PALLIATIVE RADIOTHERAPY ALONG WITH NIMORAZOLE AS HYPOXIC RADIO SENSITIZER IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

A SINGLE ARM PROSPECTIVE STUDY

DEPARTMENT OF RADIOTHERAPY
MADRAS MEDICAL COLLEGE
&
RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL
CHENNAI - 600 003

Dissertation submitted in partial fulfillment of

DOCTOR OF MEDICINE
MD BRANCH IX RADIOTHERAPY
APRIL 2016 EXAMINATION

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600 032

CERTIFICATE

This is to certify that **Dr. RAGAVENDRA A.** has been a Post Graduate MD Student during the period from May 2013 to April 2016 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled **"PALLIATIVE RADIOTHERAPY ALONG WITH NIMORAZOLE AS HYPOXIC RADIO SENSITIZER IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA"** is a bonafide 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 April 2016 examinations.

Prof. **Dr.R.Vimala**, M.D.,
Dean,
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai.

CERTIFICATE

This is to certify that **Dr. RAGAVENDRA A.** has been a Post Graduate MD Student during the period from May 2013 to April 2016 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled **"PALLIATIVE RADIOTHERAPY ALONG WITH NIMORAZOLE AS HYPOXIC RADIO SENSITIZER IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA"** is a bonafide 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, April 2016 examinations.

Dr. S. SHANMUGA KUMAR, B.Sc., M.D, D.M.R.T.,
Professor and Head,
Department of Radiotherapy,
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai.

ACKNOWLEDGEMENTS

I thank **The Lord Almighty**, for his eternal grace and guidance in helping me to carry out this study.

I am very much delighted to acknowledge my lovable wife, **Dr. Gayathiri, M.D.S.,** for her constant encouragement especially in times of poor will-power and feel of inferiority, without whom I would not have joined this course and without whom I would not have done this dissertation, a successful one, who is the sole backbone for getting a special prize for the paper presentation on my dissertation topic in AROITNPYCON 2015. I want to acknowledge that all such good times became a possibility on the arrival of **our son**.

I also thank my mother and my family members, for their support which made me to join the medical field and thereby a possibility to render service to the humanity.

I express my sincere gratitude to **Prof. Dr. R. VIMALA, M.D.,** Dean, Madras Medical College, Chennai - 03, who has been a continuous source of encouragement. I am grateful to her for permitting me to conduct this study.

I express my sincere gratitude to **Prof. Dr. SUDHA SESHAYYAN, M.S.,** Vice Principal, Madras Medical College, Chennai – 03, for her kind words of encouragement.

I express my gratitude to Chairman **Dr. C. RAJENDRAN, M.D.,** and the members of the Institutional Ethics Committee of Madras Medical College and Rajiv Gandhi Govt. General Hospital, Chennai - 03, affiliated to The Tamil Nadu Dr. M.G.R Medical University, Chennai – 32, for having approved my study and for their valuable suggestions.

I express my gratitude to **Prof. Dr. VANITHA**, M.D., Director, Barnard Institute of Radiology and Oncology, Madras Medical College and Rajiv Gandhi Govt. General Hospital, Chennai – 03, for her kind words of encouragement and inspiration.

I am extremely grateful to **Prof. Dr. S. SHANMUGAKUMAR, B. Sc., M.D, D.M.R.T.**, Professor and Head, Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai – 03, for giving me this topic and guiding me to finish it. And also for bringing out an attitude of questioning everything and not accepting anything at face value and for his probing questions to get to the basics of all subjects and making me to think. I have benefitted immensely from his case discussions.

I am extremely thankful to **Prof. Dr. N.V.KALAIYARASI, D.C.H**, **M.D.R.T,** Additional Professor, Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai – 03, for her support, encouragement and motivation rendered throughout the study period.

I am extremely thankful to **Prof. Dr. P. BALASUBRAMANIAM, M.D., D.M.R.T.**, Additional Professor, for his periodic monitoring, intellectual input, kind encouragement and support. Apart from his teaching, his systematic approach, dedication and sincerity are lessons I would like to inculcate for my life.

I wish to express my sincere gratitude to all the **Assistant professors** of my department (past and present) for guiding me during my study period. They guided me in acquiring the cases; planning the treatment, executing the radiotherapy, manage the side effects during the treatment and much more.

Dr. BASKAR P. K., M.D.R.T.,

Dr. MADHUMATHI S., M.D.R.T.,

Dr. SUNDARESAN C., M.D.R.T.,

Dr. PRABAGARAN V., D.M.R.T.,

Dr. ARUN RAMANAN V., M.D.R.T.,

Dr. SYED MADHAR SHAH K., D.M.R.T.,

Dr. SANJAL, M.D.R.T.,

Dr. CHANDRALEKHA K., M.D.R.T.,

Dr. VIJEY KARTHIK P. R., M.D.R.T.,

I am indebted to the Medical Physicists of The Department of Radiation Physics who helped plan the radiotherapy and offered guidance during difficult situations:

Prof. Dr. MUTHUVELU K., Head of the department, Radiation physics.

Mr. THIRUMAVALAVAN M.,

Mrs. KOPPERUNDEVI A.,

My words of appreciation and gratitude go out to the radiographers **Mr. MOORTHY, Mr. PURUSHOTHAMAN, Mr. VIVEKANANDAN, Mr. UDHAYA KUMAR, Mr. VELU, Mr. GABRIEL RAJSEKAR** and **Mr. ARUL** and their team of student radiographers for their sincere execution of the planned treatment for the patients of this study.

I am grateful to **Prof. Dr. S. JAGDISH CHANDRA BOSE**, **M.S., M.Ch,** Professor and Head, Department of Surgical Oncology, and **Prof. Dr. K. KALAICHELVI**, **M.D., D.M.,** Professor and Head, Department of Medical Oncology, for their prompt help rendered whenever approached.

My sincere gratitude goes out to my fellow post graduates and friends of our department for the magnanimous assistance offered to me throughout the study period.

Lastly and most importantly, I wish to acknowledge the co-operation of my patients during the study period without whom this study would have been impossible.

DECLARATION

I solemnly declare that the dissertation titled

“PALLIATIVE RADIOTHERAPY ALONG WITH NIMORAZOLE AS HYPOXIC RADIO SENSITIZER IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA”

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. N.V.KALAIYARASI,** D.C.H., M.D,R.T.

The Dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment for the award of M.D. Degree (Branch IX) in Radiotherapy, April 2016 examinations.

Dr. Ragavendra A,

M.D. Radiotherapy Post Graduate Student,

Department of Radiotherapy,

Madras Medical College & Rajiv Gandhi General Hospital,

Chennai.

TABLE OF CONTENTS

ABBREVIATIONS

1. SCCHN : Squamous Cell Carcinoma of Head and Neck
2. LASCCHN: Locally Advanced Squamous Cell Carcinoma of Head and Neck
3. HNC : Head and Neck Cancer
4. HPV : Human Papilloma Virus
5. ECOG : Eastern Cooperative Oncology Group
6. PS : Performance Status
7. RT : Radiotherapy
8. PRT : Palliative Radiotherapy
9. SAS : Symptom Assessment Scale
10. BSC : Best Supportive Care
11. MMTR : Madras Metropolitan Tumor Registry
12. RECIST : Response Evaluation Criteria In Solid Tumors
13. QoL : Quality of Life

Study of Palliative Radiotherapy along with Nimorazole as hypoxic radiosensitizer in locally advanced head and neck squamous cell carcinoma

Dr.Ragavendra A*, Dr.N.V.Kalaiyarasi, Dr.S.Shanmuga kumar

Department of Radiotherapy, Madras Medical College, Chennai

Introduction:

Solid tumors may contain oxygen-deficient hypoxic areas and such areas may cause tumors to become radioresistant. Many studies in the past showed modification of tumor hypoxia significantly improved the loco-regional tumor control.

Aim:

To assess the immediate loco regional response rates of LAHNSCC with palliative radiotherapy along with Tab.Nimorazole; to assess the degree of symptom relief; to assess acute toxicity of treatment protocol.

Materials and methods:

30 patients presenting to our department with biopsy proven LAHNSCC (stage IV A with ECOG 3 and IV B with ECOG 2 or 3) from sites oropharynx, hypopharynx and larynx, non metastatic, ineligible to receive chemotherapy along with radiotherapy, in the age group of 18-70, treatment naive and willing to participate in the study were included. Patients were treated with hypofractionated radiotherapy 48Gy/300cGy#/3.2 weeks and Tab.Nimorazole 1.2 gm/m² (1500 mg) daily 90 minutes before RT. The response to treatment was assessed after 6 weeks clinically and radiologically using RECIST criteria. The symptoms experienced by the patients before and after treatment were recorded using symptom assessment scale. The toxicities of radiation and nimorazole were recorded.

Results:

21 patients were in stage IV B and 9 in stage IV A. 14 among 21 showed partial response and others had static response in stage IV B. Among the 9 in the stage IV A, 6 had complete and 3 had partial responses. 20 patients showed significant (>50%) improvement in symptoms. None of the patients developed severe toxicities specific to Nimorazole. We observed grade 2 nausea and grade 1 vomiting in 4 patients and these had dose reduction for nimorazole. None of the patients developed rashes or flushing. None of the patients developed grade 4 mucositis. None developed significant haematological toxicities except for grade 1.

Conclusion:

Hypofractionated Radiotherapy along with Nimorazole demonstrated a significant benefit in the palliative treatment of LAHNSCC in patients with poor performance status without added toxicities. Yet long term studies with larger population groups are needed to arrive at a statistically significant conclusion.

Key words: palliative radiotherapy, hypoxia, hypoxic modification, nimorazole.

INTRODUCTION

Head and neck cancers (HNC) comprise a heterogeneous group of malignant tumors which can arise from any of the structures cephalad to the clavicles. These generally do not include those arising from the brain, spinal cord, base of the skull, and the skin. These malignancies can arise from epithelium or connective tissue mesenchymal structures. In this dissertation we restrict our discussion to epithelial malignancies alone. For a clear understanding of these malignant tumors, head and neck region is anatomically separated into those cancers arising from the sites such as oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, nasal cavity and paranasal sinuses, thyroid and major salivary glands.

Squamous cell carcinoma is one of the most common cancers presenting in our country which constitutes at least 25% of the overall cancer burden. Around the world, squamous cell carcinoma of the head and neck (SCCHN) accounts for more than 5 million new cases every year. Globally it is the 5th most common malignant disease. About 300,000 head and neck cancer patients die annually, which is a very huge burden on our community.[1.] The distressing feature in this magnitude of problem is about two thirds of the new cancer cases are from developing countries and many such countries are from Asia, where the medical facilities are still struggling to reach the people under poverty. Significant proportion of oral cavity cancers is reported from

counties like Australia, India, South Africa and Western Europe[2]. According to South Asian journal of cancer, the incidence of cancer is highest in India among the SAARC countries[3].

Based on the present data, no single cause or mechanism is postulated as responsible for causation of cancer in human beings. But it is an established fact that the incidence and prevalence of cancer in a geographical area is very much influenced by the specific environmental conditions existing in that area as well as the life style and cultural habits and behaviour of that particular population. Hence the cancer trends vary from population groups to population groups. In our country and in other developing countries like South East Asia, some of the African countries and South American countries the incidence and prevalence of HNC is very high. On a contrary, the incidence of HNC is very low in the developed countries like Northern Europe and USA.

Because they show a wide variation in their natural history, prognosis and response to treatment, Head and neck cancer is felt to be of great importance to the researchers and oncologists. One more reason for its importance is because of the physical and psychological morbidity it produces; and also the resulting significant burden on the family and society.

Face is the index of soul. The organ system of Head and neck is designed for the most important physiological functions such as respiration,

nutrition, language and expression, many of which are characteristic to mankind. Any surgery, reconstruction, toxicities of radiation and chemotherapy will produce a lot of alterations and compromise the normal physiological functions; any extensive surgery causes disfigurement and a diminution of quality of life.

INDIA

HNC represents a major public health problem in India. These cancers are most often related to the cultural, behavioural and life style changes of individuals and mostly occurs in 6^{th} and 7^{th} decades. The infectious diseases being kept under control, the incidence of HNC in India is on the rise, and its subsequent increased longevity of the population.

About 200,000 new cases of head and neck cancer arise in India every year, of which 80,000 cases are diagnosed from oral cavity, 40000 cases from pharynx excluding nasopharynx and 29,000 cases from larynx. Majority of these cases (60%-80%) are presenting to health care centers in advanced stage only[4].

TAMIL NADU

In men the single and most common cancer reported is head and neck cancer, as per Madras Metropolitan Tumor Registry (MMTR) data; stomach and lung follows it in succession. In women also the burden has increased and

today HNC is the 4th commonly occurring cancer. 17.8% of all cancers have been registered in Government general hospital, Chennai alone during the period 2006-2008. Men suffer from HNC more commonly than women and in comparison it is attributable to 25.62% versus 11.35%[5].

Most of the cases present in loco regionally advanced stage and even in the early stage disease less than half of the patients achieve cure. The advanced nature of the disease carries a poor prognosis and this leads to uncontrolled loco-regional disease and hence its sequelae of death. Because of this, the 5-year survival is less than 20% even with combined modality treatment.

HNC registered in Barnard institute of radiology and oncology constitutes a bulk of 35 to 40% of all new cases registered in a calendar year all over Tamilnadu. Among them, 65 to 75% of the patients present in advanced stages.

ETIOLOGY

Important etiological factors established in the development of SCCHN:

1) tobacco in all forms,
2) alcohol abuse,
3) quid chewing,
4) HPV-16 infection (Human Papilloma Virus),
5) Diet and nutritional factors,
6) Occupational hazards,
7) Immune suppression and genetic predisposition,
8) Oral hygiene and dental factors.

Smoking

Smoking was established independent risk factor for oral, pharyngeal and laryngeal cancers and it was the first identified one.[6.] In India, Tobacco can be used as smokeless forms such as ghutka, as quid with beetel nut chewing, etc. and smoke forms such as ganja, beedies, cigars, pipes, etc. All are responsible for the development of SCCHN. Beedi smoking is more hazardous than any other as it is not filtered and the contents of tar, nicotine are more compared to manufactured cigarettes. Also there are of different

ways in using them like reverse smoking which is more harmful. Till date it was identified that Tobacco contains almost 3800 chemicals among which 62 are established carcinogens.

Betel quid chewing

Betel quid consists of pieces of areca nut, slaked lime and tobacco. Additional substances to this are spices, cardamom, cloves, which are added as per the local preferences and they are called as gutkha, zarda, mawa, khaini.

Quid is the most common form of tobacco abuse in India which causes oral cavity cancer leading from premalignant lesions mainly sub mucosal fibrosis and at later date invasive cancer.

Alcohol

Alcohol consumption has been found to increase the risk of development of SCCHN. The quantity, frequency, type, duration of consumption have all been correlated with the development of SCCHN.[7]

More worser than this is tobacco smoking and alcohol together have synergistic and supra additive effect. There is a significant relationship with duration of consumption, amount, heavy and light smokers/drinkers, in the development of oropharyngeal/laryngeal cancer[8]. Landmark analysis by International Head and Neck Cancer Epidemiology found the population

attributable risk (PAR) for SCCHN and concluded that PAR for tobacco or alcohol was 72% for HNC. Out of this 72%, 33%, 4% and 35% were due to tobacco alone, alcohol alone and due to combination of alcohol and tobacco respectively[9].

