SEQUENTIAL THERAPY WITH INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

A SINGLE ARM PROSPECTIVE STUDY

INSTITUTION

DEPARTMENT OF RADIOTHERAPY
MADRAS MEDICAL COLLEGE
&
RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL
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DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

MD BRANCH IX RADIOTHERAPY

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CERTIFICATE

This is to certify that **Dr. S. MOSES ARUNSINGH** has been a Post Graduate MD Student during the period from May 2010 to April 2013 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled **"SEQUENTIAL THERAPY WITH INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK"** is a bona fide work done by him during his study period and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch IX Radiotherapy examination.

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DECLARATION

I solemnly declare that the dissertation titled

“SEQUENTIAL THERAPY WITH INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK”,

A **SINGLE ARM PROSPECTIVE STUDY** was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during my study period, under the guidance and supervision of Prof. Dr. S. SHANMUGAKUMAR, B. Sc., M.D., DMRT.

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CONTENTS

SEQUENTIAL THERAPY WITH INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

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AIMS & OBJECTIVES:

To assess the immediate loco regional response rates and to assess the toxicity profile of sequential therapy with three cycles of induction PFT followed by Concurrent Chemo Radiation with weekly Cisplatin in Locally Advanced Head and Neck Cancers.

MATERIALS AND METHODOLOGY:

30 consecutive patients with locally advanced head and neck cancers attending the OPD at our institute were included in the study. All patients were treated with 3 cycles of Induction chemotherapy with PFT regimen (Paclitaxel 175mg/m^2 Day1, Cisplatin 100 mg/m^2 split to (Day 1-3), 5-FU 750 mg/m^2 Day 1 to 3) every 21 days. The patients were then taken up for concurrent chemo radiation (66 Gy RT along with weekly Cisplatin 40mg/sq.m.). The immediate loco regional response rates were assessed by clinical and radiological imaging. The toxicity profile of the treatment was assessed with RTOG acute morbidity scoring criteria and CTCAE Version 4.

RESULTS:

30 patients (3 female) were recruited for the study. Among them 3 were laryngeal cancer patients and the hypo pharyngeal, oropharyngeal and the oral cavity cancers were 9 each. 63% of them had complete response and 30% had partial response. The sub-sites of hypopharynx and the oropharynx had the best outcomes from this treatment protocol. 2 patients did not complete the planned treatment.11 patients had grade 3 leukopenia and 2 patients had grade 4/febrile neutropenia. There were no grade 3 thrombocytopenia in the study group.

CONCLUSIONS:

Sequential therapy with three cycles of induction PFT followed by concurrent chemo radiation is a feasible alternative for moderately advanced and very advanced head and neck cancer. Patient selection and supportive care during treatment are very important for successful outcome.

INTRODUCTION

1. INTRODUCTION

Face is what makes the man. It distinguishes us and gives us a unique identity. Face is what helps us human beings to socialize. It helps us to communicate the thoughts of our minds and hearts through expressions and spoken words. Perhaps this unique ability to express ourselves vocally or by just facial expression is the single most important thing that separates us human beings from all the other species on this planet. The very essences of our lives, air and nutrition reach us through the organs in the face. Besides this, it is also the gateway to the special senses such as vision, smell, hearing and taste.

In this context, cancers involving the face result in a variety of problems for the patient related to the functions of the face as written above. Head and neck region cancers represent a heterogeneous group of cancers involving the various structures in the region. It comprises the cancers in the following anatomical regions including nasal cavity, nasopharynx, oral cavity, oropharynx, hypopharynx, the larynx, the salivary glands and the para-nasal sinuses.

EPIDEMIOLOGY:

Every year around 5 million new cases of head and neck cancers are diagnosed worldwide. It accounts for 10% of all the malignancies diagnosed and is the sixth most common cancer in the world.[1, 2] It is one of those cancers which can have a devastating effect on the individual by way of functional and cosmetic consequences. It is a significant public health problem afflicting the developing countries. The incidence of head and neck cancers have come down in the developed countries with the awareness that smoking is one of the commonest causes and the subsequent decrease in smokers.[3] However, the incidence has not shown a decline in the developing countries despite steps to create awareness.

With regard to India, it is one of the commonest cancers in our country due to the widespread use of tobacco products in its various forms.[4] Oral cavity cancer was the commonest and the commonest sub site to be involved was the tongue.[5] This is despite the steps taken by our governments to create awareness with graphic warning labels on the tobacco products and a ban on the advertisements for tobacco products[6]. What was once a problem of the adults, tobacco addiction has now become a common thing among youngsters resulting in the incidence of cancer at a very young age.

In our institute too, head and neck cancers constitute the majority of cases registered in our OPD. Majority of them are squamous cell carcinomas (~95%) with other histology making up the remaining. Nearly three quarters of them present in the locally advanced stage. Only around 20 to 25% of the cases present in the early stages. Most of them are tobacco users either in smoked form such as cigarettes, beedis or in smokeless forms such as pan etc.

AETIOLOGY:

The state of our health has become increasingly dependent on our environment and our lifestyle habits. This is more so in the case of head and neck cancers. The various etiological factors of head and neck cancers point to the impact, life style changes in past century had on our health. The incidence of head and neck cancers keep increasing with the increase in age. Of late the incidence is also increasing in younger age groups too. This may be due to behavioral changes in this age group.

1. **Smoking:** Tobacco is by far the most important etiological factor[7, 8]. Smoking of tobacco in the form of cigarettes, cigars, beedis, and loose tobacco in pipes is common in our country. Beedis are more dangerous than cigarettes. Also reversed

smoking, common in some regions are associated with increased incidences.

2. **Smokeless Tobacco**[7, 8]: In our country and in the South Asia region, smokeless tobacco forms such as pan, ghutka, khaini etc., play a very important role. It is also used in combination with other irritants such as betel leaf, arecanut, slaked lime etc. The age group of the users of these products is ever decreasing. This is despite the various prohibitory orders in effect such as prohibition of sale of tobacco products near educational institutions etc.

3. **Alcohol**[7, 8]: Alcohol intake also has long been associated with the incidence of H & N cancers. Consumption of alcohol is a synergistic factor along with tobacco use.

4. **Human Papilloma Virus**[9]: HPV is associated with around 35% of all head and neck cancers. It is more commonly associated with oropharyngeal cancers especially in the case of tonsillar cancers. HPV 16 is the most common virus associated with incidence of oral cancers in around 22% and the next most commonly associated is HPV 18 in around 15%.[10-13]

5. **Deficient diet**[7, 8]: Deficiency of certain nutrients has been implicated with the development of oral cancers although this is controversial. This is attributed to be the reason for around 10 – 15 % of oral cancers in European countries.

6. **Others:** other common factors implicated in the development of these cancers are sharp tooth, spicy foods, sub mucous fibrosis, aromatic hydrocarbons, asbestos, wood dust, nickel, chromium, heat fumes etc.

PREMALIGNANT CONDITIONS:

These are conditions which have chance of progression to invasive malignancies.[14] But a vast majority of head and neck cancer patients do not present with any identifiable premalignant lesions and they may not represent an opportunity to reduce the incidence of these cancers.

1. **Leukoplakia:** Oral leukoplakia (a white mucosal patch or plaque) is the commonest premalignant lesion of the oral cavity, and is a marker of an increased risk of cancer anywhere in the oral cavity. It is associated with smoking. They have a very low rate of progression to malignant changes. They also resolve with cessation of smoking.[15]

2. **Erythroplakia:** Reddish discolouration of the mucosa that is associated with more risk of malignant transformation than that of leukoplakia up to 15%.

Other lesions considered to be premalignant lesions are oral lichen planus, oral mucous fibrosis, epidermolysis bullosa, discoid lupus erythematosus etc.[16]

HISTOLOGY:

The most common histology in head and neck cancers are squamous cell carcinomas arising from the epithelial lining of the upper aero digestive tract. Differentiation of these tumors varies from site to site. The cancers from sub sites of the oral cavity are usually well differentiated, in more than 95%. Cancers of the oropharynx are usually moderately differentiated in around 65%. Cancers of the larynx are usually well differentiated and that of the hypopharynx are moderate to poorly differentiated. Less common variants of the squamous cell carcinomas include verrucous carcinomas, which are very well differentiated and have warty gross appearance.[17] It is very difficult to identify the malignancy in this variety. Another variant is the squamous cell carcinomas with spindle cells features. The significance of the spindle cell in this variety is debatable. Other histologies arise from minor salivary glands, lymphoid

follicles in the waldeyers ring, neuroendocrine (small cell) tumors, sarcomas etc.

SYMPTOMS:

The patients present with a wide range of symptoms such as, pain, swelling in the neck, non healing ulcers in the oral cavity, proliferative growth in the tongue, difficulty in swallowing, difficulty in breathing, hoarseness of voice etc. The symptoms give an indication as to the primary site of involvement and also to the extent of the disease. They also present with emergencies such as bleeding from the lesion, stridor etc. The wide range of presentation influences the treatment considerations of the treating oncologist.

NATURAL HISTORY:

Head and neck cancers are mostly loco regional diseases with the primary tumor slowly increasing in size and involving the adjacent structures. Certain sub sites in this region have vital structures as adjacent structures. For instances in hypo pharyngeal and laryngeal cancers the airway may be compromised either as direct result of tumor obstructing the airway or as a result of the tumor encroaching on to nervous structures. This will result in the patient presenting with stridor as a symptom to the emergency room. Oropharyngeal, hypo pharyngeal and laryngeal cancers

may compromise the digestive tract resulting in difficulty in food intake or painful swallowing. This will have an adverse impact on further treatment plans for the patient as he may be malnourished at the time of presentation. Cancers of the oral cavity can spread to involve the deep extrinsic muscles of the tongue resulting in ankyloglossia. Cancers of the buccal mucosa may erode the entire cheek up to skin resulting in leakage of food. Cancers of the head and neck region, particularly of the tonsil may erode onto a blood vessel and result in torrential bleeding which is again an emergency. Oral cavity cancers can spread and erode adjacent bony structures resulting in a change in the primary modality of treatment. There can also be perineural invasion which is an adverse prognostic factor.

As the size of the primary increases, the incidence of regional spread to involve the draining lymph nodes increases. Each sub site involves certain levels of the cervical nodes more commonly. The hypo pharyngeal cancers most commonly involve the Level III and IV nodes. The oropharyngeal cancers most commonly involve the Level II and III nodes, whereas the cancers of the buccal mucosa usually spread to the Level Ib region. The Level Ia is usually involved only in cancers of the lip and in cancers involving the tip of the tongue.

Literature review claims the incidence of distant metastasis in head and neck cancers to be around 15 – 20%[18-19]. But most patients die of loco

regional disease, as around 50 – 60% of those who are cured with combined modality therapies recur within the first 2 years of follow up.

WORKUP: [20, 21]

1. History of symptoms.
2. Thorough clinical examination of the primary site and the regional lymph nodes. Thorough examination of the entire head and neck region to rule out second primary malignancies has to be carried out. Indirect and video laryngoscopies, esophagoscopy in case of the post cricoid region cancers to rule out involvement of cervical esophagus.
3. Biopsy of the primary tumor.
4. Imaging studies: Computed Tomography (CT) of the Neck extending from the base of skull to the root of the neck.
5. Magnetic Resonance Imaging (MRI): Soft tissue delineation is better in MRI.
6. Chest X ray to rule out distant metastasis in the case of locally advanced head and neck cancers.
7. Basic Metabolic Panel: Renal function tests and Liver function tests.
8. Complete Blood Count.
9. Assessment of anesthetic fitness if decided for surgery as modality of treatment.

10. HPV DNA or HPV – prognostic information in case of oropharyngeal cancers.

PROGNOSTIC FACTORS:

Prognosis of patients with head and neck cancers depends most importantly on the stage of the disease at the time of initial presentation.[22] Involvement of nodes in head and neck cancers upgrades it to stage III and also the survival of these patients is decreased by as much as 50%. Involvement of regional lymph nodes and also advanced T stages have higher incidence of loco regional recurrences and also distant metastasis. They also require multimodality treatment than the early stage cancers in which single modality will achieve cure in more than 90% of cancers. Even with these aggressive approaches more than 50 – 60% will fail the treatment and have local recurrences and in the rare cases develop distant metastasis. Death in such cases is usually due to loco regional recurrences. Other well-known prognostic factors are perineural invasion, positive or close margins after resection of the primary, extra caspular extension[23-24], depth of invasion, extent of nodal involvement[22, 25].

Nutrition of the patient at presentation also plays a very important role[26, 27]. Malnourishment rules out implementation of aggressive multimodality therapies which are the order of treatment in locally

advanced cancers and are straight away put on palliative treatment or on supportive care.

MOLECULAR BIOMARKERS:

1. **EGFR overexpression:**

   EGFR receptors are overexpressed in over 95% of the squamous cell carcinomas of the head and neck. It has been corroborated as a worse prognostic factor. However it also gives a therapeutic target in manipulating the receptor pathways in cancer cells. Several targeted agents, monoclonal antibodies like cetuximab are available in the market and also have shown benefit in the advanced stages.[28]

2. **Tyrosine kinases:**

   These are the downstream kinases responsible for several functional pathways in tumor and normal cells. They also provide a target for manipulation with tyrosine kinase inhibitors (TKI) like geftinib and erlotinib.

3. **TP53 mutation:**

   The frequent observation of p53 gene deletion or mutation in head and neck cancer has prompted the development of gene therapy. Mutation of the p53 tumour suppressor gene has been associated with field cancerization, resistance to induction

chemotherapy, increased risk for advanced disease, and poor prognosis. Mutation of the p53 gene is higher among patients exposed to tobacco or alcohol than among patients without exposure.[29]

TIMELINE OF HEAD AND NECK CANCERS TREATMENT:

In the treatment of head and neck cancers, the first and only tool available to mankind was surgery. First of the modern surgery for cancer was carried out in United States for an ovarian tumor. This showed that surgical removal of the cancer was possible and it was possible to cure cancer. Later with the advances in cancer biology came the understanding about the cellular nature and origin of cancer. The discovery of X-Rays by William Roentgen in 1985 and the use of the first chemotherapy agents, nitrogen mustards in the 1940 have changed the face of oncology.

The first of the head and neck cancer to be cured by Fractionated Radiotherapy was in 1928 and since then various modalities and combinations of treatment have been tried to increase the cure rate in these cancers.

TREATMENT OF HEAD AND NECK CANCERS:

SURGERY:

Surgery was the first modality to be used in the treatment of head and neck cancers. In the early years, surgery used to result in significant alteration of the body shape and also a significant loss of function too. However since then there has been significant improvement in surgical approaches and the development of plastic surgery has led to less morbid surgeries.

All patients should be seen by a surgical oncologist before the start of the treatment. Surgery should aim to achieve surgical margins clear of the tumor.[30] Positive margins are to be avoided as they have a poor prognosis and have a very high chance of local recurrence. Margins should be assessed by either frozen section or by formalin fixed samples of the tumor tissue. A clear margin is defined as a distance of more than 5mm from the tumor margin to the resected margin. A close margin is less than 5 mm distance. A positive margin is defined as carcinoma in situ or invasive tumor at the resected margin.

Surgery is the primary modality of choice in early stage cancers of oral cavity. Whereas in cancers of the hypopharynx and larynx they are indicated in the case of advanced stages, as early lesions are treated with the organ preservation intent. Lymph nodal dissection is also part of the surgical approach when it is carried out as a primary modality. Either

elective, selective or comprehensive neck node dissections are carried out on the basis of stage of the primary tumor and on the basis of the sub site involved. Tumors that have bilateral drainage will need bilateral neck dissection. The type of dissection can be summarized as follows:

N0 – Selective dissection

Level I – III for Oral Cavity

Level II – IV for Oropharynx

Level II – IV for Hypopharynx and Larynx

N1-2 - Comprehensive neck dissection / Selective Neck dissection

N3 – Comprehensive neck dissection

Surgery also has role in recurrent tumors as a salvage modality. Patients who had surgery or radiation as a primary modality can undergo salvage surgery to achieve cure. They may also have a role in emergency settings such as bleeding due to erosion of blood vessels. Feeding vessels can be ligated to stop the bleeding as a palliative procedure.

