய்ச்சியிலிருந்து விடுவிக்கலாம் என்பதையும் நான் அறிவேன்.

10) மேற்கொள்ளப்படும் ஆராய்ச்சியில் என் பங்களிப்பிலிருந்து கிடைக்கும் தகவல்களை நிறுவனத்தின் ஆராய்ச்சி குழுவிற்கும், அரசாங்க நிறுவனத்திற்கும், ஆராய்ச்சியின் ஆதரவாளர்களுக்கும் பகிர்ந்து கொள்ள சம்மதிக்கிறேன். மேலும் இத்தகவல்கள் பொதுவாக விவாதிக்கப்படும் என்பதையும் அறிவேன்.

11) நான் என்னுடைய தனிநபர் அடையாளம் பொதுவாக வெளிப்படுத்தப்படாது என்பதையும் அறிவேன்.

12) நான் என்கேள்விகளுக்கு திருப்தியான பதில்களை பெற்றேன்.

13) நான் இந்த ஆய்வில் பங்கேற்க முடிவெடுத்துள்ளேன்.

நான் இந்த ஆராய்ச்சியில் ஏற்படும் சந்தேகங்களை எனது ஆய்வாளரிடம் அணுகி தெரிந்துக் கொள்ள வேண்டும் என்பதையும் அறிவேன். இந்த ஒப்புதல் படிவத்தில் கையொப்பமிடுவதன் மூலம் இந்த ஆராய்ச்சி பற்றிய முழுவிவரமும் எனக்கு எடுத்துரைக்கப்பட்டது என்பதும், அதை நான் முழுமையாக புரிந்துக் கொண்டேன் என்பதையும் அத்தாட்சி அளிக்கிறேன். இந்த ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு அளிக்கப்படும்.

பங்கேற்பாளர் பெயர்: _____ கையொப்பம் _____ தேதி _____

உறவினர் பெயர்: _____ கையொப்பம் _____ தேதி _____

ஆராய்ச்சியாளர் பெயர்: _____ கையொப்பம் _____ தேதி _____