HPV

Human papillomavirus associated HNSCC should be distinguished as a different disease from the usual HNSCC, since the treatment aspect will be in a distinct line. The important thing to be remembered is HPV positivity is associated with a improved response to treatment and survival benefit, which was independent of any treatment modality. Recent trend in the treatment, based on these findings is the treatment can be de-escalated to avoid unnecessary toxicities. But there are no randomized controlled trials to support this principle; at the same time still some researchers feel that aggressive form of combined modality treatments may represent an overtreatment[10, 11].

Genetic

Researchers have found that GST gene alleles were responsible for determining susceptibility to head and neck carcinomas[12].

Fanconis Anemia is associated with mutations of the genes like FAA, FAD and FCC, lymphoid malignancy and the resulting risk of development of second primary in tongue, Pyriform fossa and post cricoid region[13]

Bloom Syndrome is associated with mutations in helicase genes and they are predisposed to develop solid tumors, about 6-8% risk of getting tongue and larynx cancers[14]

Homozygotes with ataxia telangiectasia who survive into the adulthood are at increased risk of developing T-cell Leukemia. These patients are predisposed to develop cancers of the oral cavity, Stomach, Pancreas, Breast, Ovary and bladder[15]

Xeroderma pigmentosum manifests second primary in the oral cavity in addition to primary skin malignancies[14,16]

Cowden disease (PTEN), Multiple Endocrine Neoplasia type 1 (MEN I) and type 2 (MEN II), Neurofibromatis Type II (NF-2) and Retinoblastoma (Rb) are some of the syndromes associated to primaries in head and neck.

Diet and Nutrition

The American Institute of Cancer Research (AICR) and World Cancer Research Fund (WCRF) says fruits and vegetables seem to protect against several cancers in the aero digestive tract and also pancreas and prostate. The

exact extent of the protection and how it works has not yet been fully understood[17].

There is an entity called ‘Energy balance’ which means eating and drinking about the same amount of calories leading to the optimal body functioning. It is the main way to maintain a healthy weight. Other systems of medicine also talks about this. Maintaining a healthy weight is one of the most important ways as a protection against cancer, as we always say ‘prevention is better than cure’.

Plummer-Vinson syndrome:

This syndrome representing a triad of dysphagia, iron-deficiency anemia and esophageal webs carries a higher risk of malignancies of upper digestive tract. The characteristic dysphagia occurring in this is painless and intermittent, limited only to solids with or without weight loss. Iron deficiency is thought to be the etiological factor for predisposition to malignancy.

Oral hygiene and dental considerations:

Poor oral hygiene, ill fitting dentures and faulty restorations, and sharp teeth may be associated with the development of oral cavity cancers, though their exact etiological link is not known. Chronic trauma might be the

possible cause for the malignant transformation of epithelial cells with additive effect from other carcinogens.

Through a process called chemical carcinogenesis the microorganisms from dental plaque may generate nitrosating enzymes which are toxic. In individuals with poor oral hygiene, this carcinogen will not get diluted and together with the various tobacco related habits leads to the development of malignancy. **(Shah 2003)**

HEAD AND NECK FIELD CANCERIZATION:

The clinical evidences provided by studies such as the impact of tobacco and viral exposure in Head and Neck tumorigenesis, categorizing the distant second lesions into 2nd primary/ 2nd field tumor and the degree of incidence of tumors arising from the pre malignant lesions help us to gain knowledge on this.

A) Impact of Tobacco and Alcohol Abuse:

HNC has been shown to be highly associated with tobacco and alcohol exposure. In fact, it is estimated that 50-70% of deaths resulting from oral and laryngeal cancer can be attributed to tobacco smoking. The risk of developing HNC increases as a function of both the intensity (e.g., packs per day) and the duration (e.g., pack years- no of pack per year * no of years of exposure) of

tobacco exposure and decreases gradually following cessation of tobacco exposure[20]**. (Blot, W. J 1988)**

B) HPV:

While the majority of head and neck cancers were attributable to tobacco and alcohol exposure, nearly 30% of them occur in nonsmokers. The etiologic agents or intrinsic factors responsible for head and neck cancer in nonsmokers are less understood. However, they may also influence the head and neck region in a field cancerization manner. For example, mucosa of the entire upper aerodigestive tract can be infected by human papillomaviruses (HPV), albeit in a potentially more focal fashion than that affected by tobacco exposure. While the reported frequency is highly variable depending on the detection technique, more than 50% of head and neck cancers, especially in the tonsil and base of tongue, have been reported to harbor (HPV). It has been shown that high-risk HPV16 is present in 90% of HPV-positive HNC cases and that the gene products of HPV 16 are reported to be especially potent with regard to interfering with cell cycle regulation, altering cellular response to injury, promoting genomic instability, and facilitating immortalization. These findings suggest that HPV 16 can facilitate the acquisition of genetic events leading to development of tumors of head and neck region or can act in combination with other etiological agents**. (Li S L, 1992).**

C) Second Primary Tumor

The incidence of second primary tumor has started increasing and it was reported as high as 10%. It could be either synchronous or metachronous; analysis of metachronous lesions show the frequency of second primary tumor (SPT), a third primary tumor (TT), and a fourth primary tumor (QT) as 3 to 5%, 0.5% and 0.3% respectively. The second primary tumor behaves in an aggressive manner and is much more resistant to treatment, and metastasizes early, so that it emphasizes the importance of a more aggressive treatment strategy. **(Mehdi I 2010)**

PRECANCEROUS LESIONS:

Leukoplakia

It is the most common precancerous lesion in head and neck. It is treated by excision. The estimated 10-yr risk of malignant transformation for leukoplakia is about 10%, and this goes even upto 40% if there is advanced histology pattern within. More important than this is **only half of these patients developed cancer in the site of leukoplakia (Silvermann S Jr 1984).**

Erythroplakia

It is more dangerous because of higher risk of malignant transformation than leukoplakia[18]. It has been found in studies that 51% of the erythroplakia

patients had invasive cancer; 40% had carcinoma in situ; and 9% had mild or moderate dysplasia.

Submucosal fibrosis

Malignant transformation is very compared to other two. Recently it is the main risk factor in the increase in incidence of oral cavity cancers in young individuals (< 35 years) in India.

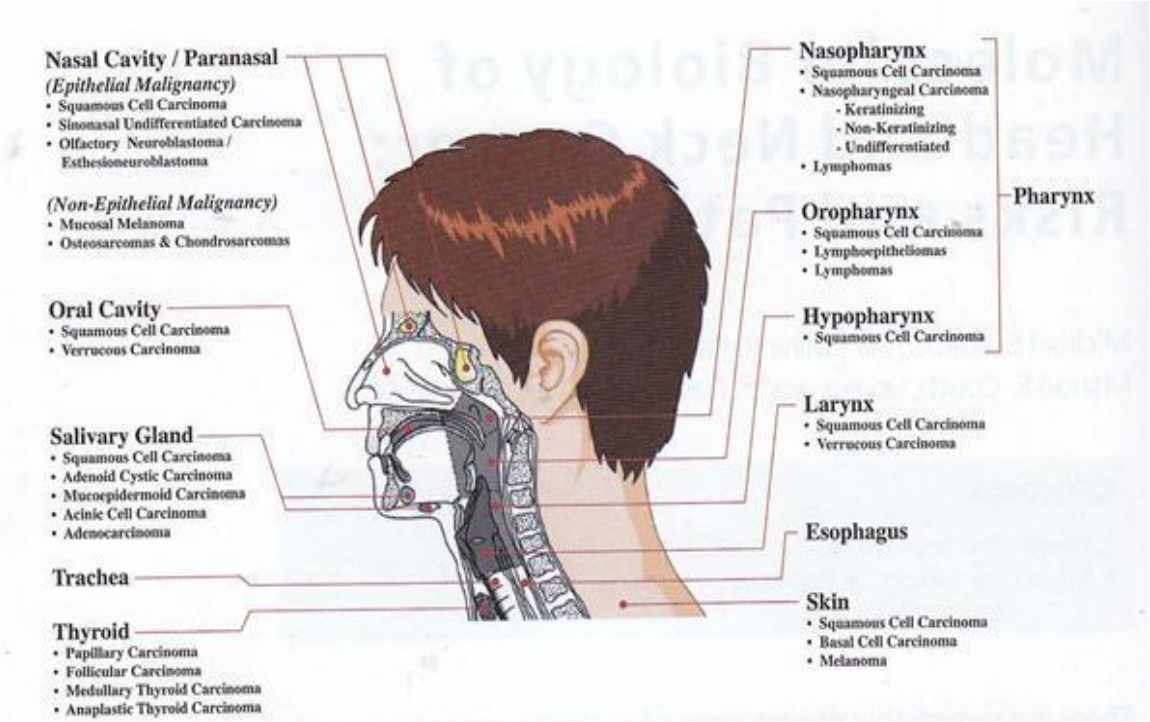
ANATOMY

For the benefit of staging, stratifying treatment protocols and comparing the results of all modalities of treatment, it is must to divide the head and neck epithelial regions into sites such as oropharynx, hypopharynx and larynx, which were included in this study and oral cavity, nasopharynx and nasal cavity and paranasal sinuses which were not.

Oral cavity:

It is further subdivided into subsites such as lips, anterior 2/3rd tongue, buccal mucosa, alveolar ridge, hard palate, retro molar trigone and floor of mouth.

Figure -1: Head and neck anatomy



Oropharynx:

The oropharynx is the postero inferior continuation of the oral cavity. From above downwards, it extends from the superior surface of soft palate to the superior surface of the hyoid bone or vallecula. The oropharynx contains base of tongue, soft palate and uvula, tonsillar pillars- anterior and posterior. It also contains the glossotonsillar sulci, the pharyngeal tonsils, and the lateral and posterior pharyngeal walls.

Base of tongue: It is bounded anteriorly by circumvallate papillae, its lateral limit is the glossotonsillar sulci, and posterior limit is the epiglottis. The vallecula is a strip of mucosa that is in the transition from the base of the tongue to the epiglottis. But it is considered a part of the base of the tongue.

The muscles of the base of tongue are continuous with the anterior two third of the tongue.

Tonsillar fossa: Its anterior limit is anterior tonsillar pillar; posterior limit is posterior tonsillar pillar; inferiorly bounded by glossotonsillar sulcus and pharyngoepiglottic fold. Laterally the tonsillar region is bounded by the pharyngeal constrictor muscle and its fascia, the mandible, and the lateral pharyngeal space. Glossotonsillar sulcus separates it from base of tongue. Beneath the mucous membrane of the sulcus the styloglossal muscle and the stylohyoid ligament are present.

Soft palate: It is a thin, mobile muscle complex .The epithelium of oral side of the soft palate is squamous while the epithelium of the nasopharyngeal surface is respiratory type. It is continuous laterally with the tonsillar pillars.

Larynx

The larynx is composed of many cartilages connected by ligaments and muscles. It is divided on anatomic considerations into the supraglottic, glottic, and subglottic regions.

Supraglottis: Contains of the epiglottis (infra and supra hyoid), false vocal cords, ventricles, aryepiglottic folds and arytenoids. The arytenoids are cartilages which articulate on the cricoid.

Glottis: It contains the true vocal cords and includes their superior and inferior surfaces and their anterior and posterior commissures.

Subglottis: The subglottis is 2 cm long. It extends from five millimetres below the free edge of true vocal cords to the inferior border of cricoid cartilage.

The preepiglottic space is a potential space bounded by the epiglottis posteriorly, the hyoepiglottic ligament and vallecula superiorly, and the thyroid cartilage and thyrohyoid membrane anteriorly and laterally. It can be seen as a low-density area on a computed tomography.

The supraglottic structures have a moderate to rich lymphatic supply. The lymphatic vessels pass via pre-epiglottic space and thyrohyoid membrane to the level II group. Some trunks drain directly to level III or IV group. Lymphatics capillaries are absent in the true vocal cords; hence, if any lymphnode spread from carcinoma glottis, is usually due to tumor extension to supraglottis or sub glottis. The sub glottis has few lymphatic capillaries.

The lymphatic vessels pass via thyrocricoid membrane to pretracheal nodes in the region of isthmus of thyroid, or the trunks may drain into the level IV nodes. The pretracheal nodes are midline and, their salient feature is even when clinically positive, are 1 cm or less in diameter.

Posterior drainage of subglottis to the level IV nodes is through the cricotracheal membrane.

Hypopharynx

The posterior pharyngeal wall extends from base of skull low down to lower border of cricoids cartilage. The lateral pharyngeal wall is a narrow strip of mucosa that lies behind the posterior tonsillar pillar in the oropharynx, and then continues down into the hypopharynx. Here it forms the lateral wall of the pyriform fossa.

The pyriform fossa is made up of three walls: the anterior, medial, and lateral (there is no posterior wall). The pyriform sinus tapers inferiorly to the apex and usually terminates variably at a level between the superior and inferior borders of the cricoid cartilage. Superior limit of pyriform sinus is opposite the hyoid. The thyrohyoid membrane is lateral to the upper portion of the pyriform sinus, and the thyroid cartilage, cricothyroid membrane, and cricoid cartilage are lateral to the lower portion. Superiorlaryngeal nerve (internal branch), a branch of vagus, lies under the mucous membrane on the anterolateral wall of the pyriform fossa. The auricular branch is sensory to the skin of back of the pinna and the posterior wall of the external auditory canal.

The postcricoid pharynx is funnel shaped to direct food into the gullet. The superior margin begins just below the arytenoids. The anterior wall lies behind the cricoid cartilage and is the posterior wall of lower larynx. The

posterior wall is a continuation of hypopharyngeal walls. Recurrent laryngeal nerve lies between the lateral wall and the deep surface of the thyroid gland.

PATHOLOGY

Most of the head and neck malignant neoplasms arise from the epithelium and are squamous cell carcinoma. There are few variants of this such as, lymphoepithelioma, spindle cell, basaloid and verrucous carcinoma.

In general, poorly differentiated cancers are more prone for the regional metastases, so prognosis is poor. Pathological grade is not a consistent predictor of prognosis. Features that predict aggressive behaviour and poor prognosis include perineural spread, lymphatic invasion and extracapsular extension (ECE) of lymphnode.

Morphologically, four types of growth patterns are recognized.

Ulcerative: It is the most commonly occurring type. It is oval or round ulcer that is friable in nature.

Infiltrative: Ulcerative lesions extending deeply into underlying tissues become an infiltrative growth.

Exophytic: It usually grows superficially and metastases occur at later stages when compared to the other types. It looks like an area of thickened epithelium.

Verrucous cancer: It is a rare variety, commonly occurs in older age group. Its occurrence is associated with poor oral hygiene and ill-fitting dentures. It is bulky, warty and raised fungating lesion. It never gives rise to metastases.