RADIOTHERAPY:

Radiotherapy has improved leaps and bounds since the first patient was cured with fractionated radiation in 1928. Radiation can used either alone or in concurrence with chemotherapy as a primary modality in curative intent. It is used alone in early stage cancers and along with chemotherapy in locally advanced diseases. It is also used in the

postoperative setting or adjuvant setting in locally advanced cancers after surgery as the primary modality. Post-operative RT is indicated in case of advanced T stage, multiple node positivity and perineural or lymphovascular invasion. Post-operative chemo radiation is indicated in the case of positive margins and extra capsular extension.[22-25]

Many a different fractionation schedules of RT has been experimented with for improving local control and for reducing normal tissue complications. No single fractionation schedule has been found to be the best for all tumors. Conventional fractionation is 2 Gy per day for 5 days a week. Data are available suggesting that fractionation schedules delivering at least a 1000 cGy per week are needed for effective tumor control when RT alone is used as a treatment modality in early stage cancers to counteract the effects of tumor repopulation. Better understanding of the radiobiological concepts led to experimentation with altered fractionation schedules.[31] These regimens are referred to as hyper fractionated and accelerated radiation. Hyper Fractionation exploits the differences in sensitivity to radiation between the tumor cells and normal adjacent tissues to achieve better tumor control and reduce the normal tissue complications. Accelerated Radiotherapy attempts to counteract the accelerated repopulation of tumor cells by reducing the duration of radiation by delivering continuous radiation. Pure acceleration is when the fractionation is similar to Conventional RT. Hybrid Acceleration is when

the fractionation parameters are changed to achieve the acceleration of radiation. The RTOG randomized trial 90-03 compared the relative efficacy of three altered fractionation regimens with Conventional RT delivering standard dose of 70 Gy in 35 fractions over 7 weeks[32]. The test radiation schedules were Hyper Fractionation (81.6 Gy in 68 fractions over 7 weeks, with 1.2 Gy given twice daily), Split Course Accelerated Fractionation (67.2 Gy in 42 fractions of 1.6 Gy twice daily over 6 weeks, including a 2-week break), and a Concomitant Boost regimen (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). Concomitant boost and hyper fractionation regimens yielded significantly higher loco regional control rates than those of standard fractionation. The split course accelerated regimen did not improve loco regional control rates over the standard fractionation regimen. The acute mucosal reactions were more severe in patients receiving the altered fractionation regimens, but there was no difference in the complication rates at 6, 12, 18, and 24 months after therapy.

Total radiation dose needed for control of the tumour depends on size of the primary tumour, nodal involvement, fractionation schedule, use of concurrent chemotherapy. The gross primary and nodal tumour requires around 66 – 70 Gy in conventional RT. Elective nodal irradiation needs around 45 – 50 Gy.

High precision radiation therapy is possible with newer technologies such as 3D CRT and IMRT. 3D CRT is shaping the radiation beam with the use of multi leaf collimators (MLC) or beam modifiers to conform to shape of the target to deliver a highly conformal radiation. The technology of modulating the intensity of radiation within the treatment field to achieve better conformity is defined as Intensity Modulated Radiation Therapy (IMRT).

Palliative RT is indicated in patients with poor performance status or in the case of very advanced diseases not eligible for curative treatment. Usually they are treated with hypo fractionated radiation. The standard hypo fractionation schedule in palliation is 300cGy per fraction to total of 30Gy in 10 fractions over 2 weeks.

CHEMOTHERAPY:

Chemotherapy has been a part of the multimodality treatment of head and neck cancers for a long time. Various chemotherapeutic agents have been tried at various times. It has been tried in the neoadjuvant setting as an organ preservation approach in laryngeal cancers. The Veterans Affairs trial used chemotherapy in the neo adjuvant setting compared to concurrent chemo radiation to achieve organ preservation.

The publication of MACHNC meta-analysis made concurrent chemo radiation as the standard of care in locally advanced cancers.[33-34] It was

established that the use of concurrent chemotherapy improved the overall survival by 8% at 5 years follow up. It was also established the Cisplatin is the chemotherapy of choice. Cisplatin can be used either in the full dose or weekly chemotherapy with equal benefits as long as the cumulative dose of Cisplatin reached 300 mg/m^2 if used weekly.[34]

Chemotherapy also plays a very important role in incurable very advanced cancers and in metastatic cancers. It can be used as a palliative modality to contain the tumor proliferation. Various chemotherapeutic agents have been tried. No single agent has been identified as superior to others.

TARGETED THERAPY:

The first of the monoclonal antibody, Rituximab for Non-Hodgkin's Lymphoma, was approved for clinical use in the year 1998. Since then there has been a burst of activity in this segment with multitude of agents being approved. Studies have shown that the EGFR receptor is over expressed in over 90% of the squamous cell carcinomas of the head and neck. This led to the speculation that they could be manipulated to control the tumor cells. This led to the development of EGFR inhibitors such as the monoclonal antibody Cetuximab and the inhibitors of downstream pathways like tyrosine kinase inhibitors such as erlotinib and geftinib. The landmark trial by Bonner et. al[28] proved that addition of cetuximab

concurrently with radiotherapy in locally advanced head and neck cancers did result in a statistically significant improvement in loco regional control and in median overall survival. The EXTREME trial also showed that addition of cetuximab to the conventionally used doublet chemotherapy like Cisplatin and 5 FU regimens in metastatic and recurrent head and neck cancers resulted in an improvement in the overall survival.[35] However the data regarding the use of the small molecules such as geftinib and erlotinib do not show any added benefit with its addition to the standard therapies in the recurrent or metastatic cancers. In addition COX-2 inhibitors, farnesyl inhibitors, and proteasome inhibitors are also being investigated in H&N.[36-37]

PREVENTION OF HEAD AND NECK CANCERS:

The concept of field cancerization has been in vogue for a long time. This concept hypothesizes that the entire upper aero digestive tract is subject to subcellular injury by exposure to carcinogens and so are susceptible to cancer formation. This implies that a person who develops and survives an upper aero digestive tract cancer is at an increased risk of another cancer in the region.[38] They had an estimated 20% increased lifetime risk of formation of second primary tumor in the same field. This is due to accumulation of multiple genetic alterations over time. This forms the basis for chemoprevention.

The premalignant conditions such as erythroplakia and leukoplakia are at increased risk of conversion into squamous cell carcinomas. But they have an unpredictable nature with most of them going in for spontaneous regression. They also regress after cessation of smoking. They were used as subjects for trials involving chemoprevention. The most widely tested chemo preventive agent is cis-retinoic acid.[39-40] Although it showed promising results in early trials; subsequent trials did not live up to the promise. The Radiation Therapy Oncology Group (RTOG) completed a trial testing chemoprevention with 13-*cis*-retinoic acid in a multi-institutional setting. Nearly 1400 patients with stage I or II cancer were accrued. Unfortunately, the RTOG trial was negative and did not show any benefit to low dose isotretinoin in the prevention of second primary cancers. So this area is still awaits further investigations for confirmation of the concept. 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[6]. Regulations controlling the sale of tobacco products.
2. Abstinence from alcohol
3. Awareness about sexual practices like oral sex resulting in HPV infection.

4. Good oral hygiene
5. Good nutrient rich diet, fresh fruits and vegetables.

RATIONALE FOR THE PRESENT STUDY:

As seen already, head and neck cancers are very common in our country. In our institution too they constitute the majority of the cancers registered in the OPD. And most of them present in the locally advanced stages. The presently available standards of the treatment with surgery and concurrent chemo radiation have a dismal performance in long term control with overall survival at 2 years hovering around the 50% mark and less than 20% surviving 5 years.[41-43] Various modalities are being devised to overcome this. This is where the intensification of the treatment is considered. The previously used induction chemotherapy regimens are considered to be suboptimal now. The three drug regimens with the inclusion of a taxane[44-45] and following the induction phase of treatment in the responding patients with concurrent chemo radiation as the loco regional treatment is being assessed as a form of intensification of treatment. The argument for induction chemotherapy before the loco regional treatment is that it results in reduction of the tumor load, thereby resulting in better loco regional control. Also it has been alleged that adjuvant chemotherapy has not any given benefit because the patient will not be able to tolerate the adjuvant therapy and also because the blood

supply to the local areas would have been altered. When the same is given in the neoadjuvant setting, the blood circulation in these areas is intact and will supposedly result in better results.

With these understandings, there has been a renewed interest in addressing locally advanced head and neck cancers with sequential therapy. So the present study justified in addressing this question.

LITERATURE

REVIEW

2. LITERATURE REVIEW

With results in single modality approach with either surgery or radiotherapy alone plateauing and no further advances being made in either of them alone, attention turned towards combined modality approaches. Radiotherapy following surgery was the standard approach in the case of locally advanced resectable head and neck cancers. Chemo radiation is the standard of care in unresectable locally advanced and neck cancers and also in resectable cases where organ preservation is the intent.

The Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) was probably the first report that definitively proved the benefit of adding chemotherapy to loco regional treatment like radiotherapy in any setting. A 12% reduction in the risk of death was the benefit that could be obtained because of adding chemotherapy in patient with squamous cell carcinoma of the head and neck. This translated to absolute increase in the 5 years survival of these patients by 4%. A more recent update of the meta-analysis has shown that this benefit is even higher. The reduction in the risk of death is increased to 19% and the 5-year survival increased to 8% improvement in comparison with treatment with RT alone. Further analysis of the study brought out clearly the fact that concurrent chemotherapy was the reason behind all this benefit and not

the addition of chemotherapy in other settings like neoadjuvant and adjuvant chemotherapy.[33-34]

Even with these advances in therapeutics, it has been observed that around 50 – 60% of the locally advanced cancers will recur within first 2 years of follow up. Literature also notes that there will be around 15 – 20% of distant metastasis. So, multiple permutations of the different modalities have been tried for achievement of maximum benefit. This resulted in the incorporation of chemotherapy in various forms along with RT in head and neck cancers. One of these was inclusion of chemotherapy in the neoadjuvant setting aiming for better loco regional control and also for organ preservation. It has long been known that platinum is the most effective agent in head and neck cancer.

The radiobiological concept behind any neoadjuvant therapy is that it will result in a reduction of the tumour load and result in lesser load for the loco regional treatment. It is well known that the cells derive nutrition and oxygen from the nearby blood vessels by way of diffusion. This diffusion is limited by the distance from the blood vessel by only up to the first 100 microns. As the load of the tumour cells increase, the cells in the periphery have easy and good access to the vessels and are very well oxygenated. Whereas the centre of the tumour is hypo oxygenated and has a necrotic area[46-47]. This will result in a less than optimal response to the fractionated radiation. There is an intermediate zone between these two

areas having intermediate oxygenation. It has been found out that any tumour exceeding a size of around 180 microns will have variable oxygenated areas and a necrotic centre.

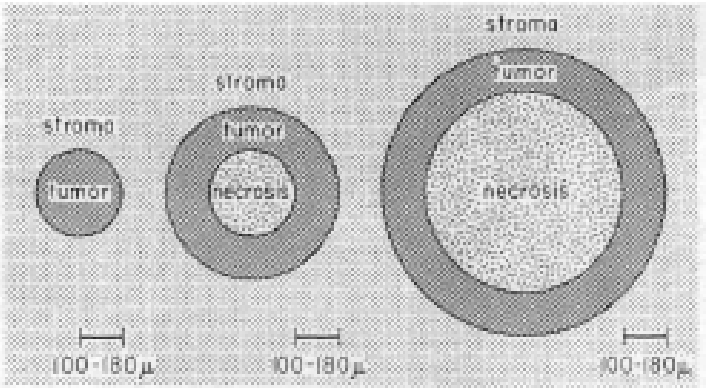


Fig: 1 – Extent of oxygenation in a tumour

Oxygen is very important for the production of free radicals which sets up the action of radiation in killing the tumour cells. But oxygen gets depleted rapidly as it diffuses from the vessels to surrounding tissue. This is about 70 microns from the arterial end of the tumour and it is less than that from the venous end. This is also the logic behind fractionated radiation. With each fraction, the cells in the periphery are killed and the cells in the intermediate zone gain better access to the oxygen supply and are sensitive to the next fraction of radiation. So it also implies that when the size of the tumour is small at the start of the radiation, it will result in better control of the tumour as it will have less hypo oxygenated areas. Similarly when induction chemotherapy is given it results in a gross

reduction of the tumour volume and the hypo oxygenated areas become well oxygenated and so becomes more sensitive to radiation.[48]

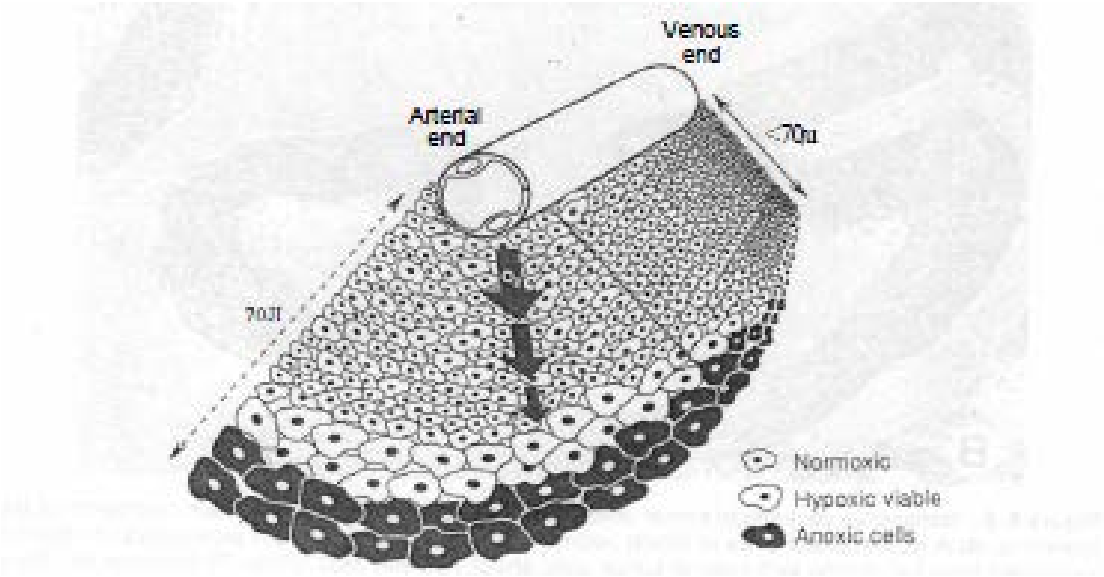


Fig: 2 -Oxygen diffusion

VETERANS AFFAIRS TRIAL:

The Department of Veterans Affairs laryngeal study group conducted a phase III randomized study in locally advanced squamous cell carcinomas of the larynx to compare the results of induction chemotherapy followed by radiation with the standard management of laryngectomy followed by postoperative radiation.[49] Three hundred and thirty two patients were randomly assigned to the two arms. The induction chemotherapy arm received two cycles of Cisplatin and 5 FU. They were assessed at the end of the two cycles. Those who had a response received a third cycle of induction chemo followed by definitive radiotherapy of 66 –

70 Gy. The patients who had no response to the induction or those who had a recurrent tumour after the treatment was over underwent salvage surgery.

After a median follow up for 33 months, the estimated 2 year survival was equal in the two groups. However the pattern of recurrence differed in the two treatment groups. The local recurrences were more in the larynx preservation arm (P= 0.0005) and the distant metastasis was less in the chemotherapy arm (P=0.016). Larynx was preserved in around 64% of the recruited patient. This showed that there is a role for chemotherapy in advanced laryngeal cancer. The strategy involving induction chemotherapy followed by definitive radiotherapy can be effective in the preservation of functional larynx in the case of locally advanced laryngeal cancers. The authors concluded that in view of the high rate of local recurrences in the case of chemotherapy arm, more effective local therapy is needed to achieve larynx preservation.

THE STUDIO TRIAL:

The Gruppo di Studio sui Tumori della Testa e del Collo conducted a phase III induction trial evaluating the role of PF induction chemo before the loco regional management[50]. The 237 patients were randomized to two arms. Arm A received Cisplatin (100mg/m^2 On D1) and 5 FU (1000mg/m^2 per day, continuous infusion from D1to 5), every 21 days for 4 cycles before they were taken up for loco regional treatment by radiotherapy with

or without surgery (n=118). Arm B received the loco regional treatment alone (n=119). The results of the study showed that in case of the upfront operable patients the addition of the chemotherapy did not add significantly to the overall survival. However, PF arm did improve the overall survival significantly at both the 5 year and 10 year follow up of the patients in the case of inoperable patients[51]. There was a reduction in loco regional recurrences and also the distant metastasis.

GETTEC OROPHARYNX TRIAL:

In a trial conducted by the Groupe d'Etude des Tumeurs de la Tête et du Cou[52], 318 patients of locally advanced oropharyngeal cancer were randomized to two arms. Patients in Arm A received neoadjuvant chemotherapy consisting of Cisplatin (100 mg per m^2) on D1 and 5 FU (1,000 mg per m^2 per day) for 5 days continuous infusion, every 21 days for 3 cycles. Chemotherapy was followed after 2- 3 weeks by radiotherapy with or without prior surgery. Arm B received upfront loco regional treatment. The study included primary oropharyngeal cancers except those involving the posterior wall and the anterior surface of the epiglottis. They included 48.1% of stage III cancers and 26.1% of stage IV cancers. The response rate to the induction chemo arm was 56%. The induction chemotherapy arm had a clinically significant benefit in the follow up

analysis. The median OS time was significantly better (5.1 yrs. versus 3.3 yrs.; p = .03).

RTOG 91-11:

` RTOG conducted a phase III trial for examining induction chemotherapy in larynx preservation in RTOG 91-11[53-54]. The trial randomized 547 patients of stage III & IV cancers of the larynx to three arms. Arm A randomized patients to fractionated RT, arm B to concurrent chemo radiation with concurrent Cisplatin and arm C to neoadjuvant chemotherapy with Cisplatin and 5 FU followed by chemo radiation or surgery. The trial included 64.2% of stage III cancers and the remaining were stage IV cancers. The loco regional control was superior in the chemo radiation arm compared to the induction arm (68.8% vs. 54.9%, P < 0.0018). The results of the trial with a median follow up of 6.9 years showed that laryngectomy free survival (LFS) was significantly superior in both the induction and chemo radiation arm compared to the radiotherapy alone arm. But the LFS was similar in both the induction and CRT arms. The end points of laryngeal preservation and loco regional control rate was significantly superior in the chemo radiation arm. The disease free survival was similar in CRT and induction chemo arm but the overall survival was similar in both arms during the first 5 years of follow up. After that it favoured the induction chemo arm.

MACH-NC META-ANALYSIS:

The meta analysis of the combined modality treatments in MACHNC showed that inclusion of chemotherapy in the management of the head and neck cancers significantly improved the absolute benefit by 4% at 5 years from 32% to 36%. The chemotherapy were used in 3 different ways

1. Neoadjuvant chemotherapy
2. Concurrent chemotherapy
3. Adjuvant chemotherapy

There was a significant interaction with respect to the timing of the chemotherapy in relation to the radiation treatment. In the subset analysis, it was shown the most benefit was derived out of the use of concurrent chemotherapy (8%, p= 0.0001). The other modalities like adjuvant and the neoadjuvant chemotherapy contributed only a non-significant 1% and 2% absolute benefit respectively[33-34].

So why give induction chemotherapy another chance in the treatment of locally advanced head and neck cancers?

- Previous studies included suboptimal chemotherapy regimens. Now we know that the optimal chemotherapy should include a platinum agent.

- Newer triple agent chemotherapy with the inclusion of taxane. Various phase II trials have shown that the three drug regimen with the inclusion of a taxane to Cisplatin and 5 FU is superior.
- Previous neoadjuvant chemo studies have mostly followed the chemotherapy phase with a single modality of loco regional treatment with either surgery or radiation. This was felt to be the reason for the failure of the induction regimens. So newer trials with chemotherapy followed by chemo radiation are being carried out.

The initial trials of sequential therapy tried out variety of combinations in the induction phase and in the concurrent chemo radiation phase. The University of Pennsylvania carried out a phase II trial with high dose paclitaxel and carboplatin in the induction regimen followed by chemo radiotherapy[55]. The chemotherapy during radiation was low dose paclitaxel. This trial was carried out in oropharyngeal cancers. With a short follow up for 31 months, the response rates of the trial were 91% following the entire course of the treatment.

Another induction regimen tried out on a weekly basis was Paclitaxel, Carboplatin and Ifosfamide[56]. This was delivered as an

outpatient treatment. But the results of this trial showed a very high response rates but longer follow up is needed to confirm this.

Other newer agents in the induction regimen are taxanes, Paclitaxel and Docetaxel. Several phase II trials were conducted to find put the efficacy of adding paclitaxel. The Spanish Head and Neck Cancer group, Hitt et al carried out two phase II trials to evaluate the feasibility of adding Paclitaxel to Cisplatin and 5 FU[57, 58]. The results are given below:

Study	Regimen	No. of evaluable patients	Response rate		Overall survival
			Complete	Overall	
Hitt et al. [39]	Paclitaxel, 175 mg/m^2, day 1; cisplatin, 100 mg/m^2, day 2; 5-fluorouracil, 500–750 mg/m^2, days 2–6	69	59%	88%	44% at 5 years
Hitt et al. [40]	Paclitaxel, 175 mg/m^2, day 1; cisplatin, 35 mg/m^2, days 1–2; 5-fluorouracil, 1,000 mg/m^2, days 1–2; leucovorin, 200 mg/m^2, day 1; leucovorin, 500 mg/m^2, days 1–4	35	51%	86%	Median, 18 months (relapsed/ refractory disease)

GORTEC:

This phase III trial was carried out by the French Head and Neck Cancer Study Group as an organ preservation trial in larynx to test the efficacy of adding docetaxel in the induction regimen along with Cisplatin and 5 FU and was compared with the standard chemotherapy regimen of Cisplatin and 5 FU alone[59]. The induction chemotherapy was delivered in

the following doses, Docetaxel (75mg/m^2 on Day1), Cisplatin (75mg/m^2 on Day 1) and 5 FU (750 mg/m^2 as a continuous 24 hour infusion from Days 1-5). Three cycles were delivered every 21 days. 220 patients were randomized to the two study arms and analysed. The overall response rate (T and N) was 82.8% in the TPF vs. 60.8% (p = 0.0013). 60.6% of patients achieved a complete endoscopic response in the TPF arm vs. 46.7% in the PF arm. In advanced laryngeal and hypo pharyngeal cancer, TPF demonstrated significantly superior overall response rate compared to the PF regimen. The TPF is better tolerated and preliminary results suggest that laryngeal preservation could be achieved for a higher proportion of patients. This trial showed that addition of docetaxel did result in an improved laryngectomy free survival. (P = 0.036) This implies that there was an improvement in the loco regional control.

TAX 323:[60]

This study accrued a total of 358 patients of head and neck cancer. It randomized 177 patients to the TPF group and the remaining 181 patients were allotted to the PF group. The patients in the PF group received 4 cycles of chemotherapy with Cisplatin (100 mg/m^2 Day 1) and 5 FU (1000 mg/m^2 continuous infusion 24 hours from Day 1- 5) alone every three weeks. The patients in the TPF group received three drug regimen with the addition of Docetaxel (75 mg/m^2 on Day1) along with Cisplatin (75mg/m^2

day1) and 5 FU (750 mg/m^2 continuous 24 hour infusion from Day 1 -5). This was administered for 3 cycles every 3 weeks. The induction phase was followed by radiotherapy within 4-7 weeks unless they had progressive disease at the end of the induction phase. Radiation was delivered in either conventional fractionation or accelerated or hyper fractionated regimens. The total dose in conventional fractionation was 66 to 70 Gy, in accelerated regimen was 70 Gy and in the hyper fractionated radiation was 74 Gy. The choice of the radiotherapy was by institutional policy, which was fixed for the institution before the start of the study. The primary end point of the study was progression free survival and the secondary end points were overall survival, time to treatment failure etc. The analysis of the results of the trial showed that the addition of docetaxel resulted in a significant improvement in progression free survival with 11.0 months in the TPF group compared to 8.2 months in the PF group (P=0.007). The secondary end point of median overall survival was 18.8 months in the TPF group compared to the 14.5 months in the PF group. This amounted to a significant decrease in death risk by 27% (p value = .02). However, as expected the grade 3 or 4 adverse events were higher in the TPF arm.

TAX 324: [61]

The TAX 324 study randomly assigned 501 patients with stage III and IV head and neck cancers all of whom had primary tumours which were unresectable or who were candidates for organ preservation, to 3 cycles of docetaxel (75mg/m^2 on Day 1), Cisplatin (100 mg/m^2 on Day 1) and 5 FU (1000 mg/m^2 on continuous 24 hour infusion days 1-4) or 3 cycles of Cisplatin (100 mg/m^2 on Day1) and 5 FU (1000 mg/ m^2 Day 1- 5) alone followed by concurrent chemo radiation with weekly carboplatin. The induction chemotherapy was given as 3 weekly cycles. All the patients received chemo radiotherapy 3-8 weeks following the completion of the entire induction chemotherapy. The radiation was delivered in conventional fractionation schedule of 2 Gy per day for 5 days a week to a total dose of 70 to 74 Gy. Weekly carboplatin was delivered at a dose of AUC 1.5. The primary endpoint of the study was overall survival. The results of this study at the end of 2 years showed a significantly more number of patients in the TPF arm surviving with a median survival of 71 months. Whereas it was only 30 months in the PF arm (P=0.0006). The loco regional control was also significantly better in the TPF arm compared to the PF arm (p=0.04). It reduced the incidence of loco regional recurrence by 27%. But the incidence of distant failure was similar in the two groups. Although the organ preservation was not the aimed at end point in this study a subset analysis of the laryngeal and hypo pharyngeal cancers did

show a better response with three drugs for PFS which can be taken as a surrogate for LFS (p =.032)

With the results of these studies it was concluded that if induction was to be used, TPF was the standard regimen. However the question still remained whether this sequential therapy with induction chemotherapy followed by loco regional treatment was superior to that upfront chemo radiation. Various studies were carried out to determine this.

HITT et al:

The Spanish Head and Neck Cancer Cooperative group[62] randomized the stage III or IV squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx, larynx to either 3 cycles CDDP (100 mg/m^2 on Day 1), 5FU (1000 mg/m^2 on Day 1-5) or 3cycles of TPF, Docetaxel (75 mg/m^2 Day 1), Cisplatin (75mg/m^2 on Day1), 5FU 750mg/m^2 Days 1-5 as 24 hour continuous infusion) followed by chemo radiation or to chemo radiation alone. The chemo radiation was delivered as once daily fractions of 2 Gy to a total dose of 66-70 Gy along with a full dose of Cisplatin 100 mg/m^2 on Days 1, 22, 43. The primary endpoint of the study was the time to treatment failure. The secondary end points were time to progression, loco regional control, overall survival and safety assessment. Both the time to progression (p=0.056) and the time to treatment failure (p<0.0001) were

significantly improved in the induction arms compared to the chemo radiation alone arm. The secondary end point of local control rate was significantly more in the induction arms (61.5% vs. 44.5%, p= 0.002)

DeCIDE: (DOCETAXEL BASED CHEMOTHERAPY PLUS OR MINUS INDUCTION CHEMOTHERAPY TO DECREASE EVENTS IN HEAD AND NECK CANCER) [63]

Patients of locally advanced head and neck cancers were randomized to either induction chemotherapy arm or upfront chemo radiation arm. The induction had two 21 day cycles of induction chemo with Docetaxel, Cisplatin and 5 FU followed by chemo radiation. The chemo radiation was delivered with twice daily radiation (150cGy BID) and five 14 day cycles of docetaxel (25mg/m2 for 5 days), 5 FU (600mg/m2 for 5 days) and hydroxyurea (500mg BID) followed by a 9 day break. The goal of this study was to find out any difference in overall survival. The secondary end points of the study were distant failure free survival, failure pattern, progression free survival and quality of life assessment. The study recruited 280 patients, much less than the planned 400 patient accrual. With a minimum follow up of 2 years, overall survival, distant failure free survival, recurrence free survival was not different between the two arms. Although high overall survival rates were seen in both arms, the reasons

why the significant decrease in the distant failure in the induction arm did not translate into a better overall survival.

PARADIGM: [64]

This is a multicenter phase III trial comparing sequential therapy and upfront chemo radiation. The study recruited 145 of the planned 300 patients. The induction chemo regimen used in this trial was 3 cycles of docetaxel, 5FU and Cisplatin followed by chemo radiation with either weekly carboplatin and conventional radiation or weekly docetaxel and accelerated radiotherapy. The upfront chemo radiation arm was treated with 2 cycles of full dose Cisplatin on week 1 and week 4 along with accelerated boost RT. The primary end point for this study was 3 year overall survival. The secondary end points were many and can be listed as follows:

- 2, 3 and 5 yr. PFS
- 5 year survival
- CR
- Tumor site specific survival
- Organ preservation
- Toxicity profile

- Quality of life

The three years overall survival and the three year progression free survival were not statistically different in the two arms.

The two studies which had compared the sequential therapy approach with TPF induction followed by concurrent chemo radiation with upfront chemo radiation, DeCIDE and PARADIGM, had failed showed to show any advantage for the sequential approach. But the question of sequential therapy in head and neck cancers is far from settled, as these studies had some serious flaws in their design which limits the significance of their outcome. Both studies did not complete the planned accrual of patients and in fact they were way short of the target. So this brings into question the statistical power of the studies to show a significance of one over the other. Also the optimal number of cycles of induction chemotherapy is not known. Most of the trials have delivered at least three cycles of chemotherapy. But the DeCIDE trial delivered only two cycles of induction chemotherapy. Also both the trials delivered sub optimal loco regional treatment. The chemo radiation schedules followed were not the ideal. We know for a fact from the MACH NC report that Cisplatin is the drug of choice for concurrent CRT. But both the trials had excluded Cisplatin as the concurrent chemotherapy. So taking into account all these facts, the question of whether sequential therapy is better than chemo

radiation alone is still to be answered. Further trials are on-going to answer this question.

GSTTC Trial:

In this phase II study conducted by the Gruppo di Studio della Testa e del Collo, [65] 101 patients with unresectable locally advanced Head and Neck Cancer patients were randomized to receive either Concurrent chemo radiation with Cisplatin 20 mg/m2 on days 1–4 and 5-FU 800 mg/m2/day as a 96-h continuous infusion during weeks 1 and 6 of RT or three cycles of TPF (Docetaxel 75 mg/m2 and Cisplatin 80 mg/m2 on day 1 and 5-FU 800 mg/m2/day as a 96-h infusion, every 3 weeks) followed by the same CRT regimen. The primary end point assessed was complete response rates. This was higher with the TPF arm (50% Versus 21.2%, P = 0.004). The secondary end points of median PFS and OS were superior in the TPF induction arm.

To sum up, the benefits of induction chemotherapy will include the reduction of load of the tumour before the start of the loco regional treatment which theoretically should increase the sensitivity of the loco regional treatment[66-67]. This should directly result in a better loco regional control rates. When irradiation is used it results in wider irradiation margins. But there are certain theoretical disadvantages which have to be

kept in mind and these have to be addressed in the future. One is the purported delay in the start of the primary modality of treatment potentially resulting in reduced response rates. Also there is the possibility of neoadjuvant chemotherapy resulting in selection of resistant clones of tumour which results in sub optimal response rates. Also there is a chance that the patient may default for primary modality of treatment with the response achieved by the neoadjuvant chemotherapy in alleviating the symptoms. There is also a chance that the patient may not be able to tolerate the full course of loco regional treatment and complete it within the stipulated time because of the toxicities of the neoadjuvant chemotherapy.

The present study is justified because despite decades of research and trials in locally advanced head and neck cancers with various modifications in radiation fractionation, inclusion of chemotherapy in the loco regional treatment, the use of targeted therapies, the response rates and overall survival is still dismal and has not improved by much. The correct combination of the all the modalities to achieve the best response is not yet known.

AIM & OBJECTIVES

3. AIMS & OBJECTIVES

AIM:

The aim of the present study was to evaluate the sequential therapy in locally advanced head and neck cancers with three cycles of induction chemotherapy with Paclitaxel, Cisplatin and 5 FU followed by concurrent chemo radiation with conventional irradiation along with weekly Cisplatin.

PRIMARY OBJECTIVE:

To assess the immediate loco regional response rates of locally advanced squamous cell carcinomas of the head and neck treated with sequential therapy, to be assessed after induction chemotherapy and after loco regional therapy.

SECONDARY OBJECTIVE:

To assess acute toxicity patterns of the treatment regimen, to be assessed during the induction phase and during the chemo radiation phase of the treatment.

METHODOLOGY

4. MATERIALS AND METHODS

STUDY DESIGN:

The present study was a **Single Arm Prospective Study** of previously untreated patients receiving sequential therapy for locally advanced head and neck cancer.

The study got approval from the Ethics Committee of the institution prior to opening for accrual and all patients signed an informed consent form in Tamil prior to participating in the study.

SAMPLE SIZE:

30 consecutive patients of locally advanced head and neck cancers attending the Out-Patient Department at our Institute who met the inclusion criteria were enrolled in the study.

Eligible patients had to have histologically or cytologically proven squamous cell carcinoma in the head and neck region in the locally advanced stage by TNM staging.

They had to be eligible for curative treatment on the basis of the extent of their disease, medical comorbidities, distant metastasis and/or combination of these factors.

INCLUSION CRITERIA:

- Biopsy proven squamous cell carcinoma of the head and neck.
- Primary tumor sites eligible: oral cavity, oropharynx, hypopharynx, larynx.
- Age >18years to < 70 years.
- Stage III or IV disease without evidence of distant metastases.
- ECOG Performance Status 0 – 2.

EXCLUSION CRITERIA:

- Patient not consenting to chemotherapy at any point in the treatment.
- Previously received treatment for any other malignancy.
- Tumors of nasal cavity, paranasal sinuses and nasopharynx.
- Non Squamous Histopathology.
- Inadequate hepatic and renal functions.