Other tumor types:

Other less common histological types are

Sarcomatoid carcinoma, Mucoepidermoid carcinoma, Adenoid cystic carcinoma, Adeno carcinoma, Melanoma, Ameloblastoma, Mucosal melanoma, Small cell undifferentiated cancer, Esthesio neuroblastoma (Olfactory neuroblastoma), Kaposi's sarcoma, Lympho epithelioma, Hodgkin's lymphoma and Nonhodgkin's lymphoma

Grades

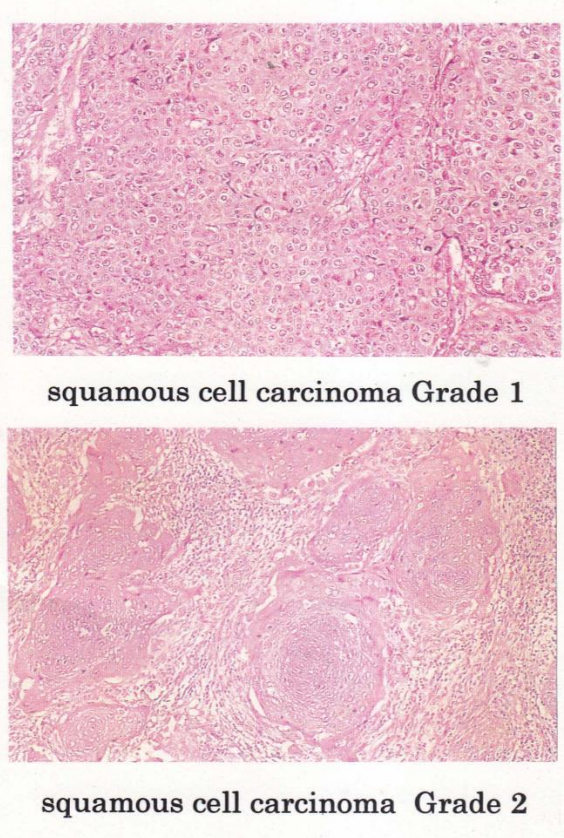
Grade 1: well differentiation

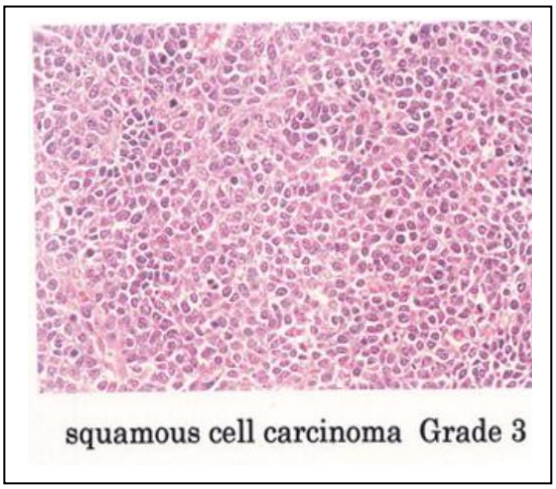
Grade 2: moderate differentiation

Grade 3: poor differentiation

Grade 4: undifferentiation

Figure – 2: Grade 1, 2 and 3 squamous cell carcinoma





PATTERNS OF SPREAD

Spread is dictated by local anatomy and varies by each anatomical site. By direct spread muscle is invaded and spread along the fascial planes to involve adjacent soft tissue structures also occurred.

Tumor may attach to periosteum or perichondrium but involvement of bone and cartilage is a late event. Bone or cartilage act as barriers to spread and its invasion is indicative of a biologic aggressiveness of SCCHN. Slow

growing neoplasms of the oral cavity may produce a smooth pressure defect of the underlying bone without actual bony erosion.

Spread of tumor into space allows superior or inferior spread from base of skull to lower neck.

Perineural spread is observed in muco epidermoid carcinoma which predicts a poor locoregional control rate. Tumors with perineural spread may track along the nerve to base of skull, central nervous system and also peripherally which may lead to neurological symptoms. Invasion of the vascular space lead to the development of regional and distant metastases.

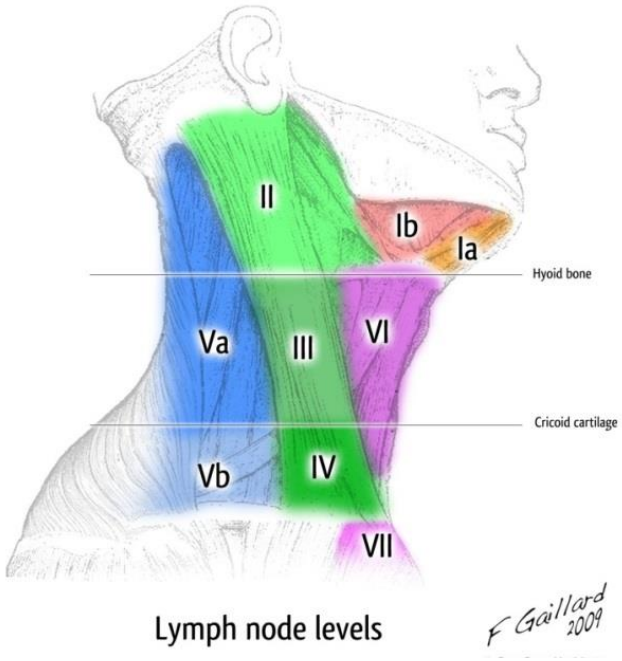
Lymphatic spread

Lymphatic involvement depends on the staging, histology, grade and site of the tumor and also the presence of vascular space invasion and the density of lymphatics. By studying the occurrence of node positive cases by elective neck dissection or by determining the probability of regional recurrence, the risk of sub clinical disease in a clinically negative neck can be obtained.

The relative incidence of clinically positive nodes is determined by the anatomic site of primary and T stage. Well lateralized lesion will spreads to ipsilateral neck. Midline lesions spread to both side; carcinoma of tongue base

and nasopharynx will involve both sides of neck even when it is situated well laterally.

Figure -3: Lymph Node Levels in the Neck



Patients with large or multiple clinically positive ipsilateral nodes are at risk of developing contralateral disease. Disturbance and obstruction of the lymphatic pathways by surgery or Radiotherapy shunts the lymphatic flow to the opposite side. Contralateral metastases from a well lateralized lesions most commonly involves the level II node; sometimes may be bypassed the level II and involves level III or level IV.

Table – 1: Lymphatic drainage of head and neck

Ia	Submental group
Ib	Submandibular group
II	Upper deep cervical group
III	Mid deep cervical group
IV	Lower deep cervical group (transverse cervical)
V	Spinal accessory chain lymph nodes
VI	Prelaryngeal, pretracheal, paratracheal group
VII	Superior mediastinal lymph nodes

The incidence of retropharyngeal adenopathy is based on the primary site and presence of clinically involved nodes. Involvement of lymph node levels is predictive of the primary site. Lip and oral cavity tumors spread to level I initially. Laryngeal and pharyngeal cancers involve levels II and III.

Distant spread: (haematogenous spread)

Risk of distant metastases is related to neck stage (N stage), lymph node location and site of primary. Risk is less than 10% for N0 or N1 neck and 30% for N3 and N1 or N2 below thyroid notch. Hypopharynx and oropharynx carcinomas give distant metastases more commonly than oral cavity. Lung is the commonly involving organ in metastatic SCCHN (50%), next coming are liver and bone.

HISTORY, PHYSICAL EXAMINATION AND DIAGNOSTIC WORK-UP

Detailed clinical history of the patient including the history of usage of tobacco, alcohol, oral sex, and other environmental exposures which are mentioned in etiological risk factors should be taken. Patient with symptoms suggestive of malignancy of upper aerodigestive tract of more than two weeks duration or with an asymptomatic neck mass should be evaluated further carefully.

PHYSICAL EXAMINATION

Thorough physical examination we can find even the early lesions of the aerodigestive tract and also the multiple primaries which are common in upper aerodigestive tract. This will also indicate the severity and the duration of the disease.

Physical examination should be done in a systematic manner so that any point is not going to be missed. Frequently overlooked part of the examination like searching for ulcers, nodules, pigmented and other suspected lesions should be done carefully.

Cranial nerve examination is must for all patients of head and neck tumor or mass. Any discharge, bleeding and drainage from eyes, nose and ear to be looked for.

Examination of the oral cavity should be done completely. Looking for halitosis and Trismus is must. Bimanual palpation of the floor of mouth, tongue, buccal mucosa should be done with one finger inside the mouth and other outside the mouth. Mandible is to be palpated for involvement; any tenderness, thickening, discharge, sinuses etc. to be noted and biopsy of the suspected lesions are to be taken.

Nose: External nose, anterior nares, alae and vestibule should be carefully examined.

Neck: Neck examination is to be done systematically to look for the location of any mass. Palpation is an important step in the examination of neck. Mass and the nodes are palpated between the thumb and index or middle finger.

The location, size, consistency, fixity and tenderness of the node are to be examined.

Posterior Rhinoscopy:- To see choanae, entire nasopharynx .

Anterior rhinoscopy:- To see the vestibule, nasal septum, lateral wall and floor of the nasal cavity.

Indirect Laryngoscopy: For examining the Base of the tongue, Vallecula, hypopharynx and the larynx. Inspection and mobility of the vocal cords is to be evaluated. This provides an overall picture of the mobility and asymmetry indicating the presence of an occult tumor.

Direct Laryngoscope:- Thorough visualization of the nasal cavity, nasopharynx, oropharynx, hypopharynx and larynx can be done and pooling of secretions to be noted. Individual subsites also to be looked into for any doubtful lesions.

Endoscopy:- Because of the field cancerisation patient with Head and neck malignancy will have a 5% of chance of Synchronous primary that is SCCHN, lung or oesophagus. Laryngoscopy(direct), oesophagoscopy and bronchoscopy (Triple endoscopy) to be done in all patients with an unknown primary and in a known primary of HNC and doubtful lesions are biopsied. These can also provide details about the extension of disease.

DIAGNOSTIC IMAGING

Chest X-ray:– to see for any pulmonary metastases or a second primary.

Orthopantomogram:- To look for involvement of bone in oral cavity lesion.

USG: It can pick up few non palpable nodes; can provide information on whether a node is malignant or benign; can differentiate a thyroid gland mass from lymph nodal mass.

CT scan

It delineates the extent of the tumor (both primary and secondary) and can differentiate the solid from cystic lesion.

The site of an unknown primary with secondary neck node can be identified by CT scans of chest, abdomen and pelvis. It has advantage over MRI in detecting bony erosions. With its high spatial resolution fat, muscle, bone and other soft tissues are easily identified.

Dynamic contrast CT [DCC]: With the use of less contrast agent, it is able to differentiate blood vessels from malignant mass and lymph nodes.

Spiral CT: It is faster than DCC and it has the capacity for multiplannar reconstruction without compromising on the quality of scan.

MRI: It gives information about the size, location and the extent of the tumor accurately. Gadolinium enhanced MRI is very useful than CT for imaging nasopharyngeal and oropharyngeal carcinoma. Main disadvantage is movement artifact particularly in larynx and hypopharyngeal carcinomas.

STAGING

The staging for the primary lesions (T) is done by using The American Joint Committee on Cancer (AJCC) (2010). The AJCC (2010) neck staging (N) is common to all head and neck sites, except the nasopharynx[19].

T staging is done purely depending on the individual site. But N staging remains common for all. The size of the node (≤3cm, 3-≤6cm, >6cm), whether ipsilateral, contralateral or bilateral, should be taken into account for N staging. The level of the involved lymph node is also considered in nasopharyngeal carcinoma staging. In general, the level of lymph nodal involvement helps in aiding the plan for treating elective lymph nodes.

PROGNOSTIC FACTORS

Neck node involvement (any stage) is the single most important prognostic factor in determining the survival of a HNC patient (besides tumor status).

Neck node involvement reduces the 5 year survival rate by 50%.

Nodal size (N2 or N3) and extra capsular extension are distinct prognostic features. The risk of neck failure and poor survival are fairly high.

Multiple lymph node involvement or contralateral nodal metastases denote a poor treatment outcome.

TREATMENT OVERVIEW

For practical purposes, SCCHN can be divided into 3 clinical stages:

1) early disease
2) locoregionally advanced disease
3) Metastatic/recurrent disease.

Of these 50-60% is locally advanced at presentation. Treatment approaches for each stage vary.

EARLY STAGE DISEASE

Usually single modality treatment with either Surgery or Radiotherapy provides comparable and efficacious locoregional control and survival results.

Surgery:

Surgical resectability of a head and neck cancer is assessed by a multidisciplinary team. An adequate margin of 1.5 cm to 2cm is required to obtain a clear frozen section. Any suspected margin of < 2 cm has to be

examined by a frozen section. A clear margin and close margin can be defined as a distance of ≥ 5 mm and <5mm from the resected margin to the invasive tumor, respectively. Primary is usually approached through trans oral, transcervical routes or, through mandibulectomy.

Reconstruction is done by using skin graft, free tissue transfer, regional flap, or by primary closure. Reconstructed area should functionally and cosmetically resemble the resected tissue.

Neck dissection:

Elective neck dissection is done in clinically node negative neck. Therapeutic neck dissection is done in clinically apparent nodal disease. Based on the clinical, radiological and preoperative finding, therapeutic dissections may be either selective or a comprehensive neck dissection. Tumors approaching midline or tumors with bilateral lymphatic drainage like base of tongue, palate, and supraglottis should undergo dissection in both sides of neck.

Radiotherapy:

Primary disease and involved neck nodes are to be treated by 66 to 70 Gy of radiotherapy in conventional 2 Gy fractions. Low to intermediate risk lymph nodes are to be treated electively between 44 and 60 Gy. Advanced tumor stage, depth of invasion, perineural invasion, multiple node positivity,

vascular invasion and lymphatic invasion require postoperative radiotherapy. Post operative chemo radiotherapy is indicated when there is extra capsular extension and positive margins. Postoperative radiotherapy is usually administered in 6 weeks or less. Radiation may be delivered either in conventional or altered fractionation.

Surgery Vs Radiotherapy

The advantages of surgery over radiotherapy are one time procedure, limited amount of tissue is exposed to treatment and shorter hospital stay. Also disadvantage of radiation like acute and late toxicity can be avoided and radiation can be reserved for salvage purposes and second primaries. The advantage of radiation therapy is organ preservation and thereby function preservation.

LOCOREGIONALLY ADVANCED CANCERS

Aggressive multimodality treatment is needed to achieve cure in these patients. Therapy for locally advanced SCCHN has the major goals of eradicating locoregional disease, treating distant micrometastases, preserving organ function, and minimizing toxicities.

In the past, 5 year survival for loco regionally advanced cancer was only forty percent (ten to thirty percent for patients with stage IV A and IV B tumors). Most of the patients developed recurrence due to loco regional

failure. Any treatment which produces good locoregional control is the best one. Altered fractionation schedules have also been studied clinically. Even with the best possible modification of RT regimens, only a 50% to 70% local control rate and 30% to 40% Disease Free Survival (DFS) was achieved[21].

Hence multimodality treatment is necessary to achieve good locoregional control. 50% to 60% of locoregionally advanced cancer patients develop locoregional recurrence within two years even after surgery, radiotherapy, or both and 20% - 30% of patients landed in distant metastases. So, chemotherapy was investigated to maximize the response along with radiotherapy, either as induction, concurrent or adjuvant[21].

Induction chemotherapy

Overall response rate of induction chemotherapy using cisplatin and 5FU that was shown in various trials was complete response in 20 to 30%. It also decreased the occurrence of distant metastasis because of the early effect on micro metastasis in the circulation. But induction chemotherapy failed to show any survival benefit. The recent phase III randomised trial (DeCIDE trial) which using docetaxel, cisplatin and 5FU as an induction chemotherapy followed by concurrent chemo radiation also failed to show any survival benefit when compared to concurrent chemo radiation[22].