PRE-TREATMENT WORK UP AND GENERAL MEASURES:

1. Elucidate the history of the symptoms.
2. Visual examination and palpation of oral cavity and proximal oropharynx.
3. Neck examination for regional lymph nodes involvement.
4. Thorough clinical examination of the entire upper aero digestive tract to rule out a second primary. IDL and VDL scopy, direct nasal examination, anterior and posterior rhinoscopy.
5. Biopsy from tumor or FNAC from neck node.
6. Complete blood count, renal and liver function tests before every cycle of induction chemotherapy.
7. CT scan Neck (From Base of Skull to Root of Neck) – Plain and Contrast before start of treatment and after completion of induction chemotherapy and at first follow up.
8. Chest X-Ray – PA view.
9. X-Ray Mandible to rule out cortical bone involvement.
10. Weekly blood counts and renal function tests during radiotherapy.
11. Cardiology fitness for chemotherapy.
12. Nasogastric intubation as required before starting treatment.
13. Dental prophylaxis by extraction, filling and scaling.

STUDY PROTOCOL:

INDUCTION PHASE:

All patients were treated with three cycles of induction chemotherapy given every 21 days over a period of three days on an in-patient basis.

The schedule followed for induction chemotherapy regimen delivered was:

Premedication given half an hour before every chemotherapy:

- Inj. Ondansetron 8 mg IV.
- Inj. Dexamethasone 8mg IV 12 hours and 6 hours before chemotherapy and half an hour before chemotherapy.
- Inj. Ranitidine 50 mg IV.
- Inj. Chlorpheniramine 1 vial.

The chemotherapy per se was delivered in the following schedule every 21 days:

- Inj. Paclitaxel 175mg/m^2 D1 as a 3 hour infusion.
- Inj. Cisplatin 100mg/m^2 split in three days D1-D3 as a three hour infusion.
- Inj. 5-FU 750mg/m^2 D1-D3 as bolus injection.

All the patients were assessed on Day 8 -10 of every cycle with complete blood count for myelosuppression. Patients with suppression were kept under close observation. No intervention was allowed. If the patient had febrile neutropenia/Grade 4 neutropenia, they were treated with G-CSF 300mcg s.c. on days 1-3. All other grades of myelosuppression were kept under observation and assessed before the start of the next chemotherapy. If myelosuppression still persisted they were treated with G-CSF with the above mentioned schedule.

All patients who needed secondary prophylaxis in previous cycles as per the above mentioned protocol were given primary prophylaxis with G-CSF in the subsequent cycles of chemotherapy during Days 8-10 of the cycle.

ASSESSMENT AFTER INDUCTION:

Patients were reassessed both clinically with all the initial investigation which were abnormal to begin with and with an imaging, CT or MRI Neck from Base of Skull to Root of Neck after completion of the entire course of the induction chemotherapy.

CONCURRENT CHEMORADIATION:

The patients with a response to chemotherapy were then taken up for Radical Concurrent Chemo Radiation.

Radiotherapy Technique:

The radiation was delivered in conventional fractionation with a Theratron Phoenix Tele Cobalt – 60 machine. The radiation was delivered on an out-patient basis for local patients or on an in-patient basis for patients from other localities. All the patients were delivered the weekly chemotherapy on an in-patient basis every week.

Dose per fraction: 2 Gy per fraction over 5 days a week.

Total dose: 66Gy to the gross tumor and positive nodes and 50 Gy to the elective nodes.

Radiotherapy was delivered by opposing lateral fields in a Theratron Phoenix Tele-Cobalt machine in 200cGy per fraction for 5 days a week. Patients are given a break on Saturday and Sunday.

Appropriate shielding of the spinal cord was done after the tolerance dose of spinal cord was reached at 40 Gy.

In view of the intense regimen of induction phase chemotherapy which is being followed up with concurrent chemo radiation, all patients were started on prophylactic measures to prevent development of mucositis and infection during radiotherapy. The measures taken were:

1. Soda Bicarbonate Solution mouthwash at least 4 times a day, before and after food and at bed. After one week on radiation, patients were instructed to rinse every 3 – 4 hours.
2. Alcohol free antibacterial mouth wash.
3. Daily brushing of teeth with soft baby toothbrush.
4. Inj. Dexamethasone 8 mg IV BD was started after 10 fractions of RT and was continued till the end of radiotherapy. Then it was tapered and stopped after the end of RT.

Weekly Chemotherapy: The patients also received concurrent chemotherapy of weekly Cisplatin at a dose of 40mg/m^2 after assessing the renal parameters and the hemoglobin levels.

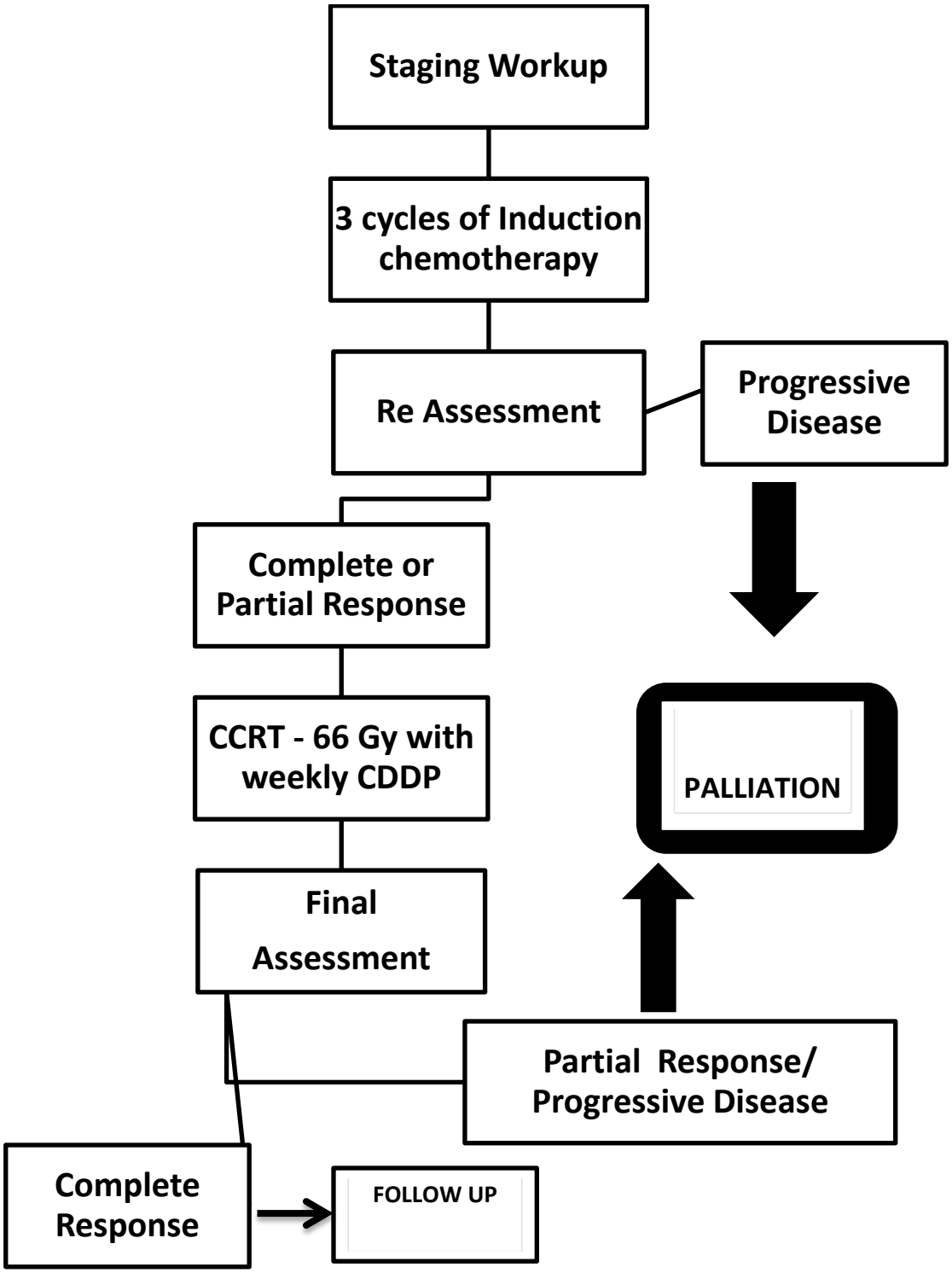
Premedication were given half an hour before every weekly chemotherapy:

- Inj. Ondansetron 8 mg IV.
- Inj. Dexamethasone 8mg IV.
- Inj. Ranitidine 50 mg IV.
- Inj. Chlorpheniramine 1 vial.

The entire treatment schedule was to be completed in 6.3 weeks.

Patients with progressive disease after induction chemotherapy were taken up for palliative chemotherapy/radiotherapy.

Fig. 3- Protocol Scheme



TOXICITY:

Toxicity in the present study was graded using Common Toxicity Criteria Version 4 and RTOG Acute Radiation Morbidity Scoring Criteria.

All blood parameters like complete blood count and the basic metabolic panel were assessed before the start of every cycle of induction chemotherapy and during the nadir period, 8^{th} to 12^{th} day of every cycle. In the case of WBC less than 1000/µl or platelets less than 50,000/µl for a period longer than 5 days, drug doses were reduced by 10% in the next cycle.

Complete blood count and biochemistry were performed on a weekly basis during chemo radiotherapy. In the case of any severe grade 3 or 4 toxicities, radiation therapy was interrupted until recovery and appropriate treatment instituted as discussed in following sections.

TABLE - 1: CTCAE Version 4 for Nausea & Diarrhea:

GRADE	NAUSEA
1	Loss of appetite without alteration in eating habits.
2	Oral intake decreased without significant weight loss, dehydration or malnutrition.
3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
	DIARRHOEA
1	Increase of 2-3 stools/day.
2	Increase of 4-6 stools/day, nocturnal stools or moderate cramps.
3	Increase of 7-9 stools/day or incontinence, or severe cramping.
4	Increase of >10 stools/day or grossly bloody diarrhea, or need for parenteral support.

TABLE - 2: RTOG Acute Morbidity Scoring Criteria

Grade	0	1	2	3	4
MUCOSITIS	No Change	Injection / Mild pain not requiring analgesic	Patchy mucositis Moderate pain needs analgesia	Confluent Mucositis Severe pain, needs morphine	Ulceration, hemorrhage and Necrosis
DERMATITIS	No Change	Follicular, faint, dull erythema/ epilation/ desquamation	Tender, bright patchy moist desquamation	Confluent moist desquamation	Ulceration, hemorrhage and Necrosis
SALIVARY GLAND	No Change	Mild dryness / Altered taste	Moderate to complete dryness	---------	Necrosis

PHARYNX	No Change	Mild dysphagia requiring analgesics	Moderate dysphagia requires narcotics. Liquid diet	Requires IV fluids or NG tube	Ulceration, perforation and fistula
LARYNX	No Change	Mild Hoarseness, Cough not needing antitussive	Persistent hoarseness, Cough requiring antitussive	Whispered speech, throat pain requiring narcotics	Dyspnea/ stridor, hemoptysis with tracheostomy
WBC (X1000)	>= 4.0	3 – 4	2 – 3	1 – 2	<1
PLATELET (X1000)	>=100	75 – 100	50 – 75	25 – 50	< 25 or spontaneous bleeding
HEMOGLOBIN (gm %)	>11	9.5 – 11	7.5 – 9.5	5.0 – 7.5	-------

RESPONSE EVALUATION:

Tumor response will be evaluated 4-6 weeks after end of course with CT Neck from base of skull to root of neck and clinical examination. The criteria used were RECIST 1.1 Criteria.

- **Complete Response (CR):** Disappearance of all target lesions.
- **Partial Response (PR):** At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

FOLLOW UP PROCEDURE:

Patients were assessed for disease status 1 month after the end of treatment and every month thereafter. During follow up, a thorough history, physical examination and complete clinical examination were done.

ANALYSIS:

Patients were analyzed for local response rate after the induction chemotherapy and the end of the concurrent chemo radiation. The toxicity of treatment and the factors affecting the treatment response were analyzed.

The probability test used to identify p value is FISHER'S EXACT PROBABILITY TEST.

RESULTS AND ANALYSIS

5. RESULTS AND ANALYSIS

The present study enrolled a total of 30 patients with histologically proven locally advanced squamous cell carcinoma of the head and neck region. The method of selection was enrolling 30 continuous patients at the OPD who met the eligibility criteria of the study as laid out previously.

All the patients underwent baseline investigations and work up before the commencement of the treatment.

SEX:

Among the 30 patients enrolled for the study majority of them were males accounting for 27 of the total. This skewed selection towards the male gender is probably due to the higher incidence of head and neck cancers in males, as they are more commonly exposed to the carcinogens than the women.

AGE:

The age group eligible for the study was from 18 to 70 years of age. The age of the patients ranged from 24 to 69 years. The median age of the patients enrolled in the study was 50 years. Age distribution analysis of the sample showed that, majority of the patients were in the 36 to 64 year

group. However all the patients had an ECOG performance status either 1 or 2.

SITE DISTRIBUTION:

The site wise distribution of the cancers in the enrolled patients when analyzed, they were almost equally distributed.

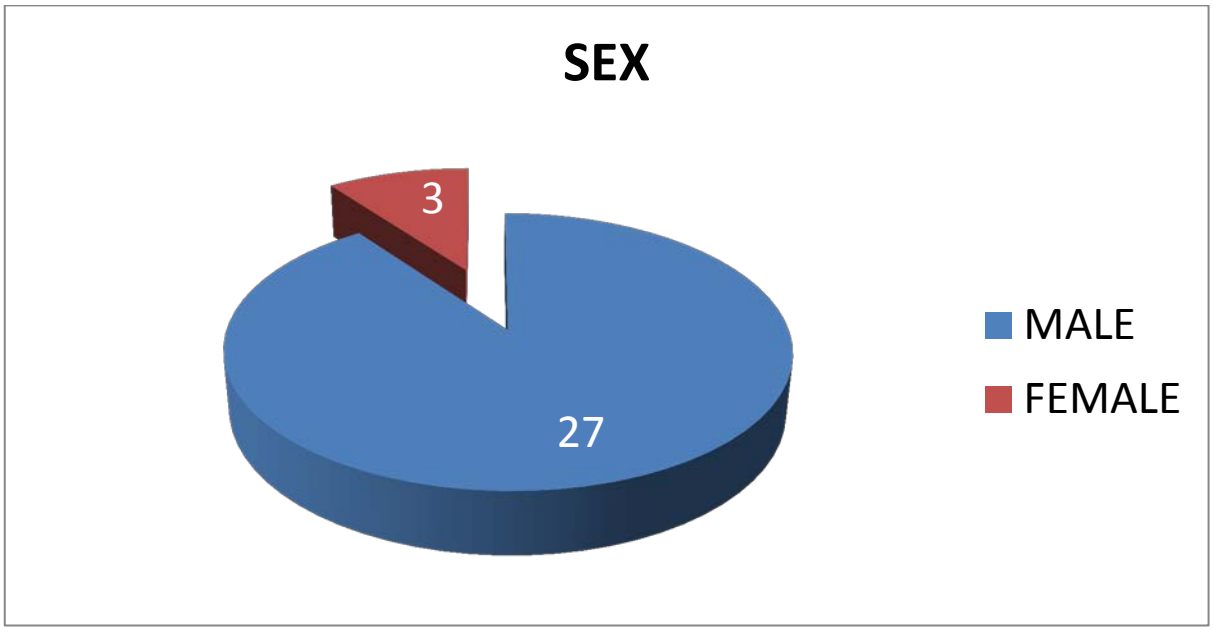
1. Oral Cavity – 9 (29.97%)
2. Oropharynx – 9 (29.97%)
3. Hypopharynx - 9 (29.97%)
4. Larynx – 3 (9.99%)

SUBSITE INVOLVEMENT:

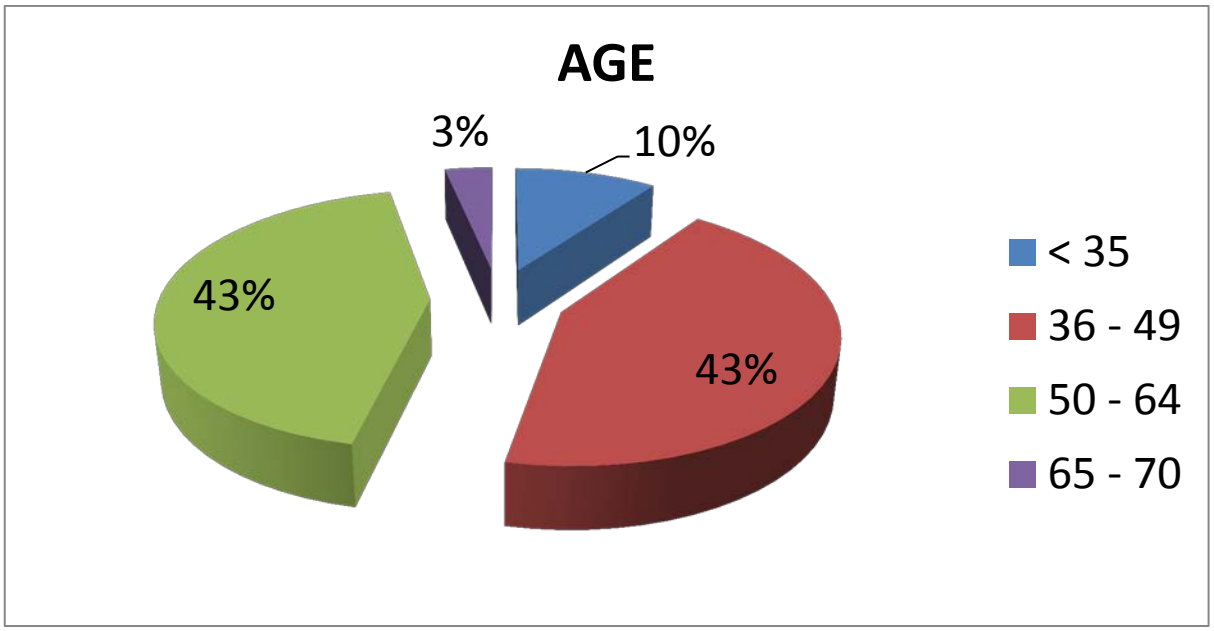
The patients with oral cavity cancers had involvement of the anterior two thirds of the tongue in 4 patients and 1 patient had involvement of the floor the mouth. In the patients with cancer of the oropharynx, 3 had involvement of the tonsillar fossa and the soft palate. There was involvement of the posterior third of the tongue in the other 6 patients.

The hypo pharyngeal cancers were mostly pyriform fossa cancers with only two of them having post cricoid cancers.

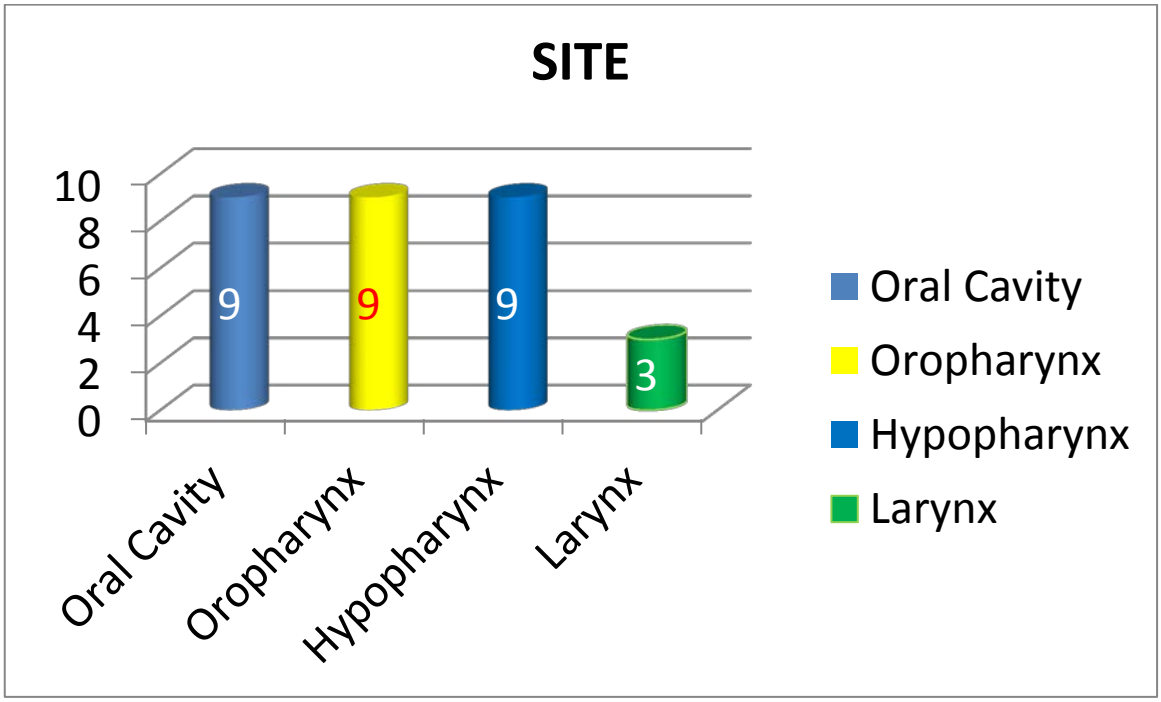
Graph 1: Sex Distribution



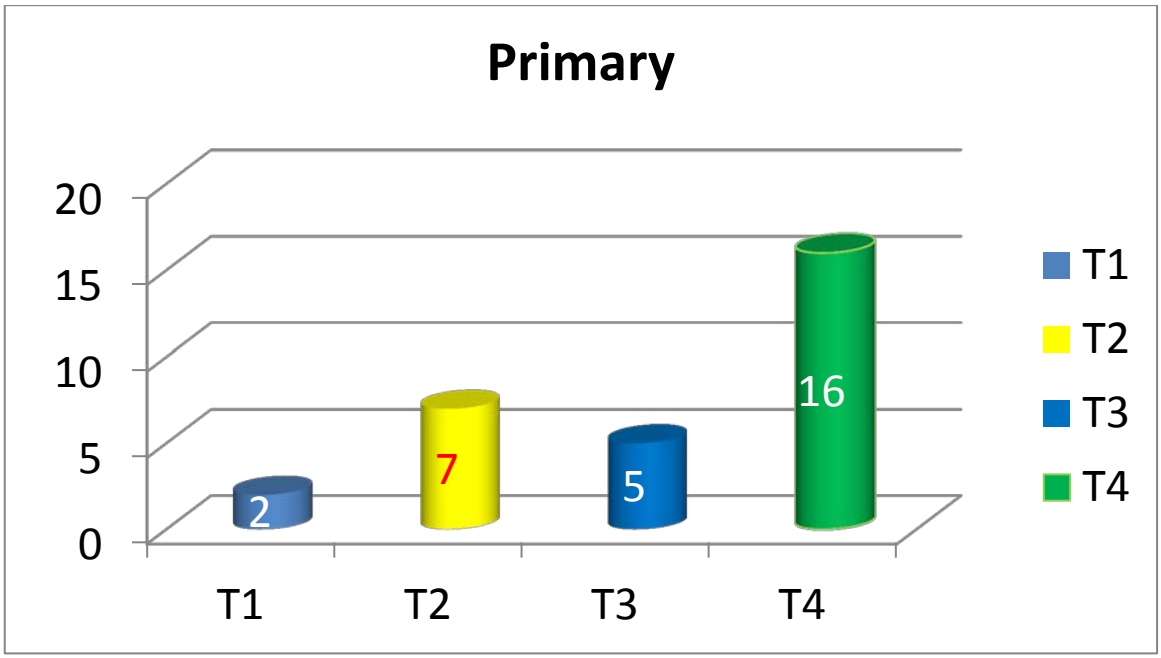
Graph 2: Age Distribution



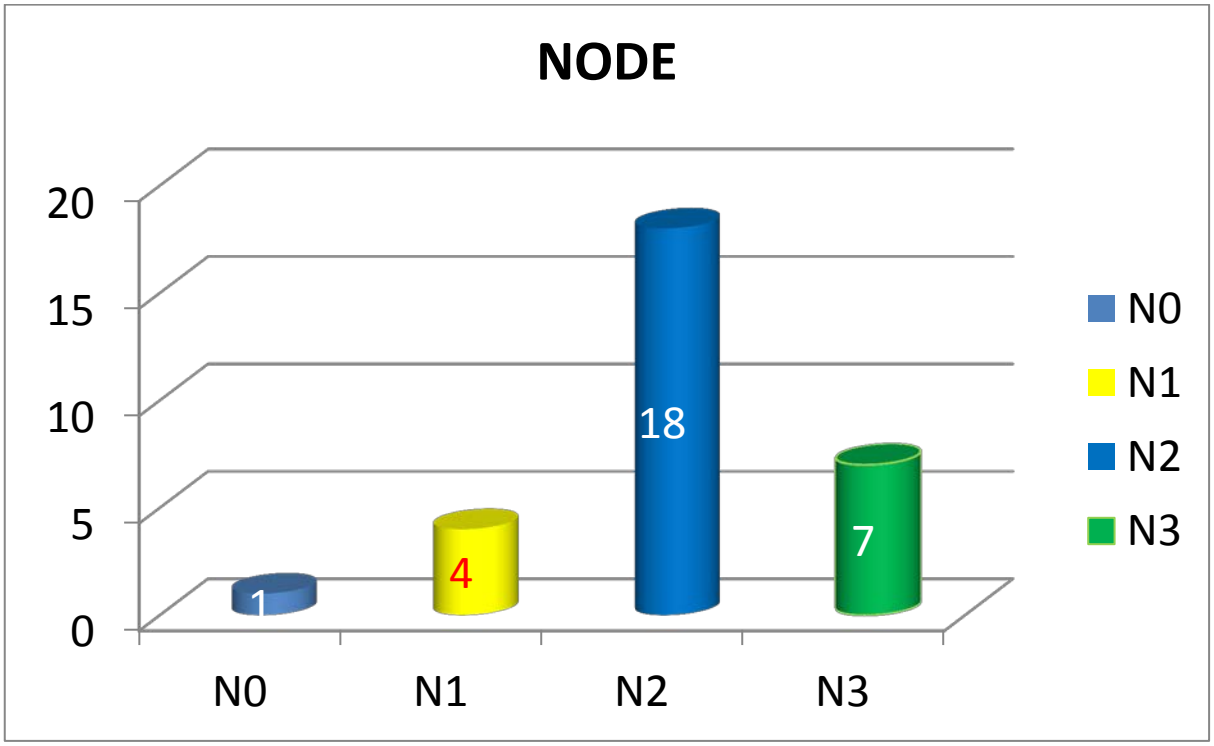
Graph 3: Site Distribution



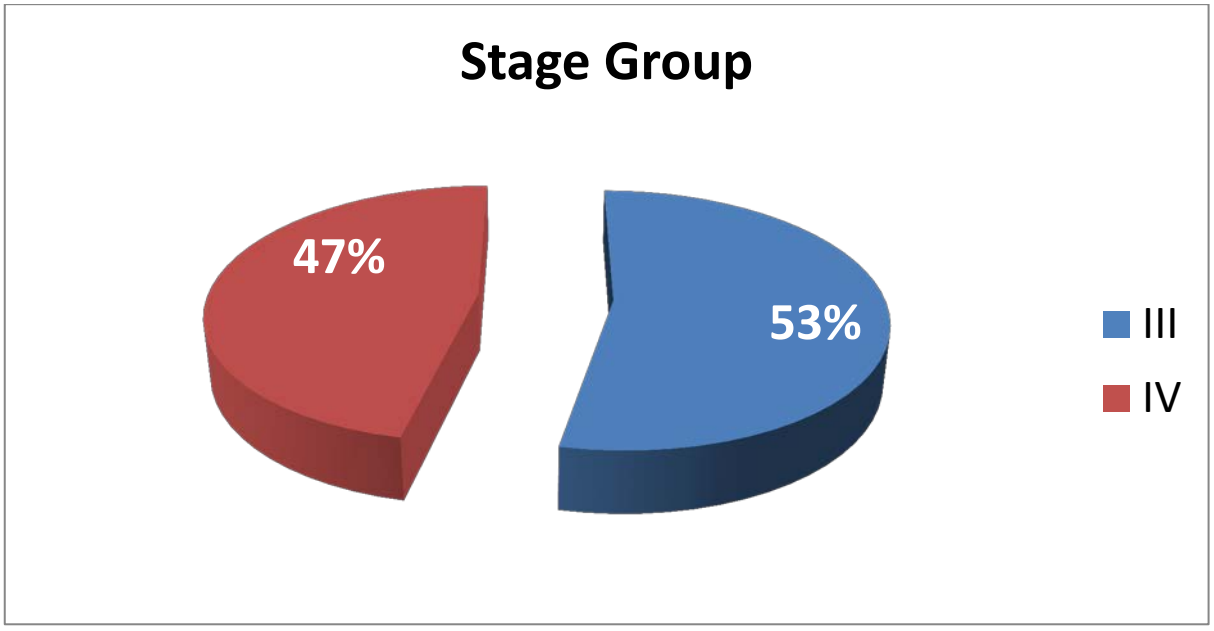
Graph 4: Primary Stage



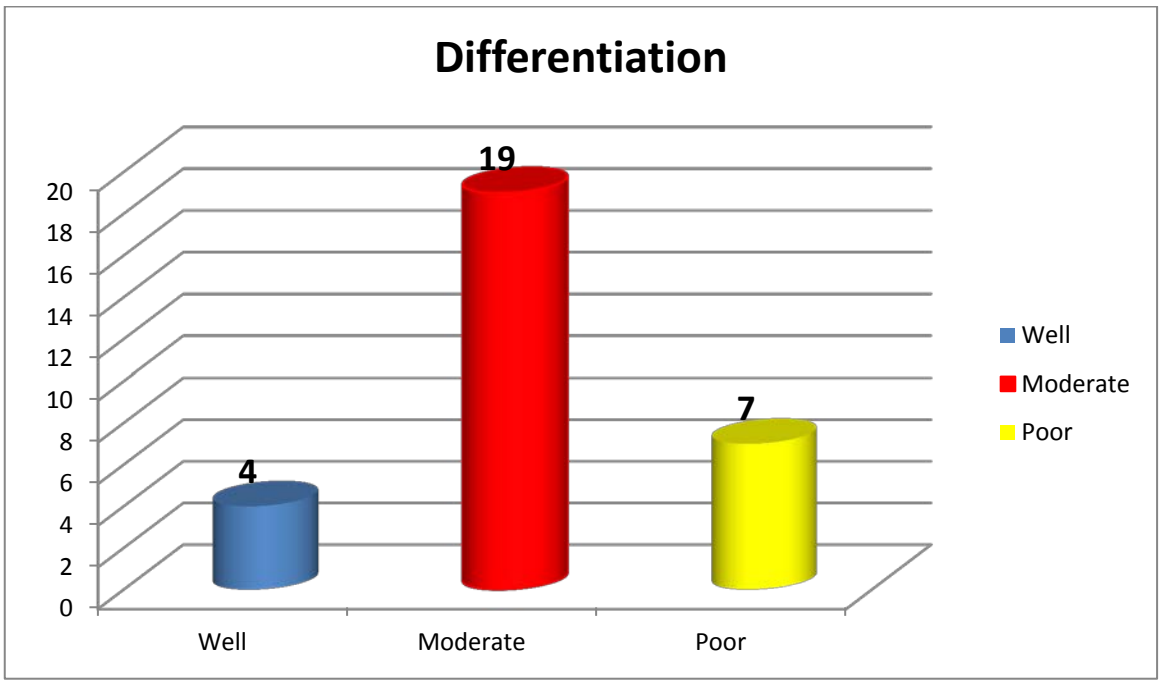
Graph 5: Nodal Stage



Graph 6: Stage Grouping



Graph 7: Differentiation



STAGE GROUPING:

The patients had an almost equal representation of the AJCC stage grouping with 16 patients in the Stage III (53.28%) and 14 patients in the Stage IV (46.62%).

TNM STAGING:

The TNM staging of the patients showed majority of the patients being in the T4 stage (n=16, 53.28%) and the N staging most commonly seen was N2 (n=18, 59.94%).

There were 7 cases of N3 disease included in the study. The majority of the patients with N3 disease were hypo pharyngeal cancers accounting for 4 patients, with oropharynx following next with 2 patients. The remaining one was oral cavity.

HISTOLOGY:

Majority of the study population had histology which was moderately differentiated accounting for 63.27% (n=19 patients). They were distributed among the sub sites, with oropharynx being the majority having 7 cases. The poorly differentiated carcinomas were commonly seen in the hypo pharyngeal cancers.

Table 3: Age distribution

Age	No of Patients	Percentage
<35	3	9.99%
35 – 49	13	43.29%
50 – 64	13	43.29%
65 – 70	1	3.33%

Table 4: Site-wise distribution

Site	No of patients	Percentage
Oral cavity	9	29.97%
Oropharynx	9	29.97%
Hypopharynx	9	29.97%
Larynx	3	9.99%

Table 5: Histology Distribution

Differentiation	No of patients	Percentage
Well Differentiated	4	13.32%
Mod. Differentiated	19	63.27%
Poorly Differentiated	7	23.37%

HEMATOLOGICAL TOXICITIES IN INDUCTION CHEMOTHERAPY:

All the patients enrolled in the study received 3 cycles of Paclitaxel, Cisplatin and 5 FU with all the necessary precautions and pre medications. The significant hematological toxicities encountered during the induction phase were graded with RTOG grading and CTCAE V.4.