Concurrent chemo radiation

Concurrent chemoirradiation has shown clinically significant benefit with better locoregional control as well as survival benefit. During the past 2 decades definitive concurrent chemoirradiation has shown to improve survival and organ preservation in locally advanced Head and Neck Cancer[23]. Recent meta-analysis reveals an survival benefit (absolute) of 4.5% for chemoirradiation (neoadjuvant, concurrent, adjuvant chemoradiation) in SCCHN, and 6.5% for concurrent chemoradiation over RT alone[24]. The advantage of the adding chemotherapy to historical treatment is same in all sub sites of SCCHN[25]. Concurrent platinum based chemoradiation regimens have demonstrated improved disease control rates compared to those obtained using radiotherapy alone and is the most commonly used chemotherapeutic agent in clinical use[24], with manageable toxicity. So at present the standard of care in patients with locally advanced and unresectable head and neck cancer is concurrent chemo radiation using single agent high dose cisplatin.

Increased toxicity is noticed in combination chemotherapy group. The purpose of adding chemotherapy to radiation is to enhance the effect of radiation. So it is important to complete the radiation therapy within the scheduled time. It is not good to interrupt radiation in between because of acute toxicity of combination chemotherapeutic agents. So single agent chemotherapy is the preferred option.

Adjuvant chemotherapy

The use of adjuvant chemotherapy has a theoretical benefit of eradicating the sub clinical disease left behind after chemo radiation. The increased sensitivity of minimal residual disease to anticancer drugs has been shown by cell cycle and growth fraction studies. It is also postulated that adjuvant chemotherapy sterilizes the micro metastasis present in the circulation and thereby prevent distal recurrence rate and improve overall survival rate. Unfortunately these theoretical benefits are not proved by any randomised control trials. So its use is far from definitive.

PALLIATION

Majority of the patients presenting to the clinicians come in locoregionaly advanced stage, in our country and these cases are found to be unresectable and also not fit for any form of curative treatment. Also many patients presenting in stage III will have poor performance scores. These patients will not tolerate curative treatment. Few patients presenting in older ages also fall under the same category. These patients will be benefitted with palliative radiation and supportive care.

PALLIATIVE RADIOTHERAPY (PRT)

Most of the cancer patients, in fact all, have many distressing symptoms to be addressed with or to be palliated. Some of the important

symptoms are pain, dysphagia, odynophagia, earache, difficulty in speech, trismus, bleeding from the tumor site, respiratory difficulty, stridor, etc. The ideal method of palliative treatment should be like this. It should produce the best possible symptom relief and good quality of life to the patient at the same time with least possible side effects and toxicities.

This palliation can be achieved with either palliative radiotherapy alone or in combination with other agents such as weekly chemotherapy, metronomic chemotherapy, targeted agents or hypoxia modifying agents.

Palliative radiotherapy (PRT) carries the advantage of effective palliation and good QOL in advanced and unresectable SCCHN[26]; also a significant amount of cancer care across the world is constituted by PRT. But, looking into the literature, there are very few studies about Palliative radiotherapy in HNC. Especially for palliative RT, because the patients completing the treatment protocol were very less and also poor accrual to prospective trials the assessment of outcome becomes difficult. And also in our country the personnel and radiation equipments are very much limited which led to delay in treating the patients with radiotherapy[27]. Because of this, the comparison of the trials which are available in the literature on radiobiological aspect is not a possibility and so is the toxicities and the leading QOL outcome obtained. Severe toxicities both early and late, due to radiotherapy should be avoided when treatment is aimed for palliation. And

hence the treatment protocol should be individualised and the patients are treated as per the department protocols. Multiple factors such as performance status, comorbidities, patient preference, etc. should be considered while decision making.

Recommended PRT schedules were the following

50 Gy in 20 # (fractions) over 5 weeks

30 Gy in 10 # over 2 weeks

30 Gy in 5 #, 2 # per week +/- 6Gy boost

37.5 Gy in 15 # over 3 weeks

3.125 Gy * 16# over 3.2 weeks (Christie Scheme)

3.7 Gy twice daily for 2 consecutive days, repeated after 4 weeks (RTOG 8502 regimen, QUAD-SHOT)

3 Gy twice daily, day 1 and day 3, repeated every 2 weeks for 4 cycles

24 Gy in 3#, 0-7-21 schedule

When treating an end stage patient with limited prognosis and survival, more hypofractionated schedule can be considered.

According to the current guidelines, the benefit of curative intent treatment should be given even to patients with an advanced SCCHN also taking into consideration the recent advancements in treatment.

Still few factors can be considered about patient's selection for palliative intent treatment alone.

1) fixed, unresectable and inoperable tumors (primary and secondary)

2) very advanced, incurable loco-regional cancer with poor general condition and medical comorbidities;

3) metastatic disease and patients with limited expected survival.

BEST SUPPORTIVE CARE

The treatment provided for cancer apart from altering the disease process, can affect the patient's physical, psychosocial and cognitive health, etc. And the additional steps taken to improve them along with the cancer-specific treatment are collectively called supportive care. In few circumstances such as incurable disease post treatment, the only possible way left behind for the benefit of the patient is Best Supportive Care.

Best supportive care includes[28]

1) The management of pain, vomiting, anemia (due to cancer and cancer treatment), fatigue and distress

2) Prevention and treatment of infections due to cancer.

3) Palliative care and nutrition support.

Very advanced head and neck diseases can be any of the following[29]:

1) Locoregionally advanced disease, newly diagnosed

2) Unresectable nodal disease, newly diagnosed

3) Persistent or recurrent tumors

4) Metastatic disease newly diagnosed or post treatment

5) Patients not fit for surgery

While deciding the treatment options for these advanced and unresectable cases the Eastern Cooperative Oncology Group (ECOG) status should be taken into consideration. For patients with ECOG 0 - 2 and treatment naive without metastatic disease, concurrent chemoradiation with curative intent can be given. Best supportive care with Palliative RT is the option for patients with ECOG 3. For ECOG 4, only best supportive care is the possibility. Patient's preference to decide treatment option should also be taken into account. Early referral to hospice care should also be considered for ECOG 3 and 4 patients, post treatment recurrence and incurable cases.

REVIEW OF LITERATURE

Palliative radiotherapy trials:

From a large study of the past, it was observed that PRT neither improves survival, nor positively impacts on QOL of patients with SCCHN[30]. Further studies are contradictory to this observation. Eventhough there is no large randomized controlled trials to show high level of evidence for using PRT in head and neck cancers, a general conclusion can be obtained from several retrospective studies [31.32.33] case-control studies [34, 35] and single arm prospective studies [36, 37, 38, 39, 40] and they confirm that palliative treatment is associated with an improved outcome at least in the locoregional and symptom control.

Lok BH et al.,(2015)[41] reported on the results of palliative RT using **RTOG 8502 regimen** that is popularly known as QUAD-SHOT (3.7Gy twice daily over 2 consecutive days repeated after 4week interval). 37% patients completed atleast 3 cycles of RT. They recorded a palliative response in 65% of patients. Median survival was 5.67 months. Grade 3 toxicity was observed in 5% of patients only. Those with palliative response are those who received more number of RT cycles. Palliative response, good PS and more number of RT cycles are the independent predictors of survival.

Nguyen et al.,(2015)[42] treated advanced HNSCC patients using hypofractionated regimen named as "0-7-21", which treated patients with

24 Gy in three fractions. Among 110 patients, complete response for symptoms and tumour size was seen in 40% and 31%, partial response was seen in 42% and 50%, respectively; stable disease was seen in 15%. Also there was a median 6-month OS of 51% and 39% PFS within the irradiated field. They found that advanced TNM stage resulted in a poorer tumour response, significantly.

Monnier et al.,(2013)[43] reported on 78 patients treated with palliative radiotherapy using the IHF2SQ regimen (Irradiation HypoFractionnée 2 Séances Quotidiennes). Patients were treated with 3 Gy BD per day (days 1 and 3), during the week 1, 3, 5 and 7 of treatment. All patients were fit to receive concurrent platinum-based chemotherapy; Tolerance was excellent. They observed a complete or partial response in 41% of patients. A very excellent median OS of around 13 months and median PFS of about 11 months were observed. One-year OS, specific survival (SS), and PFS were 58%, 71%, 51.5%, respectively.

Erkal HS et al.,(2001) [31] studied retrospectively, the results of palliative RT to 40 cases of unknown primary with advanced neck node, with 30 Gray in 10 fractions over 2 weeks and 20 Gray in 2 fractions with one week break in between. That resulted in a good one year local control of 77%, along with a 68% improvement in symptom relief. Hence higher doses of palliative RT were associated with better outcomes.

Carvalho et al.,(2000)[35] studied on patients with advanced HNC who received treatment and those who did not receive any treatment until their death. They reported on the survival rates of the untreated group and the treated groups and found a significant difference between them. Also this difference was significant and independent of any type of treatment received or the tumor response obtained.

Paris KJ et al.,(1993)[36] conducted a palliative RT study which has used fractionated radiotherapy of 370 cGy per fraction given 2 times daily for 2 consecutive days, totally 4 fractions, which was repeated every three to four weeks achieving a total dose of 42 Gray over a period of 9 weeks. Good palliation was reported in 33 of 37 patients with tolerable acute toxicity. They achieved a mean survival of 4.5 months.

Ghoshal S et al., [38] **(2004)** treated 25 advanced SCCHN patients with short course palliative radiotherapy of 30 Gy in 10 fractions over 2 weeks. 11-point numerical symptom assessment scale was used to assess baseline symptoms. After 1-month of PRT, >50% symptomatic relief was seen in all 22 patients with pain and more than 90% of the patients with swallowing difficulty, respiratory distress and insomnia. 60% patients were relieved of cough. The median duration of symptom relief achieved was 3 months. A point to be noted was none developed grade 3 toxicity.

Evidence for the presence of Hypoxia in solid tumor:

Tumour hypoxia in human neoplasms was proved with histologic evidence and was first reported in **1955.** Later on, direct measurement by microelectrodes within the tumor has shown much heterogeneity in oxygen concentrations. Researchers have found a low oxygen concentration is associated with poor locoregional control by either by RT or chemotherapy. These earlier findings along with the recent results of nuclear imaging studies using radiolabelled misonidazole, provide strong evidence for the presence of tumour hypoxia. These findings influence not only RT but also any treatment outcome. **(Lee DJ et al. 1996)**

Moulder JE et al.,(1984)[44] reviewed determinations of hypoxic fraction in 42 tumor systems. From these, they found that radiobiologically hypoxic cells appear to be present in most of the macroscopic solid rodent tumors. Also the hypoxic fraction increases as the tumor size increases; but the dependence of hypoxic fraction on tumor size at macroscopic sizes was not well established. Few factors that may influence the hypoxic fraction were the site of tumor implantation, the use of anesthesia, and certain host characteristics. Also there was a correlation between the hypoxic fraction, the tumor growth rate, transplantation history and the histology. Their final conclusion was that the hypoxic cells are present in solid tumors in rodents

and also **shows no evidence that hypoxic cells should not be present in human tumors.**

It has been shown from many preclinical studies that solid tumors may contain oxygen-deficient areas known as hypoxic areas and because of these cells, tumors may become radioresistant. Hence identification of hypoxic cells in human tumors has become important and this can be accomplished with the use of new imaging and physiologic techniques. Also there existed a considerable heterogeneity among individual tumors **(Overgaard 2007)**[45].

There are evidences to conclude that a high level of hypoxia in solid tumors has a direct link with adverse prognostication in the evolution of a malignant tumor, especially after treatment. **The lack of oxygen in the blood has been correlated with poor tumor response to treatment [32, 33].** This resistance can be explained on the radiobiological effects of hypoxia. **Hypoxia is also a marker of aggressive tumor phenotype and it is blamed for the resulting poor prognosis and high likelihood of recurrence** after surgery [34, 35]. Furthermore, hypoxia may be responsible for tumor resistance to some oncological agents [36].

Hypoxia is a common phenomenon in HNSCC and increases resistance to chemotherapy and radiotherapy. Quantification of hypoxia with PET has been attempted and it is used for evaluating the extent of benefit of using

radiosensitizing drugs. F18-FDG PET-CT is the most commonly used investigation for monitoring response to treatment in HNSCC. Few other PET radiopharmaceuticals have been discovered and they have a role in assessing the response when biological agents such as EGFR inhibitors or VEGF inhibitors are used [37].

There are radiopharmaceuticals such as 18F-Fluoromisonidazole that selectively accumulate in the hypoxic tissue, with minimal uptake in well oxygenated normal tissues. This tracer compound provides several advantages such as, the biological characterization of head and neck tumors prior to radiotherapy, and hence gives an idea about the prognostic information in response to treatment [38]. This characterization leads to an advantage of using more specific treatment, in addition to radiotherapy, when tumor hypoxia is found in molecular therapy using PET-CT [38]

THE OXYGEN EFFECT:

Ionizing radiation produces free radicals which lead to cell death by causing single and double strand breaks. Oxidation is the process involved in fixing this damage. Molecular oxygen can react with these free radicals to produce many downstream molecules which are highly lethal to the cell. But when there is hypoxia within the tumor cells this beneficial effect will not occur. Oxygenated cells respond to ionizing radiation 2.5 times more than the hypoxic cells.

HYPOXIA AND HYPOXIC MODIFICATIONS:

Several strategies[46] have been putforth by the researchers to modify and target hypoxia related therapeutic resistance, such as

1. Enhancing the oxygen delivery, by using hyperbaric oxygen or cargogen breathing, **ARCON** (accelerated radiotherapy with carbogen and nicotinamide) treatment,

2. Hypoxic radiosensitizers, by using misonidazole and nimorazole and

3. Hypoxic cytotoxin, such as tirapazamine.

G.E.Adams et al. (1979)[47] studied on nitroaromatic and nitroheterocyclic compounds that can be used as "radiosensitizers". They tested these compounds for their cell kill efficacy toward hypoxic Chinese hamster cells in vitro. They found a directly propotional correlation between the cytotoxicity and the resultant electron affinity. One important observation is that **Non-nitro-containing compounds of similar electron affinities (such as quinones) eventhough acted as radiosensitizers, did not show this specific toxicity toward hypoxic cells.** This observation tells that the presence of a nitro group is important for a compound to produce the hypoxic cell toxicity.

R.J.Knox et al., (1981)[48] studied on the various compounds that act as radiosensitizers. **Since the mechanism of producing the desired**

cytotoxicity is identical in each case (viz. DNA damage) it shows a directly propotional correlation between different rates of reduction of the drugs, and their relative electron affinity. It has been established from the previous studies that the nitroimidazoles in hypoxic cells had good metabolic reduction rates. **Olive (1979a, 1980)** studied on this and showed a correlation with electron affinity and electrolytic reduction at constant potential. The results of these studies support their hypothesis that **the cytotoxic mechanism of action of reduced nitroimidazoles is very similar in hypoxic mammalian cells, bacteria and protozoa.**

A meta-analysis of 50 randomized trials treated more than **7000 patients with this hypoxic** modification. **It resulted in improvement in the loco-regional tumor control after radiotherapy with an odds ratio of 1.17**. Site wise categorization showed an improved response in head and neck **and to a lesser extent in bladder tumors was responsible for the significant difference**; yet there was no significant difference in other tumor sites such as cervix, lung, central nervous system, and esophagus. **The overall survival rate was improved with an overall odds ratio of 1.13**. But there was no significant chemosensitization or direct bioreductive effect. The main confounding factor that may be responsible for this reduced observed benefit was less number of patients included. It had been concluded that however, the overall results prove that the biological modification of tumor hypoxia

appears to be very effective, at least in head and neck and bladder carcinoma. Future studies related to the hypoxic problem should focus on these sites **(Overgaard 1994)**[49].

For eliminating or modifying the source of radiation resistance, clinical trials conducted during the last 40 years have come out with a conclusion that this can be achieved **by the use of normobaric or hyperbaric oxygen or by the use of nitroimidazoles as hypoxic radiation sensitizers**. Recent studies have also focused on **hypoxic cytotoxins, a group of drugs that selectively or preferably destroys cells in a hypoxic environment.** The review of results from 86 randomized trials on modification of tumor hypoxia in 10,108 patients treated with curative attempted primary radiation therapy alone, found a significant improvement in the effect of radiotherapy, with an odds ratio of 0.77 for locoregional control and an odds ratio of 0.87 for overall survival benefit. But still the hypoxic modification has no impact on general clinical practice **(Overgaard 2007)**[45].

Hypoxic modification by various nitroimidazole group of drugs has been explored in a large number of clinical studies. Nine different drugs such as misonidazole, metronidazole, benznidazole, desmethylmisonidazole, etanidazole, pimonidazole, nimorazole, ornidazole, and RSU 1069, have been tested fit for clinical evaluation as hypoxic radiosensitizers. Trials had shown a significant relationship between the drug tolerance and expected hypoxic

modification. **The most tolerable drugs among all are found to be 5-nitroimidazoles**, but they had smallest activity. Still, **they may be more clinically active than others, due to higher tumor/plasma concentrations.** The extent of benefit obtained with this additional drug cannot be exactly measured, since clinically important hypoxia can be observed only indirectly.

A major breakthrough in the treatment using hypoxic radiosensitizer is the report published by Danish head and Neck Cancer Study (DAHANCA) Protocol 5-85. **Jens Overgaard et al. (1997)**[50] assessed the efficacy and tolerance of nimorazole given as a hypoxic radiosensitizer concurrently with primary radiotherapy of invasive carcinoma of the supraglottic larynx and pharynx. Among the 422 patients who were randomized between nimorazole and placebo arms, **the nimorazole group showed a significantly better loco-regional control rate than the placebo group** (49 versus 33%). **A final loco-regional control (including surgical salvage) and cancer-related deaths were calculated and they too showed similar significant benefit in favour of nimorazole**. **This benefit was also translated into the 10-yr overall survival but was not significant**. They found that the most important prognostic parameters for loco-regional control to be

1. Positive neck nodes
2. T3–T4 tumor and
3. Nimorazole

The compliance to treatment was at its best and about 98% of the patients received the planned dose of radiotherapy. Late radiation-related morbidity was same in both the arms and was about 10%. Transient nausea and vomiting were the commonest drug-related side-effects. They concluded that **Nimorazole significantly improves the effect of radiotherapy in supraglottic and pharyngeal tumors and can be given without major side-effects.**

Sugie C et al., (2005)[51] from Japan, reevaluated the radiosensitizing effects of sanazole (3-nitrotriazole) and nimorazole (5-nitroimidazole) compounds in vitro and in vivo, in comparison with a fluorinated 2-nitroimidazole derivative KU-2285. They found no sensitizing effect under aerobic conditions at 1 mM in vitro. But in vivo, under hypoxic conditions, the sensitizer enhancement ratio (SER) determined at 1% cell survival level for sanazole, nimorazole and KU-2285 was 1.55, 1.45 and 1.95, respectively. Hence in vivo, all three compounds had significant radiosensitizing effects; **their effects appeared to decrease in the order of KU-2285, sanazole, and nimorazole. It was suggested that sanazole may be more suitable for clinical trials than nimorazole.**

Another hypoxic radiosensitizer drug used in clinical trials was etanidazole. This drug was used in 374 patients in **European Etanidazole (ETA) trial** and they concluded no advantage of adding the drug to RT. The

RTOG ETA trial which included 504 patients also showed no global benefit. However, under subset analysis positive results were observed in patients with early nodal disease (197 patients) **(Lee DJ et al. 1996)**[52].

Rischin et al. (2010)[53] reported on the clinical outcome and the effects of tirapazamine in combination with cisplatin and radiation in patients with advanced HNSCC; and reported a good response with a 3-year failure-free survival rate of 69%. The 3-year local progression-free rate and overall survival rate were 88% and 69%, respectively.

Nimorazole:

Nimorazole is a 5-nitroimidazole of same structural class as metronidazole. It is the only hypoxic radiosensitizer drug proved to be beneficial in phase III randomized clinical trials. Also this drug has the advantages of easy administration through oral route and low cost compared to other methods of hypoxic modification. Nimorazole was lack of any significant side effects except for mild nausea, vomiting, flushing and skin rashes. This drug is available in the 500mg tablet formulation. Recommended dose in trials was 1.2 gm/m^2 BSA and hence they used three, four or five tablets for patients with ≤ 1.6 m^2 BSA, $>1.6 - \leq 1.9$ m^2 BSA, > 1.9 m^2 BSA, respectively.

Misonidazole:

This compound mimics the effects of oxygen due to its high electron affinity, and thereby fixes the radiation damage and restores the radiosensitivity. Nimorazole and misonidazole, both produced significant improvements in the clinical outcome. But one major problem with misonidazole was peripheral neuropathy, at doses used for radiosensitization. Overgaard reported on the randomized controlled trials using misonidazole in 626 pharynx and larynx carcinoma patients. The tumor control results were excellent but 26% of patients developed significant peripheral neuropathy.

Hypoxia and Radioprotective agents:

Travis EL (1984) reviewed the role of oxygen in the protection of both normal tissues and tumors in vivo by **WR-2721 (aminothiol)**. It is hypothesized that sulphydryl compounds by acting on both tumors and normal tissues removed the OER differential between them and thus remove the natural advantage (radioresistance) of the tumor when treated with radiation. He concluded that there was no loss of therapeutic benefit when sulphydryl compounds were given along with radiation in conditions with the normal tissue being better oxygenated than the tumor, because tumor contains hypoxia.

PREVIOUS ARTICLES RELEVENT TO THE PRESENT STUDY

Al mamgani A et al. (2009)[54] treated LAHNSCC patients, with a hypofractionated radiotherapy consisting of 16 fractions of 3.125 Gy **(Christie Scheme)**. Most of the patients were male, of which 31% had oropharyngeal primaries and 81% were in stage IV disease. They observed an enthusiastic **overall response rate of 73%** (45% CR + 28% PR) **and 6% stable disease. 21% of patients had progressive disease.** A good median survival time of 17 months was achieved and 62 patients (40%) survived ≥ 1 year after RT. The loco-regional control, DFS and OS rates were 62%, 32% and 40% at 1-year, respectively; and the 3-years figures were 32%, 14% and 17%, respectively. 45% and 65% of patients developed acute grade ≥ 3 skin and mucosal toxicities, respectively. **50% gained in weight, 77% improved in pain, 47% improved in performance status among the patients surviving ≥1 year after RT**; and at the end, patients who were feeding-tube dependent was 29%.

Mohamed A. Hassan Metwally et al. (2014)[55] retrospectively studied the compliance and toxicity profile of 1049 patients with HNSCC, treated in Denmark between 1990 and 2013. Their protocol was radical RT (+/- chemotherapy) [66 – 70 Gy; 33 – 35 fractions]. All patients received concomitant hypoxic radiosensitizer nimorazole 1.2 g/m2 body surface area as oral tablets. Those patients, who were treated with accelerated fractionation

regimen, received a second daily dose of 1g. The compliance to treatment was calculated as the percentage of the initially prescribed dose received by the patient. They concluded that the tolerance to nimorazole was fair: compliance was 58%. Nausea and vomiting were the major complaints recorded. 87% of side effects were due to nausea/vomiting. **All side effects disappeared when treatment was stopped temporarily and all of them were neither severe nor long lasting.** Female patients and those aged more than 70 years developed more significant nausea/vomiting. In the accelerated chemoradiotherapy arm the tolerance was less and more patients had nausea/vomiting. They concluded that nimorazole had tolerable acute, but neither persistent nor late, toxicity and can be safely administered with chemotherapy and different radiotherapy fractionation schedules.

Meta-analysis of 32 randomized clinical trials on the modification of tumor hypoxia, included 4805 patients with HNSCC treated under 5 trials of normobaric oxygen or carbogen breathing, 9 trials of hyperbaric oxygen (HBO), **17 trials of hypoxic radiosensitizers and 1 trial on HBO and radiosensitizer together.** The overall hypoxic modification of radiotherapy produced a significant improved therapeutic benefit for all types of modifications. There was a very little advantage in the reduction of risk of distant metastasis. The important observation was that there was no significant change in the radiation related late complications. **Different**

fractionation schedules, including large doses per fraction, have been used in these trials, which were thought to result in relatively more hypoxia and hence greater benefit. However, analysis of HNSCC trials using conventional fractionation only, showed that the significant effect of hypoxic modification was maintained **(Overgaard 2011)**[56].

AIMS and OBJECTIVES of present study

Primary Objective:

- To assess the immediate loco regional response rates of locally advanced head and neck squamous cell carcinoma after 6 weeks of treatment protocol
- To assess the degree of symptom relief

Secondary Objective:

- To assess the acute toxicity of the treatment

INCLUSION CRITERIA

- Biopsy proven cases of SCCHN
- Primary tumor sites: oropharynx, hypopharynx, supraglottic larynx
- Non metastatic disease
- Unresectable and locoregionally advanced cases
- Stage IV A with performance status ECOG 3
- Stage IV B with performance status ECOG 2 or 3
- Age: 18-70

- Blood counts: TC > $4*10^3$/cu. mm, Platelet count > $100*10^3$/cu. mm, Hb. > 10 gm%
- Signed informed consent prior to initiation of protocol specific procedures

EXCLUSION CRITERIA

- Primaries of oral cavity, nasopharynx, nasal cavity and para nasal sinuses, salivary and thyroid glands
- Uncontrolled medical comorbidities, connective tissue disorders
- Prior chemotherapy or radiotherapy
- Second primary malignancies in any site
- Recurrent or relapsed disease

PRE-TREATMENT WORK UP AND GENERAL MEASURES

- History and physical examination (with complete Head and Neck examination)
- Base line symptom assessment using symptom assessment scale (SAS).
- ENT examination and OGD scopy, as clinically indicated

- Biopsy of the primary site
- FNAC from the enlarged lymph node
- Baseline complete hemogram
- Blood grouping and typing
- Renal function tests
- Contrast enhanced computed tomography (CECT) of the primary and neck, from base of skull to root of neck
- Chest X-ray PA view- digital
- HIV – 1&2,
- HBsAg, Anti HCVAb,
- Dental evaluation
- Smoking and alcohol cessation counselling
- Nutrition, Speech and Swallowing evaluation
- Prophylactic feeding tube placement, if indicated

MATERIALS AND METHODS

30 patients presenting to our department who were eligible to be included as per the study protocol, were selected. Patients were enrolled into the study after obtaining approval from the Institutional Ethics Committee for conducting this study. Information sheet on the study protocol was given to all patients and the study was explained briefly to them. After that oral and written informed consents were obtained from all the patients before including in the study.

After the pre-treatment work up, patient preparation and dental prophylaxis, patients were treated with external beam radiotherapy to the primary and neck nodes, 48 Gy in 3 Gy# over 3.2 weeks, 5# per week, using Cobalt-60 teletherapy machine (Theratron Phoenix) in palliative intent. In addition to this, patients received Tab.Nimorazole 1.2 gm/m^2 daily (only on RT days), orally, 90 min before radiation. Dose of Nimorazole is based on body surface area: ≤1.5 m^2 BSA - 1500mg (3*500mg tablets), >1.5 m^2 BSA - 2000mg (4*500mg tablets).

Response evaluation was done using RECIST criteria. The pre-treatment volumes of the primary and nodal tumor were recorded and compared with post-treatment status. The symptoms experienced by the patients at the baseline, at the end of treatment and 6 weeks after treatment were recorded using symptom assessment scale. The common side effects of

treatment protocol such as nausea, vomiting, flushing and rashes and acute radiation induced toxicities were looked for while under treatment, at the end of treatment and 6 weeks after treatment.

Patient preparation and Prevention of toxicities:

Patients who were found to be anemic were given blood transfusion. Local infection was controlled with antibiotics. Before starting antibiotics, pus culture and sensitivity was ordered, when clinically indicated. Patients were given counselling on adequate and nutritious food intake by a dietician. Patients having significant weight loss, dysphagia or those who are at risk of developing dysphagia were advised Naso Gastric tube feeds.

Those with poor oral hygiene and extensive stains of teeth were referred for scaling and oral hygiene improvement. Those patients with teeth that reside within the high dose radiation volume that demonstrate advanced caries, significant periodontal disease, etc., were referred for dental prophylaxis and extraction. All those who underwent extraction were given prophylactic antibiotics. OPG was taken if clinically indicated and any infected retained root tips or symptomatic cysts if present, were dealt with. A gap of 2 weeks was allowed for the extractions to heal, before the start of radiotherapy.

Oral care also includes prevention and treatment of mucositis and pharyngitis. They were advised to use gargling with soda bicarbonate

dissolved in water, about 4 times daily, especially after any food intake. Candidiasis was treated with topical clotrimazole oral paint for 2 weeks; if the lesions are not resolving then oral fluconazole tablets 150 mg OD were given for 10-14 days.

Nutritional support:

Most of the HNC patients lose weight not only due to cancer but also treatment related toxicities. So nutrition management is very important to prevent/ reduce the treatment related complication and thereby improve the therapeutic outcome of treatment.

All the patients were motivated to take adequate nutrition to prevent excessive weight loss. Those patients with significant weight loss (>5% of weight in the month before / >10% of weight in the previous 6 months) were advised prophylactic nasogastric tube or PEG (percutaneous endoscopic gastrostomy) placement. In extreme cases where nutritional support by enteral route was not possible or not adequate, parenteral (intravenous) nutritional support was given.

Specific meal plans were developed for individual patients. The meal plans were designed so that they were as close to the normal diet as possible. The patient's weight was checked serially every week, to evaluate the patient's nutritional intake. Depending on the weight the meal plans were revised, if needed. The meal plans were designed with the idea of the

increased caloric and protein requirements of the patient for tissue regeneration.

From the third week of treatment, side effects of radiation will start and hence the patients were advised to take liquid diet. The radiation induced dysphagia and mucositis were mainly due to pharyngitis and laryngitis. Also during this stage patients start developing xerostomia, which adds up to the difficulty in swallowing solid foods; also making the foods to stick to mucosa and induces vomiting. The patients were advised to take a sip of water with each bolus of food; plenty of fresh fruit juices like apple and guava will also help and citrus fruits like lemon and Mozambique may be avoided. A special home- made high protein food using banana, egg and milk, or protein formulations were advised twice daily.