WBC:

There were two cases of Febrile Neutropenia/Grade 4 toxicity during the induction phase. They were treated with admission and the following supportive care:

1. Empirical broad spectrum antibiotics.
2. IV Fluids.
3. G-CSF 300 mcg D1-5.

All patients were kept under admission till they became apyrexial and clinically stable for at least 24 hours and the WBC counts returned to normal.

However there was grade 3 toxicity in 11 patients (36.67%). The patients with grade 3 toxicity during the nadir period were just observed with no intervention and allowed to recover on their own. When the next evaluation of blood parameters were done for the next cycle of

chemotherapy, if still grade 3 toxicity persisted then intervention was done with the delivery of 3 days of Inj. G-CSF 300 mcg s.c. After the blood WBC levels were restored to normalcy, the next step in the management was followed. These patients were given primary prophylaxis with G-CSF during subsequent chemotherapy cycles.

Hemoglobin:

Anemia was not a significant problem in the present study with most of the patients presenting with only grade 2 toxicity. They recovered with nutritional supplements. Grade 3 toxicity was seen only in 3 patients requiring transfusion with compatible packed cells to restore the normal levels.

Platelets:

Thrombocytopenia was also not a significant problem with only 8 patients having grade 1 platelet toxicity according to RTOG grading and all others having no platelet suppression. None needed intervention.

NAUSEA:

Since Cisplatin a highly emetogenic agent was part of the treatment schedule, nausea and vomiting were a significant problem. 22 patients (73.26%) had grade 2 nausea which required continuous antiemetic

measures. And 4 patients had grade 3 nausea which prompted intervention. They were managed with

1. IV fluids to correct dehydration, if any.
2. Metoclopramide 40 mg PO every 4–6 hours for 4 days.
3. Dexamethasone 4-8 mg IV BD for 4 days.

DIARRHOEA:

Diarrhea is a common complication in any paclitaxel and 5 FU containing regimen. The present study had grade 3 or 4 toxicity in 2 patients out of 30. (6.67%). The grade 3 and grade 4 reactions were managed by plenty of fluid intake, and IV fluids in case of severe dehydration not corrected by oral rehydration alone. Antispasmodics and anti-motility agents were used to reduce the frequency of stools and to manage the abdominal cramps and pain. Regular monitoring of the biochemical parameters was done.

DELAY IN CHEMOTHERAPY.

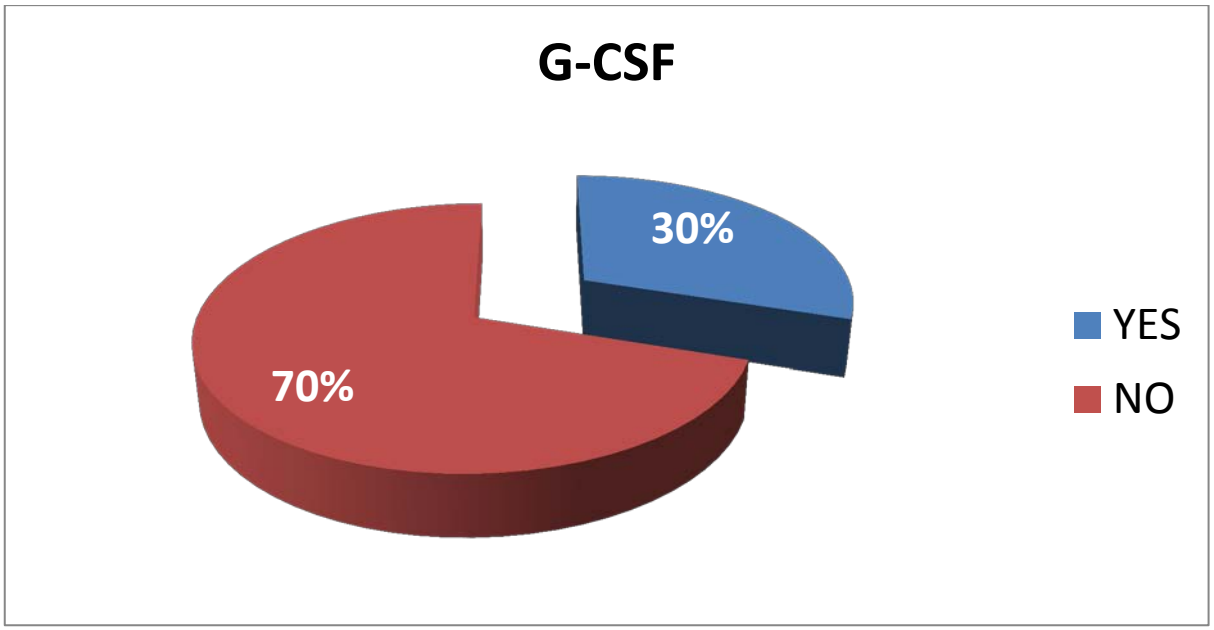
There was a significant delay in delivering the next cycle of chemotherapy due to toxicity management in 13 patients (43.29%).

However there was no undue delay of more than 3 days in any of the patients.

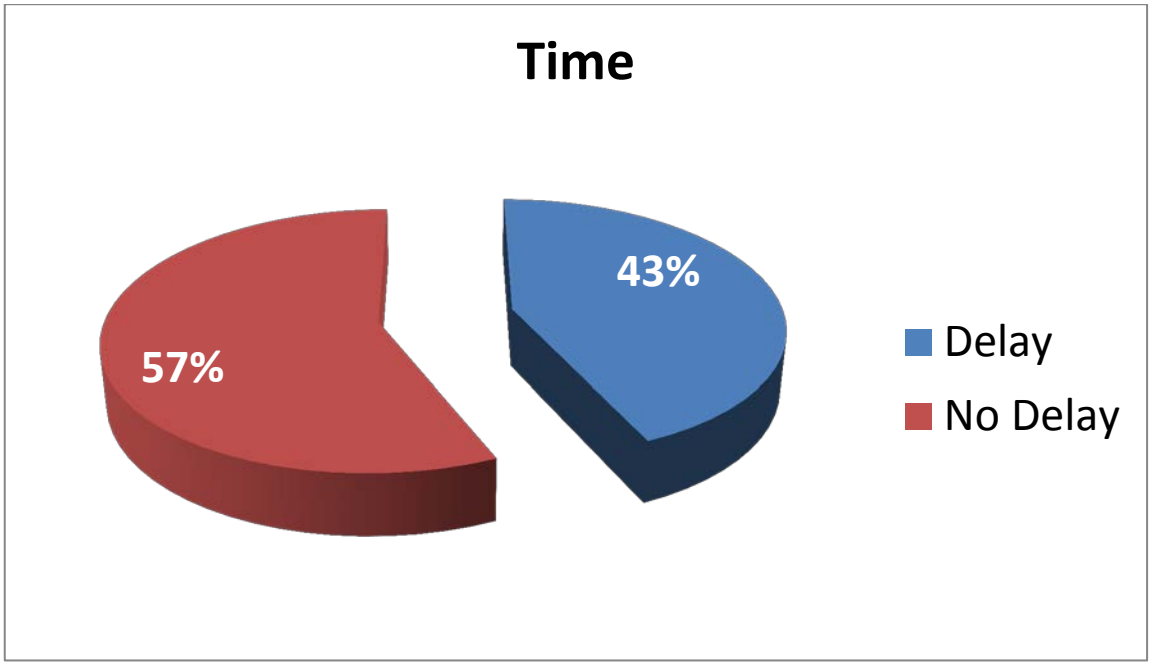
G-CSF REQUIREMENT:

G-CSF was required in 9 patients for normalizing the WBC levels before the next cycle of chemotherapy and as primary prophylaxis in the subsequent cycles when they needed G-CSF in previous cycles. All were used in only grade 3 and grade 4 patients. Two of the patients had grade 4 toxicity / febrile neutropenia

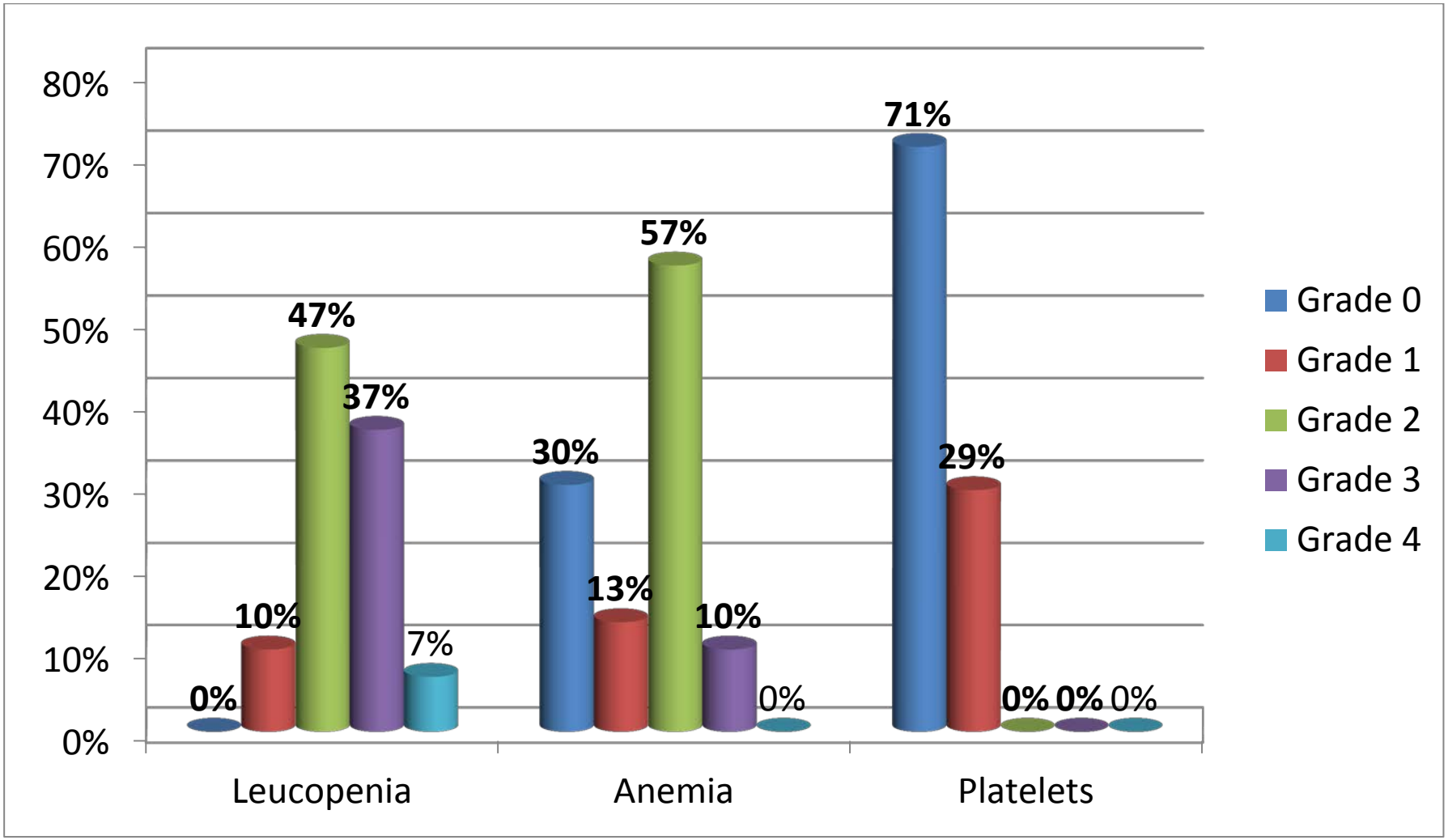
Graph 8: G-CSF Requirement



Graph 9: Time delay in Induction Chemo



Graph 10: Hematological Toxicity



TOXICITY IN RADIOTHERAPY:

Radiotherapy was delivered in conventional fractionation of 2 Gy per day over 5 days a week to a total dose of 66 – 70 Gy. The toxicities encountered during radiotherapy were graded using RTOG acute morbidity scoring criteria.

Mucositis:

Majority of the patients developed grade 2 mucositis (19 patients).

3 patients had grade 3 toxicities and treatment had to be suspended to allow for the resolution of mucositis before proceeding with further radiation.

The mucositis were managed with,

1. Inj. Dexamethasone 8 mg IV BD
2. Soda Bicarbonate Mouth Wash every 3-4 hours.
3. Alcohol free Antibacterial Mouthwash / oral lozenges.
4. Dispersible pain killer tablets to relieve pain.

Dysphagia:

Most of them developed grade 2 dysphagia during treatment (14 patients, 50.4%) they were managed with pain killer and maintained on

nutritious liquid diet. 5 patients developed grade 3 reactions and had to be maintained on nutrition by either IV Fluids or NG tube feeding.

Dermatitis:

This was not a significant problem with this study. Most of them had grade 1 and grade 2 reactions which did not warrant any treatment breaks and were allowed to resolve by itself after the completion of treatment.

Salivary gland toxicity:

Almost all of them developed grade 2 toxicity by the time of first assessment (27 patients). But none had acute necrosis of the salivary gland. All of those who had xerostomia were prescribed artificial salivary supplements.

DELAY IN RADIOTHERAPY:

Nearly one third of the patients did not complete the entire course of the radiotherapy within the stipulated time. 9 patients had treatment delays due to toxicities like mucositis and dysphagia (30%).

WEEKLY CDDP:

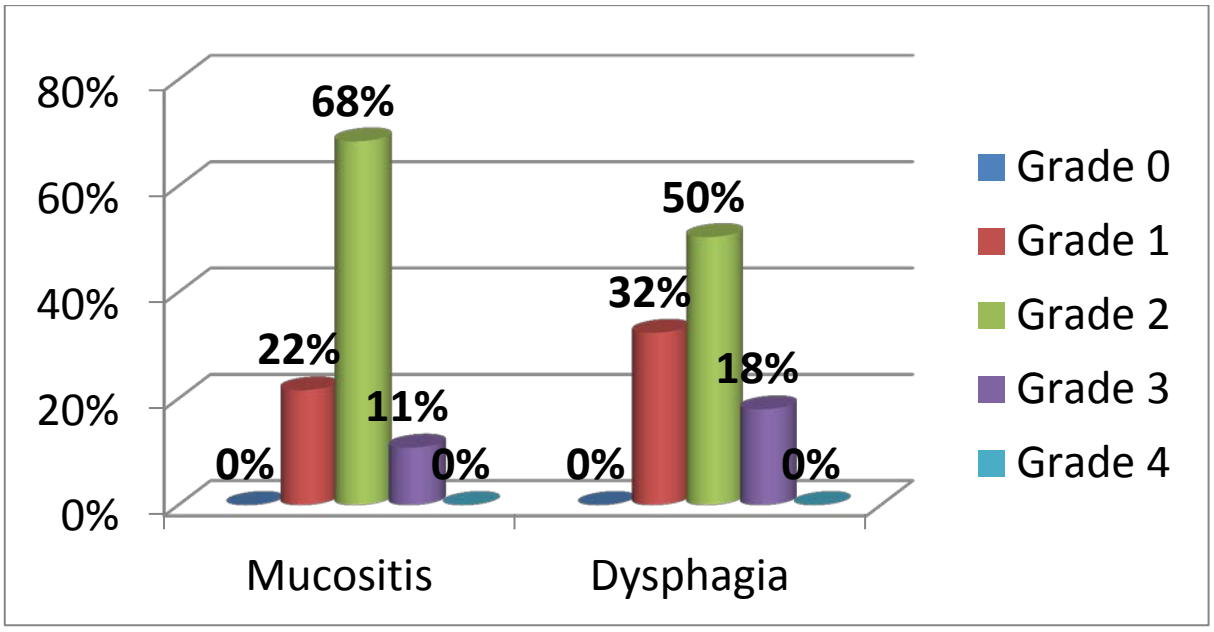
All the patients received weekly Cisplatin during radiotherapy. Two thirds of the patients (n=20) received at least 5 cycles of weekly chemotherapy. The rest received at least 4 cycles of chemotherapy. None of the patients received less than 4 cycles. There was significant nausea due to the chemotherapy with 18 patients developing grade 2 nausea and 5 developing grade 3 nausea, which warranted intervention. They were managed with

1. IV fluids to correct dehydration, if any.
2. Metoclopramide 40 mg PO every 4–6 hours for 4 days.
3. Dexamethasone 4-8 mg IV BD for 4 days.