Smoking cessation:

Smoking and alcohol cessation counselling were advised, if found to be current smokers advised to quit smoking and if they were past smokers advised to remain so.

Screening for depression:

A brief screening for depression was done and counselling +/- drug therapy was advised. Psychiatrist advice was obtained when needed.

Radiotherapy Technique:

Radiotherapy was delivered in right and left lateral parallel opposed portals and the dose was prescribed to the midline with equal weightage; with patient in left and right lateral positions; with a telecobalt Theratron Phoenix machine with 2D technique; in 300cGy per fraction, 5 fractions per week, up to 16#. Treatment volume included the primary tumor site and level II-VB neck nodal regions. Level IB was included in involved cases. 1 cm margin for setup error was added. A bolus was used when skin infiltration both by the tumor or by the lymph nodal mass, was present; and also for all ulcerated lymph nodes.

In cases with N3 neck nodes on one side with clinically N0 on the other side, a 2:1 weightage will be given in RT dose distribution. Offcording is done after 30Gy. Many of the posteriorly placed nodes interfered with usual off-cording. Hence off-cording was individualised to each patient as per the location of the nodal mass.

PRE TREATMENT ASSESSMENT OF SYMPTOMS

The most common distressing symptoms experienced by the patients were assessed at the start of treatment, during and after treatment. There are many systems to assess this. We used the 11 point symptom assessment scale (SAS).

Symptom assessment scale

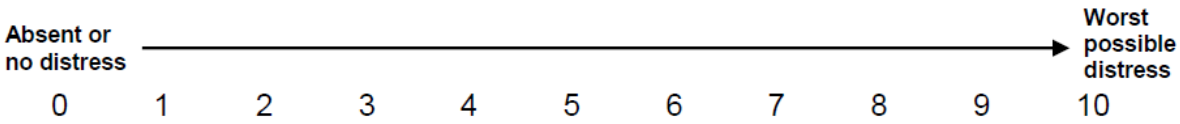
The SAS describes the patient's level of distress relating to individual physical symptoms. The instrument was very much patient-friendly and designed to be a patient rated tool.

How to assess?

Patient can himself rate the degree of distress for each of their symptom. If patient is not able to do so, family members/ attenders are asked to rate the degree of distress. But it is always better if the patients rate their own symptoms for accuracy and consistency.

Figure- 4: 11-point numeric scale

11-point numeric scale was used to assess the symptom.



If there is no Symptom, rating was given as '0'. If Symptoms present rating was given from 1 to 10.

<u>All the patients were given the information that,</u>

A score of 0: no symptoms

A score of 1: very minimal/least possible distress

A score of 10: the worst possible distress.

Assessment was done at the baseline then every week after starting the treatment and at 6 weeks post treatment.

ASSESSMENT IN BETWEEN TREATMENT

Pain and other symptoms experienced by the patients before treatment were continued to be assessed while on treatment, using SAS.

Toxicity of radiotherapy: the following toxicities were assessed for their presence and severity, at the end of every week of treatment, using RTOG acute toxicity grading.

- Skin reactions
- Mucositis
- Xerostomia
- Laryngitis
- Pharyngitis
- Hb level
- Complete blood counts

Toxicity of Nimorazole: the following toxicities were assessed for the presence and severity, at the end of every week of treatment, using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

- Nausea / Vomiting
- Flushing
- Skin rashes

SUPPORTIVE CARE AND TOXICITY MANAGEMENT

Along with the management of the treatment related toxicities, patients were given supportive care to tackle their other symptoms due to their disease. Few among them were:

- Management of cancer pain, vomiting, cancer related anemia, fatigue and distress.
- Prevention and treatment of infections due to cancer.
- Palliative care and nutrition support.

All patients were registered in palliative care OP department. After assessing the patients completely, Tab.morphine 5mg fourth hourly was given along with anti depressants, sedatives and laxatives, for those who needed. They were instructed to take morphine ‘by the clock’ method and not ‘by the pain’. Patients taking morphine were given syrup liquid paraffin or bisacodyl

tablets and advised about the possible side effect of constipation, and hence the need for plenty of oral fluids and fiber intake. All the patients were reviewed once in a week for the degree of symptom relief.

Vitamin B-complex and vitamin C tablets were given to all. Packed cell transfusion was given to the patients whose haemoglobin levels falls to <10gm%. All patients were given prophylactic vitamin B_{12} injection, once weekly during treatment. Proper cleaning and dressing of the wound was done for ulcerated, fungated nodes and primaries. Such patients were given higher antibiotics coverage for 7 to 10 days.

The nausea and vomiting were managed by antiemetics and steroids; Inj.Ondansetron 8 mg i.v. twice daily and Inj. Dexamethasone 4mg OD was given. Those patients who cannot take adequate oral fluids were also given i.v. fluids to prevent dehydration.

For the prevention and treatment of mucositis all patients were advised to maintain good oral hygiene and gargling 4-6 times a day using soda bicarbonate dissolved in water. Patients were also instructed to apply honey 15 minutes prior to the radiation, 15 minutes after radiation and 12 hours after radiation. If the patients develop mucositis, they were treated by using analgesics (NSAIDS), low dose steroids, placentrex injection and if severe, prophylactic antibiotics. NSAIDS used was Diclofenac sodium tablets 50 mg twice daily. The steroid used was dexamethasone 4 mg IV twice daily if the

patients developed grade III mucosities. All patients with grade III mucositis were treated with antibiotic, cephalexin 500 mg four times daily.

NSAIDS and antitussives were given for grade II pharyngitis and laryngitis. Steroids were included in the management of all grade III toxicities. Opioid analgesic, inj.tramadol was given for all grade III mucositis, pharyngitis and laryngitis. Candidiasis was treated with clotrimazole mouth paint.

RESPONSE EVALUATION:

Patients were evaluated **after 6 weeks** of the treatment protocol.

Subjective response:

Degree of symptomatic relief was assessed using symptom assessment scale.

The patients were grouped based on their degree of relief in symptoms, into three viz., those having <25%, 25 - <50%, ≥50% relief. Those with ≥50% improvement was said to have significant relief of symptoms[57].

Objective response:

Response in the Primary and Nodal tumor was assessed clinically and radiologically. Patients were asked to take a CT scan of the primary and neck (plain and contrast). The response was categorized using RECIST criteria:

- Complete response (CR) – absence of residual tumor at any site after treatment
- Partial response (PR) - ≥30% decrease in the size of the tumor from baseline
- Stable disease (SD): Neither sufficient shrinkage nor sufficient increase in size
- Progressive disease (PD): 20% increase in size from base line

The toxicities to the treatment such as radiation induced morbidities and toxicities specific to nimorazole were assessed at the end of 6 weeks.

FOLLOW UP OF PATIENTS

Patients who completed the treatment protocol were asked to review once in 2 weeks to assess and treat the toxicities, if any. After 6 weeks, they were asked to come for assessing the response to the treatment. All patients were advised to take a CT scan of the primary and neck with contrast. Patients were followed up every month thereafter.

RESULTS

AGE DISTRIBUTION

Totally 30 patients were enrolled in the study. Eligible age limit for the study was from 18 to 70 years of age. The age of the patients ranged from 52 to 70 years. The median age of the patients included in the study was 65 years.

Table - 2

AGE GROUP (in Years)	No. OF PATIENTS	PERCENTAGE (%)
51 – 60	13	43.3
61 – 70	17	56.7

13 patients were in the age group of 51 – 60 and 17 were in the age group of 61-70. Age distribution analysis of the sample showed that, most of the patients were in age the group of above 60 years.

SEX DISTRIBUTION

All the 30 patients were males. This skewed selection towards the male gender was probably due to the increased exposure of carcinogens in the males than in females.

SITE DISTRIBUTION:

Among the 30 patients, primary site of the disease was oropharynx in 15 patients, hypopharynx in 9 and supraglottic larynx in 6.

Table -3

Site	No.of.patients	Percentage (%)
Oropharynx	15	50.0
Hypopharynx	9	30.0
Supraglottic Larynx	6	20.0

The site wise distribution of the cancer patients included in the study showed, majority of the tumors were from oropharynx.

SUBSITE INVOLVEMENT:

OROPHARYNX- SUBSITE DISTRIBUTION

Table-4

Sub site	No.of.patients
Tonsillar fossa	9
Posterior 1/3rd tongue	4
Soft palate	2

Among the 15 cancer of the oropharynx patients, tonsillar fossa in 9, posterior one third tongue in 4 and the soft palate in 2 were the principal subsites involved.

HYPO PHARYNX-SUB SITE DISTRIBUTION

Table- 5

Sub site	No.of.patients
Pyriform fossa	5
Posterior pharyngeal wall	3
Post cricoid region	1

Among the 9 hypopharyngeal cancers patients, pyriform fossa in 5, posterior pharyngeal wall in 3 and post cricoid region in 1 were the principal subsites involved.

LARYNX- SUB SITE DISTRIBUTION

Six supraglottic cancer patients were included in the study.

PRIMARY TUMOR CHARECTERISTICS

Majority of the patients were in T3 and T4 stage.

Table -6; T STAGE

T stage	No.of.patients
T1	3
T2	4
T3	10
T4a	10
T4b	3

Among the 30 patients, 3 were in T1, 4 were in T2, 10 were in T3, 10 were in T4a and 3 were in T4b stages, respectively.

Table -7; N stage distribution

N stage	No.of.patients
N2b	6
N2c	4
N3	20

Majority of the patients were in N3 stage. Among the 30 patients, 20 were in N3, 6 were in N2b and 4 were in N2c stages, respectively. Out of them 6 patients presented with ulcerated nodes.

STAGE GROUPING

Table – 8

Stage group	No.of.patients
Stage IVA	9
Stage IV B	21

Most of the patients were in stage group IV B. 21 out of 30 patients was in stage group IV B and 9 were in stage group IV A.

DIFFERENTIATION

Majority of the patients had moderately differentiated tumors. Among the 30 patients 24 had moderately differentiated, 4 had poorly differentiated and 2 had well differentiated tumors.

Table - 9

Differentiation	No.of.patients (%)
Well differentiated	2 (26.7%)
Moderately differentiated	24 (80%)
Poorly differentiated	4 (13.3%)

SYMPTOMS AT PRESENTATION

Table -10

Symptoms	No. of cases who had that symptom
Local pain	25 (83%)
Dysphagia	18 (60%)
Cough	10 (33%)
Otalgia	15 (50%)
Dyspnoea	4 (13%)
Voice change	5 (16%)
Insomnia	23 (76%)

Pain was the most common complaint, and was reported by 83% of the patients. Next common presenting somatic complaints were dysphagia and otalgia, in 60% and 50% of patients, respectively. Insomnia was found in 76% of patients. Other symptoms to note with, in a few at presentation were dyspnoea, cough and voice change. Few of the patients had all the above said symptoms in a mixed form, while others had half or more than half of the above mentioned symptoms.

SYMPTOM ASSESSMENT AFTER TREATMENT

Those with significant improvement (≥50%) in their symptoms were taken into account.

- Local pain improved in 20 out of 25 (80%)
- Dysphagia improved in 12 out of 18 (66%)
- Otalgia improved in 12 out of 15 (80%)

All together the treatment protocol resulted in good symptom relief and hence a better QOL in a good proportion of patients.

RESPONSE ASSESSMENT IN TUMOR

Table – 11 (n=30)

Response	No.of.patients
Complete response (CR)	6 (20%)
Partial response (PR)	17 (56.7%)
Static response (SR)	7 (23.3%)
Progressive disease (PD)	0 (0%)

Most of the patients achieved a partial response with this treatment protocol. About 17 patients had a partial response, contributing to a good number of 56.7% response. Although palliation was the main aim of the

study, fortunate results were complete response in 6 patients, which accounts to 20% of patients. None had progression in the disease or tumor burden, during the 6 week response assessment.

OVERALL RESPONSE

Among 30 patients 23 (6 CR+ 17 PR) achieved some form of response in the tumor which yields an overall response rate of **76.7%**.

STAGE GROUP WISE TUMOR RESPONSE ASSESSMENT

Table – 12

Stage group	CR	PR	SR	PD
IV A	6	3	0	0
IV B	0	14	7	0

The complete response which was obtained in 6 patients was solely from the stage group IV A. Most of the patients from stage group IV B attained partial response. None of the patients in any group had progressive disease.

RADIATION RELATED ACUTE TOXICITY ASSESSMENT

None of the patients developed any grade 4 acute radiation toxicities.

Mucositis:

Most of the patients developed grade 2 mucositis after about 2 weeks of treatment. Grade 3 mucositis was seen in 12 patients. In them treatment was suspended to allow for the resolution of mucositis before proceeding with further radiation. Benzydamine mouthwash, inj.placentrex and opioid analgesics were given to hasten the recovery and improve the patient's tolerance.

Dysphagia:

Most of the patients had grade 2 dysphagia. 14 patients developed grade 3 pharyngitis. Treatment was temporarily suspended in them. They were given opioid analgesics in addition to NSAIDs and adjuvant analgesics. Xylocaine viscus and low dose dexamethasone were added.

Dermatitis:

None developed grade 2 or grade 3 skin reactions. Most of them developed grade 1 reaction which was treated with Cansafe ointment, an ayurvedic preparation specially made for radiation induced dermatitis.

Salivary gland toxicity:

Grade 2 salivary gland reaction was seen in 10 patients. Almost all other patients developed grade 1 toxicity. But none had acute necrosis of the salivary gland. All of those who had any degree of xerostomia were prescribed artificial salivary supplements – mouth gargles or mouth spray.

Laryngitis:

Almost all patients had minimal hoarseness of voice and 8 patients developed grade 3 laryngitis in the form of otalgia and opioid analgesics were added.

Haematological toxicity

None of the patients had thrombocytopenia.

None of the patients developed significant haematological toxicities, except for grade 1 anemia, leucopenia and neutropenia. Grade 1 anemia was seen particularly in patients who had low haemoglobin levels prior to starting treatment and for which blood transfusions were given previously, and they were given blood transfusions again.

ASSESSMENT OF TOXICITIES SPECIFIC TO NIMORAZOLE:

None of the patients developed skin rashes or flushing.

NAUSEA

None of the patients developed grade 3 toxicity of nausea. Grade 2 nausea was seen in 4 patients. Grade 1 nausea was seen in some of the patients.

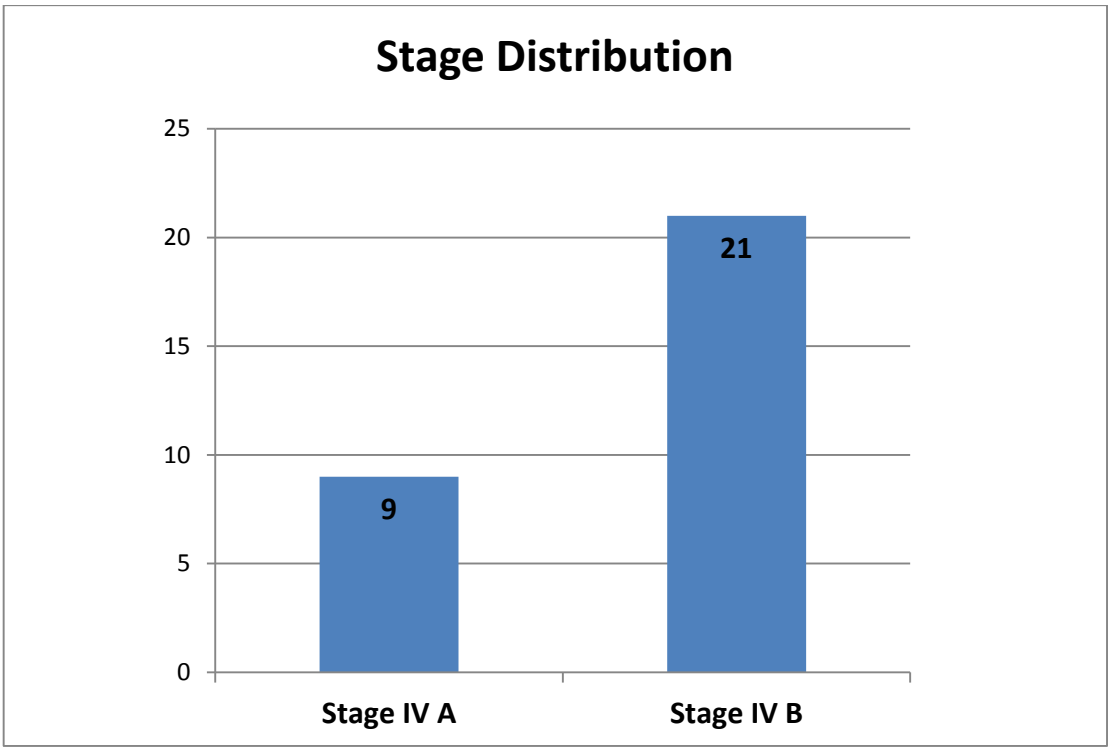
Table - 16

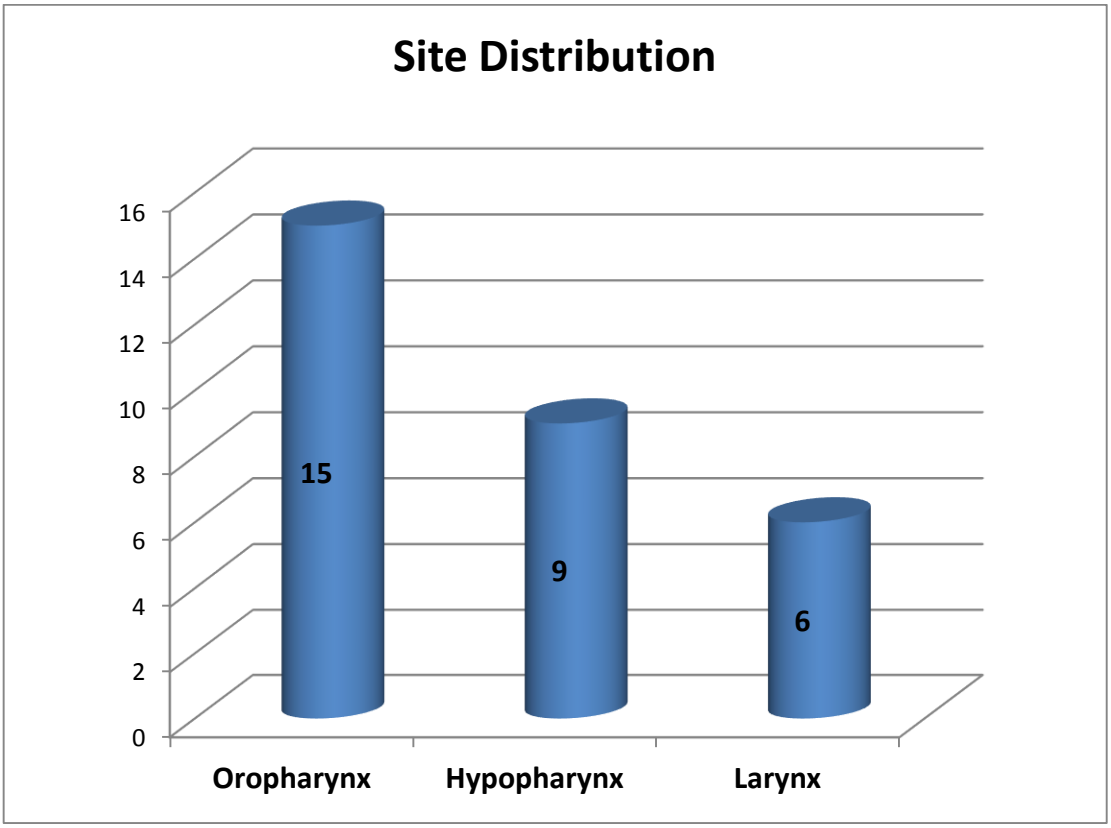
Nausea	No.of cases
Grade 1	12
Grade 2	4
Grade 3	0

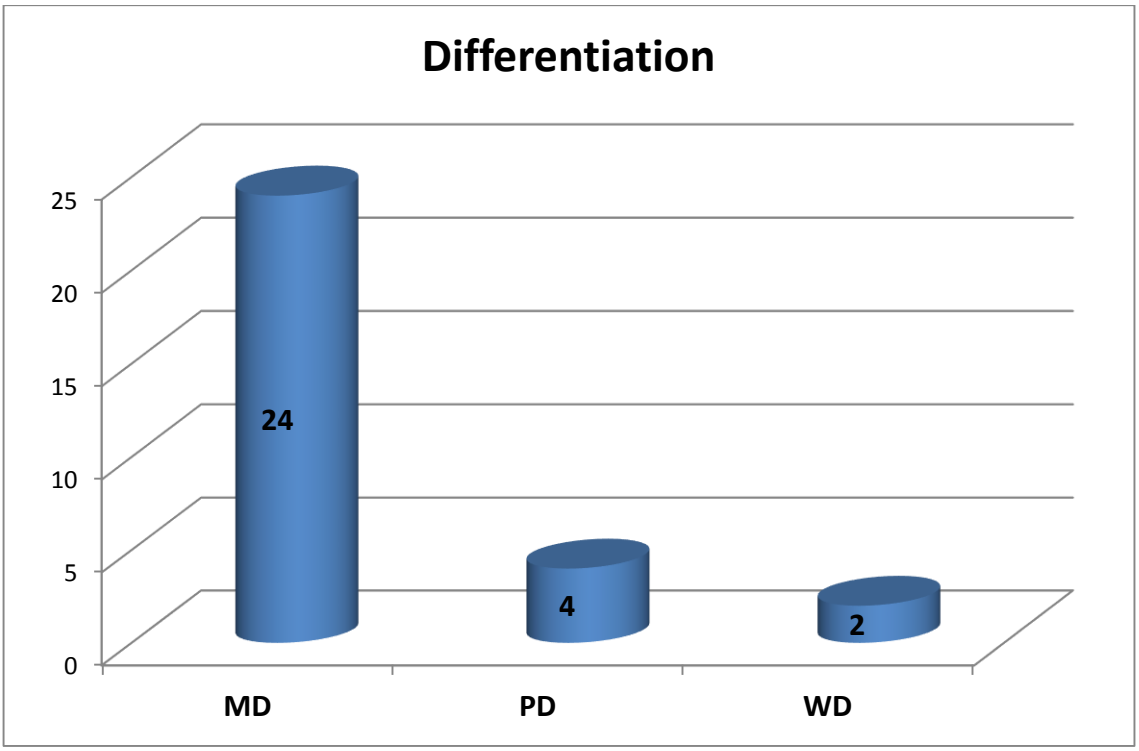
Grade 1 vomiting was seen in 4 patients. None had significant higher grades of vomiting.

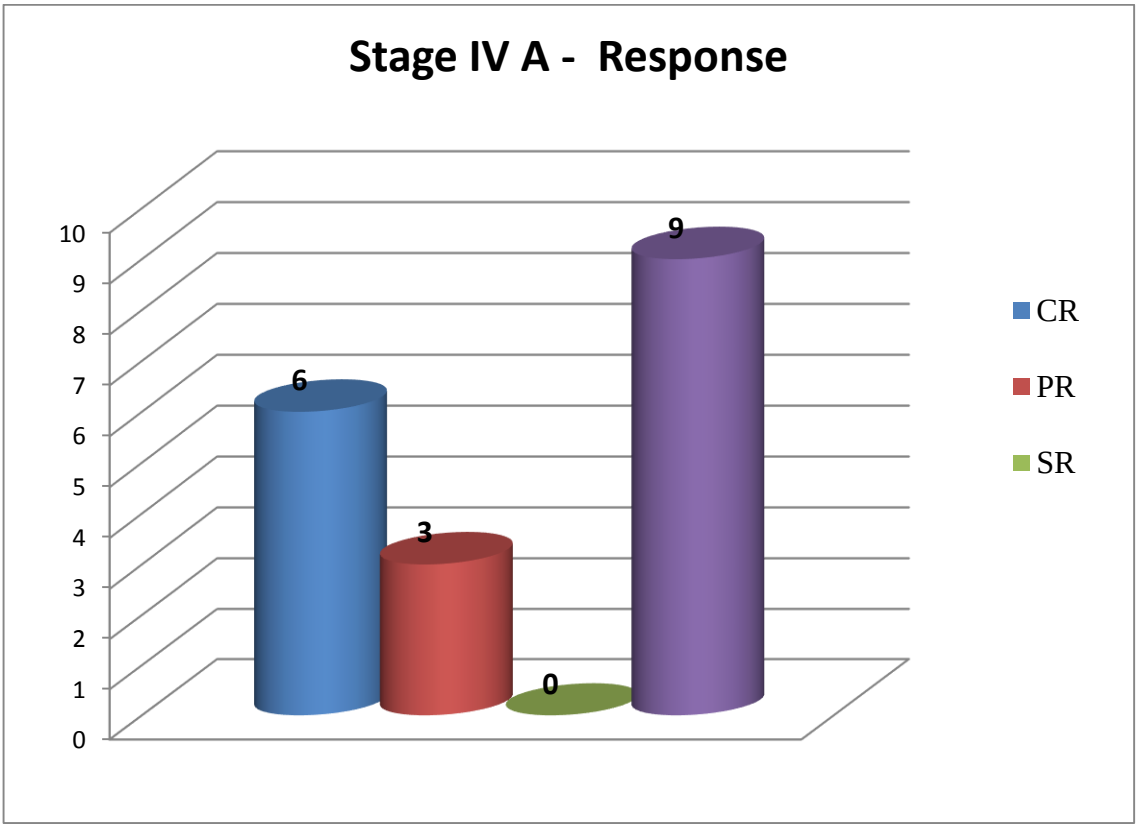
DOSE REDUCTION:

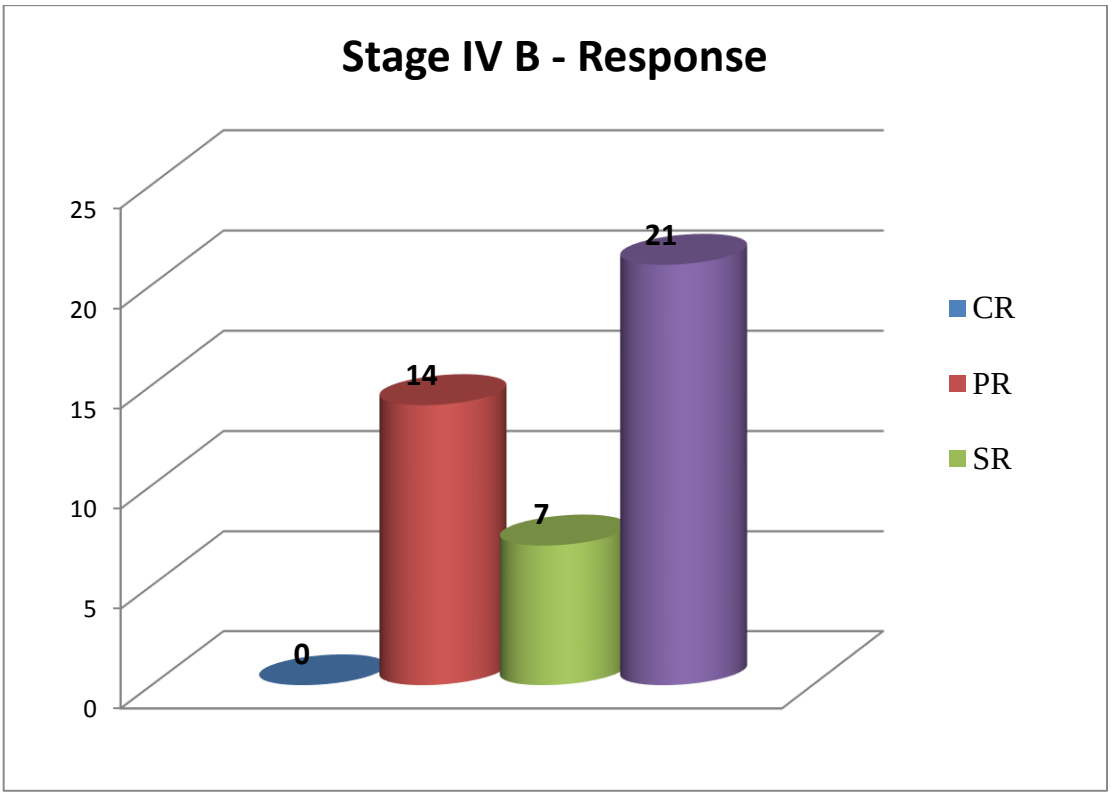
4 patients who developed significant grade 2 nausea had dose reduction in nimorazole. They received 1000 mg instead of 1500 mg per day after developing toxicities, till the end of their treatment.