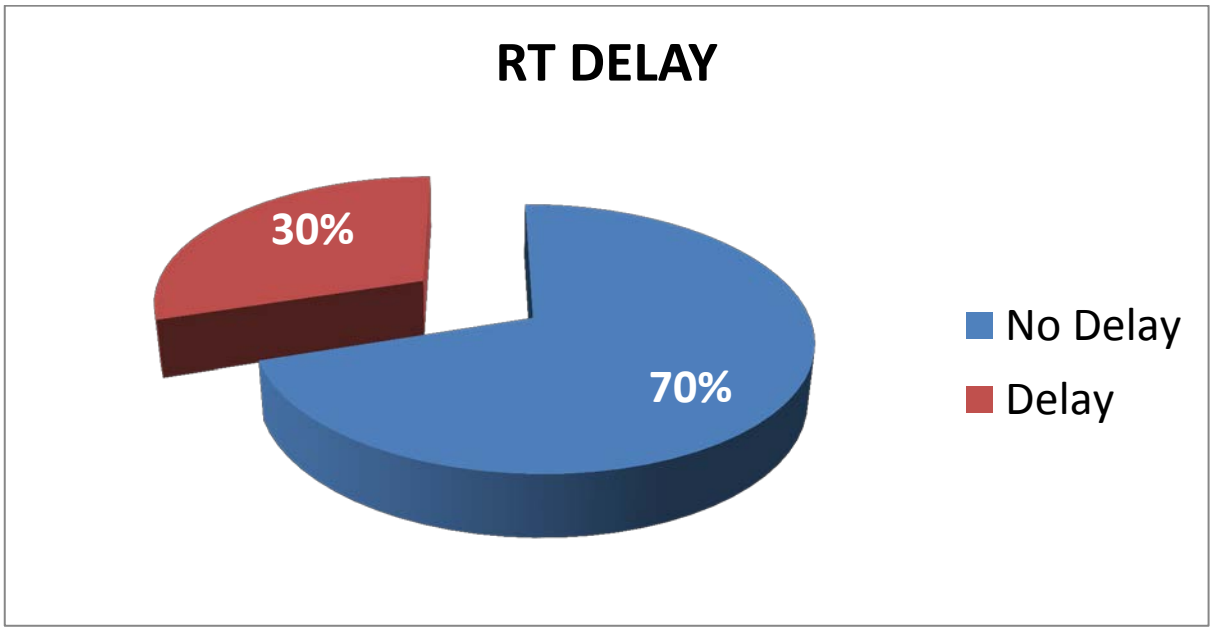
Table 6: Toxicities during Treatment

Grade	0	1	2	3	4
WBC	0	3 (9.99%)	14 (46.62%)	11 (36.67%)	2 (6.67%)
PLATELET	22 (73.26%)	8 (26.64%)	0	0	0
Hb	6 (19.98%)	4 (13.32%)	17 (56.61%)	3 (9.995)	----
NAUSEA IN INDUCTION	0	4	22 (73.26%)	4 (13.32%)	-----
MUCOSITIS	0	6 (21.6%)	19 (68.4%)	3 (10.8%)	0
DYSPHAGIA	0	9 (32.4%)	14 (50.4%)	5 (18%)	0
DERMATITIS	0	22 (79.2%)	6 (21.6%)	0	0
SALIVARY GLAND	0	1 (3.6%)	27	-----	0
NAUSEA IN RT	0	5 (18%)	18 (64.8%)	5 (185)	0

Graph 11: Toxicity during Radiotherapy



Graph 12: Delay during Radiotherapy



RESPONSE ASSESSMENT:

Following Induction:

The response was assessed following induction therapy with thorough clinical examination and imaging studies. All the patients had a clinically evaluable response after the induction chemotherapy. 9 of the 30 patients had a complete response at both the primary and nodal site (29.97%).

Subset analysis shows that 6/19 moderately differentiated and 3/7 poorly differentiated cancers achieved a complete response following induction chemotherapy. N3 nodes had a very good response rates with 5 out the 7 patients achieving complete response. The hypo pharyngeal cancers had the maximum benefit from the chemotherapy (n=4).

Following Entire treatment:

Following the completion of the entire treatment schedule of induction chemotherapy and the concurrent chemo radiation, the response rates were evaluated.

There was complete at the primary site in 19 (63.27%) and complete response at the nodal sites in 24 patients (79.92%).

The overall complete response rate at both the primary and the secondary nodal sites together was 19 (63.27%).

Table 7: Factors affecting Response

Factors	Complete response	Partial Response
T 1	2	0
T2	7	0
T3	4 (80%)	1 (20%)
T4	6 (42.85%)	8 (57.14%)
N2	12 (75%)	4 (25%)
N3	5 (71.43%)	2 (28.57%)
Oral Cavity	4 (44.44%)	5 (55.56%)
Oropharynx	6 (85.71%0	1 (14.29%)
Hypopharynx	8 (88.88%)	1 (11.11%)
Larynx	1 (33.33%)	2 (66.67%)
Stage III	13 (81.25%)	3 (18.75%)
Stage IV	6 (50%)	6 (50%)
Well Diff	0	4 (100%)
Mod. Diff	12 (70.5%)	5(29.41%)
Poorly Diff	6 (85.71%)	1(14.29%)
Delay in RT	4 (44.44%)	5 (55.56%)
No Delay In RT	15 (78.95%)	4 (21.05%)

ANALYSIS OF THE RESPONSE RATES:

Site and Response:

With regard to the site of involvement, nearly half of the oral cavity patients had only a partial response, 4 out of the 9 patients. In the case of oropharynx and hypopharynx, the response rates were near complete. 6 out of the 7 oropharynx cases and 8 out of the 9 hypo pharyngeal cancers achieved complete response. The oropharyngeal and hypo pharyngeal malignancies significantly fared better compared to the buccal mucosa and laryngeal cases (p=0.015).

TNM and Response:

T1 and T2 had 100% complete response rates and there was one failure in T3 disease. It was in the T4 group the results were poor. There was complete response in 6 out of the 14 patients (42.8%). 5 out 7 N3 node patients had a complete response, a success rate of 71.42% (p=0.6). When comparing the response rates between T3 and T4, there was no statistically significant difference between them (p=0.18). But when comparison was done between T1 and T2 taken together with T3and T4 taken together, there was significantly better response in the earlier group (p=0.01).

Stage & Response:

When analyzed with regard to the stage grouping, Stage III patient had complete response in 13 of the 16 patients who underwent complete treatment. Whereas in stage IV, only 50% had a complete response, of the total of 12 patients who completed the intended treatment. However this difference in the response was not significant. (p=0.09)

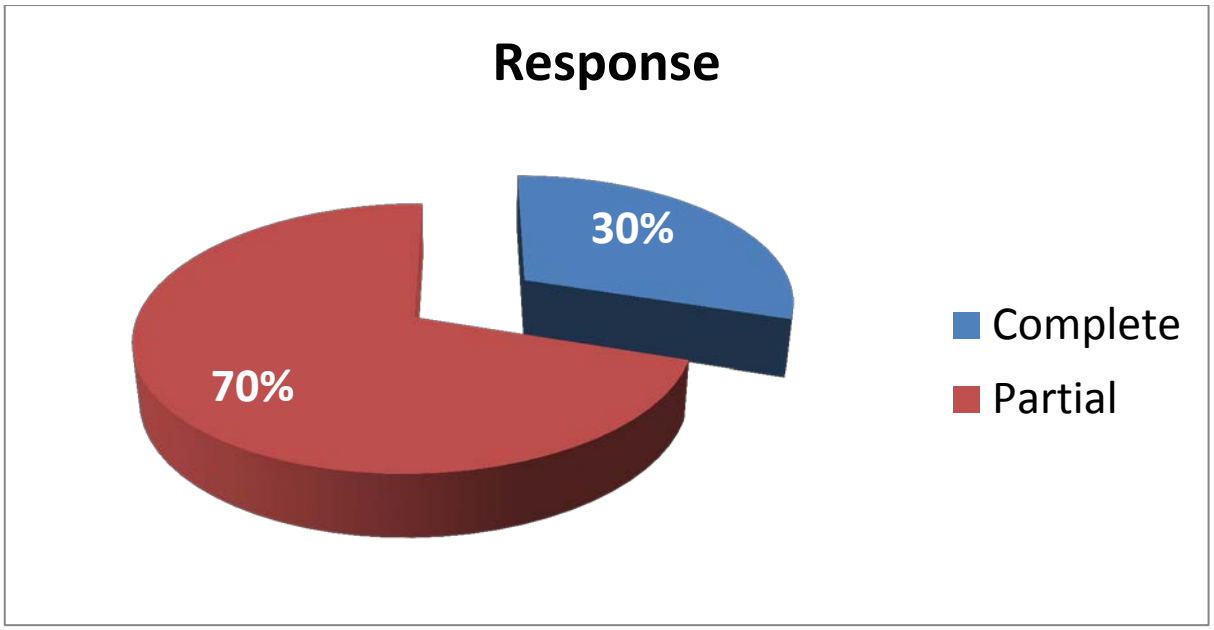
Histology:

The complete response rate was very good in the case of poorly differentiated cancers with 85.71% (6/7). Also, in moderately differentiated cancers too, the response rates were good with 12 out the total 17 achieving CR. However, there was no statistical difference between the response rates of the moderately and poorly differentiated tumors (p=0.4). Whereas, all the well differentiated cancers had a partial response. (p=0.01)

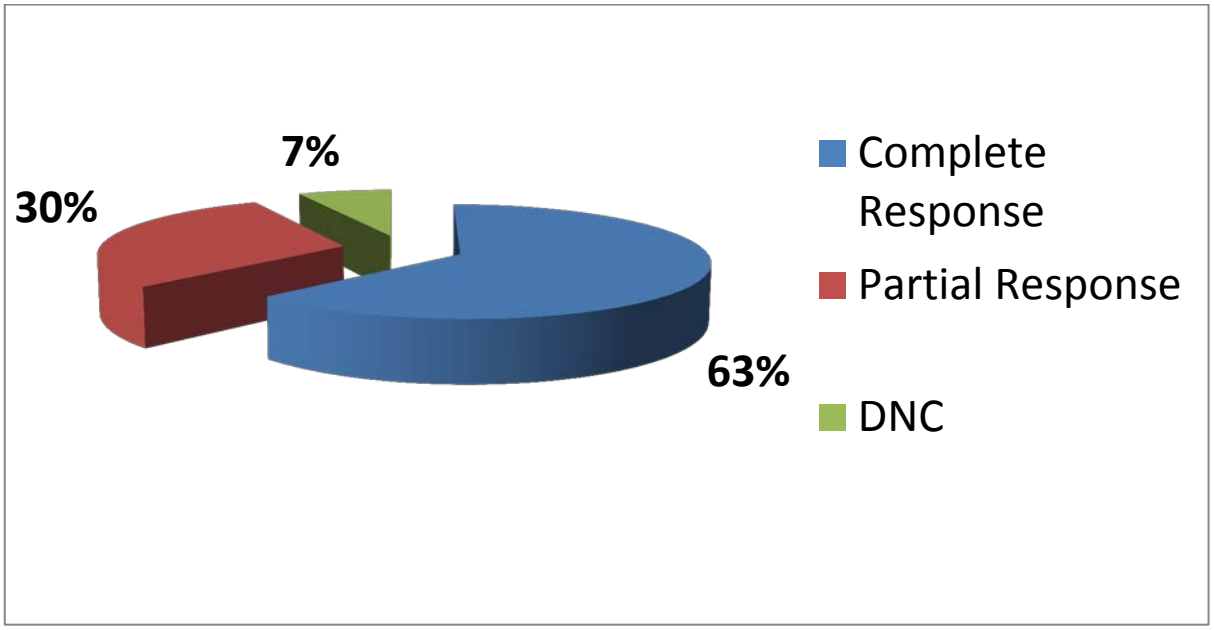
Delay in RT:

Those who had a delay in the completion of the course of radiotherapy, more than half of them had a partial response (5 out 9, 55.56%) (p=0.08). In other ways, in those achieving a complete response only 4 out the total 19 had a delay in RT (21.05%).

Graph 13: Response after Induction Chemotherapy



Graph 14: Response after Entire Treatment



DISCUSSION

6. DISCUSSION

The results of the present study show that sequential therapy is feasible in our setup and should be considered in select cases of locally advanced head and neck cancers.

The study included a wide range of patients across the age groups between the eligibility ages of 18 years to 70 years. The study population was heavily dominated by males with only 3 females. But this was probably due to higher exposure to carcinogens as males are more commonly users of cigarettes, beedis and the other smokeless tobacco forms like pan, khaini etc.

The study also included a very good sample of all the sites in the head and neck region. A good representation of all TNM stages of head and neck cancers were included.

All the patients started on the protocol completed the entire course of three cycles of the induction chemotherapy. This compliance for induction phase of the trial is similar to other trials in the available literature. But two patients did not proceed onto radiotherapy following the completion of induction phase. The probable reason for these patients defaulting was due to the alleviation of symptoms or due to the adverse effects of chemotherapy.

This implies indirectly that it is important to select cases carefully for this regimen. Patients with good nutritional status at the start of the treatment are perhaps better suited to undergo the rigors of this intense treatment regimen better. The patients should be counseled clearly before the start of the treatment that radiotherapy is the essential part of treatment and has to delivered at the right time after induction chemotherapy or else the benefits of chemotherapy will be lost. Probably literacy will play a major role in this regard with literate people being able to grasp the consequences of defaulting radiotherapy. Economic factors also have to be taken into account in our country as this prolonged treatment process may take a heavy toll on the family. Most commonly the patient, a male, turns out to be the sole bread winner of the family and if he is repeatedly in hospital for the course of the treatment then the financial burden on the family becomes manifold and this prompts the patient to default treatment.

In the TAX 324 study, almost all the patients concluded the entire induction phase in the TPF arm (98%). But only 79% of the patients in TPF arm proceeded to receive the chemo radiotherapy. In the TAX 323 study, nearly 25% discontinued the chemotherapy. But the most common reason quoted by the authors for discontinuation is progressive disease. In the present study, there were no cases of disease progression during the treatment course.

The toxicity assessment of the induction phase reveals that the addition of paclitaxel to the induction regimen does significantly increase the toxicity profile of the treatment. But this was manageable provided careful monitoring of the blood parameters were done at various times during the treatment and appropriate interventions done.

There were no deaths related to the chemotherapy in the study. The myelosuppression was mostly due to paclitaxel in the induction regimen. There were 2 cases of grade 4/ febrile neutropenia cases recorded in the trial. But there were no deaths recorded during the trial. Febrile neutropenia was 5.2% in the Tax 323 study and 4.8% in the Tax 324 study. Similar to TAX studies the grade 3 and grade 4 neutropenia were more common. The TAX studies too did not allow primary prophylaxis with G-CSF which probably resulted in a high incidence of grade 3 and grade 4 neutropenia in those studies. So, appropriate modifications were done in the study protocol. The present study also denied primary prophylaxis with G-CSF during the first cycle of induction chemotherapy. But if they needed G-CSF before the start of the subsequent cycle of induction chemotherapy, they were given primary prophylaxis with G-CSF during the subsequent cycles. Thus there was no undue delay in the subsequent cycles of chemotherapy due to hematological toxicities. And also all the patients received the entire planned 3 cycles. Thus the hematological toxicities are

less likely to affect the planned treatment provided good supportive care is given and appropriate management of the toxicities are done.

Paclitaxel did not result in any untoward allergic reactions in any of the patient but all patients were put on steroids as a precautionary measure.

The induction regimen also included a highly emetogenic drug like Cisplatin. This resulted in grade 3 nausea in 4 patients which needed IV fluid administration. The TAX studies recorded grade 3 or grade 4 nausea in around 5% of the patients. The present recorded a 13.32% grade 3 nausea but no cases of grade 4 nausea. The nausea was appropriately managed with IV fluids to correct dehydration and with antiemetic like metoclopramide and dexamethasone.

The Tax 323 study had a grade 3 or grade 4 diarrhea in 5 out of 177 patients (2.8%) and in TAX 324 study, 7 out of 251 patients (2.8%). The present study also had a similar rate of grade 3 or 4 reactions (6.67%0. These patients were appropriately managed. They were advised by plenty of fluid intake of 2-3L per day. IV fluids were administered in the case of severe dehydration which was not corrected by oral rehydration alone. Antispasmodics and anti-motility agents were used to reduce the frequency and to manage the abdominal cramps and pain. Regular monitoring of the biochemical parameters like serum electrolytes and renal function tests were done.

The study revealed the advantages of induction chemotherapy followed by concurrent chemo radiation in locally advanced head and neck cancers.

There was 30% complete response (CR) rate following the completion of the induction phase. This was similar to the 17% and 8.5% complete response rates seen in the TAX studies following induction TPF chemotherapy which was significantly higher than the comparative arm of PF induction therapy.

This advantage was more in the case of N3 nodes with most responding by the end of the induction phase. Probably N3 nodes would benefit the most from the sequential chemo radiation. Also the sub sites of hypopharynx and oropharynx had the best response to the entire treatment protocol. And this was significant when compared to the response rates of the other sub sites of oral cavity and the larynx ($p=0.015$). This probably points to the role of induction chemotherapy in organ preserving therapy.

The toxicities encountered during radiotherapy and concurrent chemotherapy did not vary much from the regular upfront radiotherapy patients. Most of them received at least 4 cycles of the planned 6 cycles of weekly chemotherapy.

Unlike the TAX 323 study which delivered 4 different schedules of radiotherapy and similar to the TAX 324, radiation was delivered in conventional fashion of 2 Gy per fraction 5 days a week up to a total dose of 66 Gy. Since the non-inferiority of carboplatin to Cisplatin has not been proven beyond doubt in the concurrent setting, the present study delivered only Cisplatin as the concurrent chemotherapy.

The toxicity encountered during radiotherapy was stomatitis due to oral mucositis, dysphagia due to pharyngitis and esophagitis, dermatitis and dryness of mouth due to salivary gland toxicity. Three patients (~10%) had grade 3 mucositis which warranted suspension of radiation and intervention with steroids and mouthwash as discussed earlier in the results section. This was similar to the rates of stomatitis encountered in the TAX studies of 8.5% and 4.6% stomatitis. There were five cases of grade 3 reactions of dysphagia which required IV fluids and NG tube feeding (17.9%). The parent study recorded a grade 3 dysphagia rate of 5.2%.

Both stomatitis and dysphagia are very important as they have serious implications regarding the time duration of treatment. It is a well-known fact that even a delay of single day in completing the radiotherapy will have a considerable reduction in local control and disease free survival. So precautions were taken to prevent the development of grade 3 toxicities by instituting steroids and regular mouthwash with soda bicarb

solutions and antibacterial solutions as described in the methodology of the protocol.

Since the radiation was delivered using only conventional 2D radiation fields with a Tele-Cobalt 60 machine, all the patients who underwent radiotherapy had xerostomia due to salivary gland toxicity. But none of the patients had serious complications like salivary gland necrosis. All those who developed xerostomia were prescribed artificial saliva.

Most of the patients also received at least 4 cycles of the planned weekly Cisplatin chemotherapy. However, there was significant toxicity like nausea to this schedule. They were managed with IV fluids and antiemetic as described above.

All these toxicities resulted in treatment breaks during radiotherapy in 9 patients out of the twenty eight who had undergone chemo radiation. (30%)

The overall complete response rates at the end of the entire schedule of the treatment was 63.27% (n=19). The TAX 323 study had recorded 72% complete response rates among those who were started on the chemo radiation schedule.

When analyzed with regard to site of involvement, the oral cavity patients had a very poor response to this regimen. Whereas the hypo

pharyngeal and oropharyngeal cancers had a near total complete response rate of 88.89% and 85.71% respectively. This better response in these two sub sites of the head and neck proved to be statistically significant (p=0.015).

Differentiation which is probably a surrogate for the mitotic rate of the tumor cells showed a significant correlation with response rates with all 4 well differentiated cancers resulting in partial responses (p=0.01). Most of them were buccal mucosa cancers. This implies that sequential therapy is not the best approach for buccal mucosa as most of the buccal mucosa cancers will be of well differentiated histology. But the poorly differentiated tumors and moderately differentiated tumors had a very good complete response rate of 85.71% and 70.6% respectively. (p=0.4)

It has already been deduced that oropharyngeal and hypo pharyngeal cancers had a good response rate. This is probably due to the fact these sites will have more of moderate and poorly differentiated tumors. So, probably these are the two sub sites which will have the best response in a sequential therapy setting. But the other factors such as stage and nutritional status of the patient will also have an implication on the treatment outcome.

It is a known fact that the T size of the primary will have an impact on the immediate loco regional control as well as the recurrence free

survival. The present study has confirmed the same fact with T1-T3 tumors achieving more complete responses. The lesser T stages T1 & T2 had a significantly better response rate when compared to the T3 & T4 stages (p=0.01). But this difference was not evident between the stages T3 & T4 (p=0.18). Also the N3 node status had a very good response to this sequence with 5 out 7 resolving completely (71.42%). But this better response rate in the patients with N3 nodes was not statistically significant (p=0.6). The prognostic significance of stage grouping is that involvement of nodes which upgrades the stage grouping to stage III reduces the survival by 50%. In the present study also stage III patients had a better response than the stage IV patients.

As already seen it is a known fact that even a single day of delay in the radiotherapy schedule is detrimental to the final outcome. More than half of those who had a delay in RT had partial responses as the outcome and this was statistically significant (p=0.08). In contrast in those who had a complete response only 21% had treatment breaks.

STRENGTHS OF THE STUDY:

1. The study delivered the optimal induction chemotherapy regimen of three drugs containing a Taxane, Cisplatin and 5 FU.
2. The definitive part of the treatment, concurrent chemo radiation was delivered following the induction phase.
3. The optimal chemotherapy of Cisplatin was delivered during radiotherapy.
4. All the toxicities were graded using standard scales like RTOG Acute Morbidity Scoring Criteria and Common Toxicity Criteria for Adverse Events Version 4.
5. The response assessment was done using a standard scale of RECIST Criteria 1.1

LIMITATIONS OF THE STUDY:

1. The induction phase included paclitaxel instead of docetaxel which was part of the TAX studies and other phase III trials of induction chemotherapy.
2. The radiation was delivered using 2D techniques. Delivering with 3D conformal techniques would have been the optimal technique.
3. There was no long term follow up of the patient which would have given the PFS and OS data for the sequential treatment.

4. The present study was a single arm study. A two arm comparative randomized study would have been better to settle the question of whether sequential therapy is better to upfront concurrent chemo radiation.

CONCLUSION

7. CONCLUSION

In conclusion, head and neck cancers continue to be a public health problem afflicting the developing countries. And most of these patients are still presenting in the advanced stages. So, studies like the present one examining intensification of the treatment regimen to achieve better results needs to be carried out.

As for the present study, it shows the benefits of the sequential therapy with the inclusion of induction chemotherapy before the loco regional treatment. It shows response rates similar to other large randomized trials carried out to address the same question. Sequential therapy will be very useful in very carefully selected cases and needs to be carried out at a tertiary center with good supportive care.

Also the question of whether the present approach is superior to the standard treatment of concurrent chemo radiation upfront still stands unanswered. This has to be settled in large randomized trials with appropriate loco regional treatment as part of the sequential approach. Other questions that need to be addressed are the optimal number of chemotherapy cycles in the induction and the correct time to start loco regional treatment after the induction phase.

So to sum up, sequential therapy has a strong biological rationale. It reduces the tumor load before the start of the loco regional treatment. Also

when the tumor load becomes low, the proliferation rate of cancer cells is probably rapid. So incorporation of a loco regional treatment like chemo radiotherapy is likely to have a better control rate, as is the case with Induction chemotherapy followed by chemo radiotherapy.

Sequential therapy is a feasible option for carefully selected patients with locally advanced head and neck cancers although with increased toxicity.

FUTURE DIRECTIONS

8. FUTURE DIRECTIONS

The future considerations for sequential therapy are finding out the optimal combination of the induction regimen and concurrent chemo radiation so as to reduce the high toxicity levels and achieve maximum response. There have been efforts to include novel agents like EGFR inhibitor, cetuximab along with induction therapy. This could be tried in the sequential therapy to get better results. Several phase II trials have been completed showing promising results[68]. It needs to be validated in a phase III trial.

Other targeted agents like geftinib and erlotinib could also be explored in the induction chemotherapy setting. These too have been evaluated in phase II trials with promising results.

Selection of patients for induction chemotherapy could be done on the basis of biomarkers. A correlative study of TAX 324[69] has shown that patients with low levels of beta tubulin II had a superior OS and PFS. This was more so in patients receiving docetaxel. This point to the fact it could be both a prognostic factor and a predictive factor for response to taxanes.

Other biomarker such as EGFR expression for cetuximab in the case of induction has not been useful, as this is almost universal in head and

neck cancers. So other biomarkers were looked. A phase II trial has low levels of VEGF and Interleukin 6 is associated with better control rates.

The other biomarker creating so much interest is HPV. HPV prognostication is known in the case of oropharyngeal cancers. HPV positive malignancies are associated with better response rates. This may preclude the need for intense therapy in such cases. But the extent to which the treatment can be less intensified is not yet known and needs to be verified.

The other method of prognosticating may be to use the response achieved to induction chemotherapy as the basis for the modality of the loco regional treatment. Response to chemotherapy may be taken as a surrogate marker for response to radiotherapy.

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APPENDIX

APPENDIX - I

INFORMATION SHEET

- You have been accepted by the Department of Radiotherapy to enrol into the study "SEQUENTIAL THERAPY WITH INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK"

- We are conducting a study on head and neck cancers among patients attending Government General Hospital, Chennai.

- The purpose of this study is to find if prior treatment of chemotherapy followed by concurrent chemoradiation will have a better response rates and lower recurrences.

- We are selecting certain cases and if your case is found eligible, we may be performing extra tests and special studies which in any way do not decrease your chance of optimum treatment.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator

Signature of participant

APPENDIX - II

INFORMED CONSENT FORM

TITLE OF THE STUDY: SEQUENTIAL THERAPY WITH INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

NAME OF THE PARTICIPANT:
NAME OF THE PRINCIPAL (Co – Investigator) : DR. S. Moses Arunsingh
NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

I,_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "SEQUENTIAL THERAPY WITH INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK"

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have informed the investigator of all the treatments I am taking or have taken in the past_____ 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 _____month(s). *
9. I have not donated blood within the past _____ months—Add if the study involves extensive blood sampling. *
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_____

APPENDIX - IV

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனைக்கு வரும் புற்றுநோய் நோயாளியிகளிடம் கதிர்வீச்சு சிகிச்சை பற்றிய ஆராய்ச்சி.

தலை மற்றும் கழுத்து பகுதியில் முற்றிய புற்றுநோய்க்கு பல வகையான கதிர்வீச்சு சிகிச்சை முறைகள் உள்ளன. முதலில் புற்றுநோய் மருந்துகளான "பாக்லிடாக்செல், சிஸ்பிளாட்டடின் மற்றும் 5 புளோரோ யுராசில்" ஆகியவற்றால் நோயின் அளவை குறைத்து பிறகு தீவிர கதிர்வீச்சு சிகிச்சையுடன் வாரந்தோரும் "சிஸ்பிளாட்டின்" மருந்து கொடுத்து புற்றுநோயை குணப்படுத்துவது பற்றி ஆராய்வது இந்த ஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை அளித்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

_____ _____

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

APPENDIX - V

ஆராய்ச்சி ஒப்புதல் கடிதம்

தலை மற்றும் கழுத்து பகுதியில் முற்றிய புற்றுநோய்க்கு, "பாக்லிடாக்செல், சிஸ்பிளாட்டடின் மற்றும் 5 புளோரோ யுராசில்" ஆகியவற்றால் நோயின் அளவை குறைத்து பிறகு தீவிர கதிர்வீச்சு சிகிச்சையுடன் வாரந்தோரும் "சிஸ்பிளாட்டின்" மருந்து கொடுத்து செய்யப்படும் ஆய்வு.

பெயர்: தேதி :

வயது: உள்/புற நோயாளி எண்:

பால்: ஆராய்ச்சி சேர்க்கை எண் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எளக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனக்கு புற்றுநோய் இருக்கும் பகுதியில் கதிர்வீச்சு சிகிச்சை செய்து கொள்ள சம்மதம்.

இந்த அராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் பங்கு பெறுகிறேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

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

எனக்கு இந்த அராய்ச்சியின்படி தீவிர கதிர்வீச்சு சிகிச்சை மற்றும் புற்றுநோய் மருந்துகள் பெற்றுக் கொள்ள சம்மதம். இந்த ஆராய்ச்சிக்கு தேவையான பிற பரிசோதனைகள் செய்து கொள்ள சம்மதம்.

இந்த அராய்ச்சியினால் ஏற்படும் நன்மைகளையும், சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்து கொண்டேன்.

நூான் என்னுடைய சுயநினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதம்.

கையொப்பம்

APPENDIX – V

ETHICAL COMMITTEE CLEARANCE

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. S. Moses Arunsingh
PG in MD Radiotherapy
Madras Medical College, Chennai -3

Dear Dr. S. Moses Arunsingh

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " Seqential therapy with induction chemotherapy followed by concurrent chemoradiation in locally advanced squamous cell carcinomas of the head and neck " No.16032012.

The following members of Ethics Committee were present in the meeting held on 22.03.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan. MD	-- Chairperson
2	Prof. Pregna B. Dolia MD Vice Principal, Madras Medical College, Chennai -3 (Director , Institute of Biochemistry, MMC, Ch-3)	-- Member Secretary
3.	Prof. B. Kalaiselvi. MD Prof of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. Of Internal Medicine, MMC, Ch-3	-- Member
5.	Thiru. S. Govindsamy. BA BL	-- Lawyer
6.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

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

Sd/ Chairman & Other Members

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

Member Secretary, Ethics Committee

APPENDIX VI

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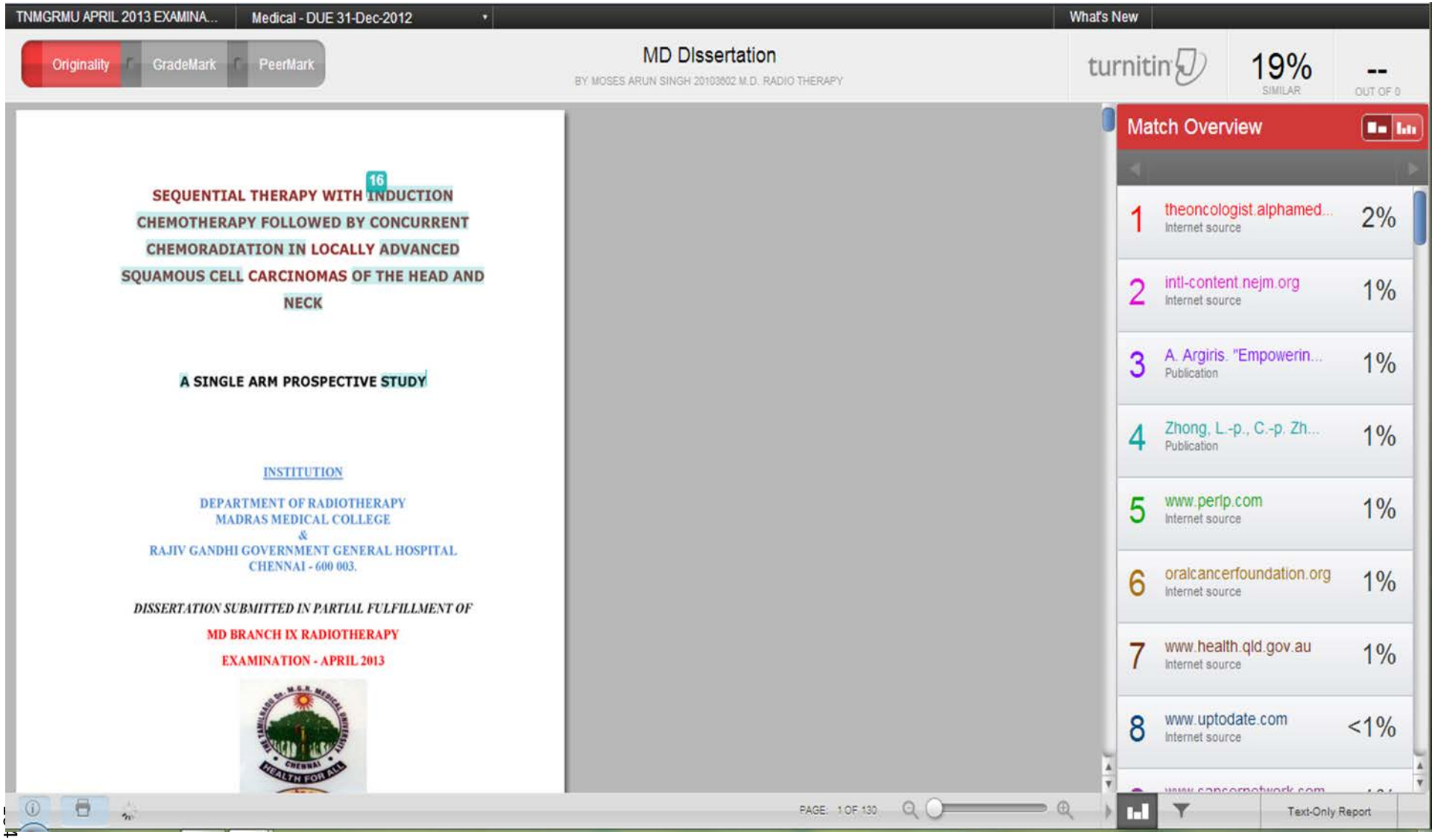
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