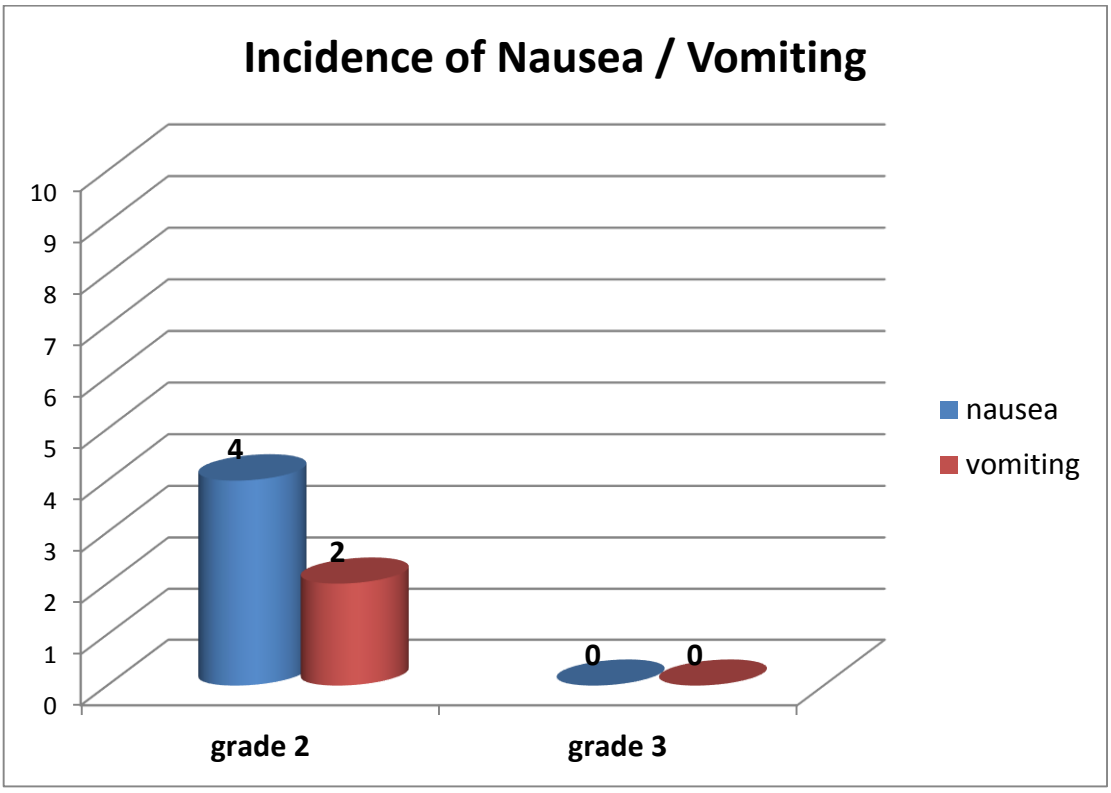

Stage Distribution
25
20
15
10
5
0
9
21
Stage IV A
Stage IV B


Site Distribution
16
14
12
10
8
6
4
2
0
15
9
6
Oropharynx
Hypopharynx
Larynx


Differentiation
25
20
15
10
5
0
24
4
2
MD
PD
WD


Stage IV A - Response
10
9
8
7
6
5
4
3
2
1
0
6
3
0
9
CR
PR
SR


Stage IV B - Response
25
20
15
10
5
0
0
14
7
21
CR
PR
SR


Incidence of Nausea / Vomiting
10
9
8
7
6
5
4
3
2
1
0
4
2
0
0
grade 2
grade 3
nausea
vomiting

DISCUSSION

Majority of the HNSCC cases (60%-80%) in India are presented in advanced stage. Radical treatment is not successful in all of these patients because of poor performance status and unresectability. These advanced and unresectable cases need palliative treatment and/or best supportive care. There is no general consensus regarding palliative schedule in SCCHN. Few researchers have evaluated conventional fractionated radiotherapy versus hypofractionated palliative radio therapy schedules for patients with locally recurrent or advanced HNC. They compared 60 Gy to 70Gy over 6 to 7 weeks with 40 Gy to 48 Gy over 3 to 4 weeks in stages III and IV surgically unresectable SCCHN. No difference was observed in terms of tumor control, acute toxicity and chronic toxicity.

Most of the institutions believe that larger tumors will respond very poorly to conventional fractions of radiotherapy. The general consensus for treating bulky solid tumors of the head and neck with radiotherapy is the use of hypofractionated regimens. The institutional protocol for this in our institute was 48 Gy in 16 fractions of 3 Gy each. Another reason to choose such regimen was the patient load for treatment using EBRT, especiallly in government institutions, so that treatment can be completed soon.

In patients deemed to be incurable, the first aim of any treatment will be improving the Quality of Life, which can be achieved with good symptom

control and to some extent by achieving at least some response in the tumor. Even a minimal response in the tumor could add up to improvement in symptom control. At the same time there should not be any added toxicities. Keeping these things in mind, what sort of further modifications in the treatment can produce such benefits, should be thought of. Hence logically thinking, improvement in the response at the tumor should also be our goal even in a palliative setting.

Patients with poor performance status are generally unfit to receive a radical regimen of chemotherapy both 3-weekly and weekly. Even the reduced dose of weekly chemotherapy will produce some toxicities such as mucositis and myelosuppression, which will land up in increased treatment breaks and more importantly reduced and unacceptable Quality of Life. But as per the guidelines even in LASCCHN cure should be the primary intention in patients with good PS. In patients with poor PS, the treatment should be individualised and hence in this study we safely avoided any chemotherapy to patients along with RT.

Hypoxia and neovascularisation are interdependent. The findings of diffusion-limited hypoxia in human lung cancer are based on the evidence of the presence of necrotic tissue beyond 180μ radius from the capillary margin. Larger and bulky tumors have less neovascularisation and hence more hypoxia. This along with its countertpart, perfusion-limited hypoxia plays a

vital role in making the cancer cells more locally aggressive, metastatic, and resistant to therapy. Hence the hypoxic modification becomes a prime thought, at least in large volume tumors.

Hypoxic modification of radiotherapy has shown clinical benefit in the treatment of HNSCC and to some extent in uterine cervix carcinoma. Nimorazole has been adapted for routine clinical use in head and neck cancer patients in Denmark since 1990, due to the outcome of the DAHANCA 2 and DAHANCA 5 studies which both demonstrated the benefit of hypoxic modification in supraglottic larynx and pharynx cancers. Nimorazole is a 5-nitroimidazole compound used as hypoxic radiosensitizer. Its high electron affinity makes the drug mimic the effect of oxygen in making the tumor more radiosensitive. Though it is less potent than misonidazole its high tumor/plasma ratio brings a similar radiosensitization; and also it lacks the neurological toxicity.

The main advantages with 5-nitroimidazole group of drugs, especially nimorazole are ease of administration through oral route, cost effectiveness, very less toxicities and easily manageable toxicities and hence good patient compliance, and finally easy titration of the dose when toxicities occur.

In the DAHANCA-5 study 51% of the patients achieved the planned drug treatment. **The current study shows that the compliance of patients with the full prescribed dose was 87% (4 patients had dose reduction due**

to side effects). When nimorazole was added to CHART regimen, about 22% of patients developed nausea/vomiting. Few trials added cisplatin with nimorazole and RT. In these it was difficult to assess retrospectively whether the nausea/vomiting were really due to nimorazole. Few studies have demonstrated it to be a fairly tolerable drug.

The patients under 'Christie Scheme' hypofractionated radiotherapy were treated using 16 fractions of 3.125 Gy. The BED equivalent of this was 65.6 Gy_{10} and the EQD_2 was 54.7 Gy and in the present study they were 62.4 Gy_{10} and 52.0 Gy respectively, which were almost similar. Most of them were under stage IV. They observed an overall response rate of 73%. In the present study we observed an overall response rate of 76.7%, which may be attributed to the addition of hypoxic radiosensitizer.

In this present study also, the side effects of nimorazole were in very few patients only and they were neither severe and nor long lasting. Most patients tolerated well. Along with the good symptom control, partial to complete response was attained in the tumor in many patients.

Limitations of the study

In the present study patients were not followed up for long term to arrive at the conclusions such as the duration of symptom relief, loco regional control rate and disease free survival in those who achieved complete response, distant failure rate, progression free survival in those who achieved partial and static responses and as a whole, the overall survival of the patients.

Larger sample size of patients is needed to arrive at a definitive conclusion on the basis of achieving statistical significance.

Radiotherapy dose of 48 Gy achieved an EQD_2 of 52.0 Gy and further dose escalation can be tried in those patients with good tolerance to achieve an EQD_2 of at least 60 Gy with the intent of increasing the response in the tumor, thereby achieving better symptom control and hence better QoL.

CONCLUSION

In patients with LAHNSCC palliative radiotherapy along with Nimorazole effectively restrained the growth of tumor and in few produced cure, achieved good palliation of symptoms and thereby increased the quality of life of patients without any added toxicities, in the short run. Yet long term studies are needed to comment more on this.

Also, this study is trying to strike a balance between economic burden, treatment time and hospital stay and patient load on the machines.

BIBLIOGRAPHY

1. Ferlay, J., Shin, H.-R., Bray, F., Forman, D., Mathers, C. and Parkin, D. M. (2010), Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer, 127: 2893–2917
2. Ferlay J et al. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. Lyon: IARC Press, 2004
3. Noronha V, Tsomo U, Jamshed A, Hai MA, Wattegama S, Baral RP, Piya M, Prabhash K. A fresh look at oncology facts on south central Asia and SAARC countries. South Asian J Cancer 2012;1:1-4
4. Head and neck cancer burden in India ,Manik Rao Kulkarni, International journal of Head and Neck Surgery, January – April 2013;4(1):29-35
5. Population based registry, Chennai Cancer data, 2001-2003, V.Shantha, R.Swaminathan, Nalini, M.Kavitha
6. Wynder EL, Bross IJ (1957). Aetiological factors in mouth cancer; an approach to its prevention, Br Med J 1:1137-1143
7. Mia Hashibe , Paul Brennan , Simone Benhamou, Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst 2007; 99: 777 – 89.
8. Talamini R, Bosetti C, La Vecchia C, Dal Maso L, Levi F, Bidoli E, et al. (2002). Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study.Cancer Causes Control 13:957-964.
9. Mia Hashibe, Paul Brennan, Shu-chun Chuang, et al. Interaction between Tobacco and Alcohol use and the Risk of Head and Neck Cancer: Pooled Analysis in the International Epidemiology of Head and Neck Cancer: Cancer Epidemiol Biomarkers Prev 2009;18:541-550.
10. ACTA otorhinolaryngologica ita lica 2013;33:77-87, Review article, New insights into human papillomavirus-associated head and neck squamous cell carcinoma, P. Boscolo-Rizzo1 et al.
11. Haraf DJ, Nodzenski E, Brachman D, et al. Human papilloma virus and p53 in head and neck cancer: clinical correlates and survival. Clin Cancer Res 1996; 2:755.
12. Laryngorhinootologie. 1999 Jan;78(1):24-7, Genetic predisposition for the development of head and neck carcinomas, Jahnke V

13. Lustig JP, Lugassy G, Neder A, et al. Head and neck carcinoma in Fanconi's anaemia-- report of a case and review of the literature. European Journal of cancer B oral oncology 1995; 31B(1) : 68-72
14. Prime SS, Thakker NS, Pring M. et al. A review of inherited cancer syndromes and their relevance to oral squamous cell carcinoma. Oral oncology 2001; 37(1):1-16.
15. Hecht F, Hecht BK. Cancer in ataxia- telangiectasia patient Cancer Genetics, Cytogenetics 1990; 46(1):9-19.
16. Keukens F,Vanvoorst Vader PC,Panders AK et al. Xeroderma pigmentosum: squamous cell carcinoma of the tongue. Acta Derm Venereology. 1989; 69(6): 530-1.
17. Foods and the cancer connection, American Institute of Cancer Research (AICR) and World Cancer Research Fund (WCRF).
18. Reichart PA, Philipsen HP. Oral erythroplakia - a review. Oral Oncol 2005;41(6):551-561
19. Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29:1446
20. Cancer Res. 1988 Jun 1;48(11):3282-7, Smoking and drinking in relation to oral and pharyngeal cancer, Blot WJ et al
21. Principles and Practice of Radiation Oncology; 5th Edition: Carlos Perez, Luther Brady
22. Ezra E.W Cohen, Theodore Karrison, Masha kocherginsky, Chao H Huang DeCIDE; A Pase III randomised trial of Docetaxel (D), Cisplatin (P), % Fluorouracil (F) (TPF)Induction chemotherapy (IC) in patients with N2/N3 locally advanced squamous cell carcinomas of head and neck, J Clin Oncol 30, 2012 (suppl; abstr 5500)
23. Jean Pierre Pignon, Aurelie le Matire, Emilie Maillard, Jean Bourhis, Meta analysis of chemotherapy in Head and Neck Cancers; An update on 93 randomised control trials and 17,346 patients ; Radiotherapy and Oncology 92 (2009) 4 – 14. Horiot J-C, Le Fur R, N'Guyen T, et al.: Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 25: 231-241, 1992
24. Overgaard, Sand Hansen H, Sapru W, et al.: Conventional radiotherapy as the primary treatment of squamous cell carcinoma of the head and neck: A randomized

multicentre study of 5 versus 6 fractions per week - preliminary report from the DAHANCA 6 and 7 trials. Radiother Oncol 40:S31 1996

25. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer, The Department of Veterans Affairs Laryngeal cancer study group. N. Engl J Med. 1991 Jun 13 ; 324(24)1685-90
26. Chow E, Wu JS, Hoskin P, Coia LR, Bentzen SM, Blitzer PH. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Radiother Oncol 2002; 64:275-80.
27. Hodson DI, Bruera E, Eapen L, Groome P, Keane T, Larsson S et al., The role of palliative radiotherapy in advanced head and neck cancer. Can J Oncol 1996; 6:54-60.
28. ,Support. Care Cancer. 2013 Mar; 21(3): 659–685. doi: 10.1007/s00520-012-1564-y, PMCID: PMC3781012, NIHMSID: NIHMS508307, Concepts and definitions for “supportive care,” “best supportive care,” “palliative care,” and “hospice care” in the published literature, dictionaries, and textbooks, David Hui,
29. Head and Neck Cancer: Emerging Perspectives, John Frederick Ensley
30. Kowalski LP, Carvahlo AL. Natural history of untreated head and neck cancer. Eur J Cancer 2000;36:1032-7
31. Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head and neck mucosal site treated with radiation therapy with palliative intent. Radiother Oncol 2001; 59:319-21.
32. Lusinchi A, Bourhis J, Wibault P, Le Ridant AM, Eschwege F. Radiation therapy for head and neck cancers in the elderly. Int J Radiol Biol Phys 1990; 18:819-23.
33. Isaacs JH Jr, Schnitman JR. Outcome of treatment of 160 patients with squamous cell carcinoma of the neck staged N3a. Head Neck 1990; 12:483-7.
34. Wendt TG, Wustrow TP, Hartenstein RC, Rohloff R, Trott KR. Accelerated split course radiotherapy and simultaneous cis-platin and 5-fluorouracil chemotherapy with folinic acid enhancement for unresectable carcinoma of the head and neck. Radiother Oncol 1987; 10:277-84.
35. Carvalho AL, Salvajoli JV, Kowalski LP. A comparison of radiotherapy or radiochemotherapy with symptomatic treatment alone in patients with advanced head and neck carcinomas. Eur Arch Otorhinolaryngol 2000; 257:164-7.

36. Paris KJ, Spanos WJ, Lindberg RD, Jose B, Albrink F. Phase I-II study of multiple daily fractions for palliation of advanced head and neck malinancie. Int J Radiat Oncol Biol Phys 1993; 25:657-60.
37. Minatel E, Gigante M, Franchin G, Gobitti C, Mascarin M, Bujor L, et al . Combined radiotherapy and bleomycin in patients with inoperable head and neck cancer with unfavourable prognostic factors and severe symptoms. Oral Oncol 1998; 34:119-22.
38. Ghoshal S, Patel F, Mudgil N, Bansal M, Sharma S. Palliative radiotherapy in locally advanced head and neck cancer: A prospective trial. Indian J Palliat Care 2004; 10:19-23.
39. Mohanti BK, Umapathy H, Bahadur S, Thakar A, Pathy S. Short course of palliative radiotherapy of 20Gy in 5 fractions for advanced and incurable head and neck cancer: AIIMS study. Radiother Oncol 2004; 71:275-80.
40. Corry J, Peters LJ, Costa ID, Milner AD, Fawns H, Rischin D, et al . The 'QUAD SHOT'-A phase II study of palliative radiotherapy for incurable head and neck cancer. Radiother Oncol 2005;77:137-42
41. Oral Oncol. 2015 Oct;51(10):957-62. doi: 10.1016/j.oraloncology.2015.07.011. Epub 2015 Aug 14. Palliative head and neck radiotherapy with the RTOG 8502 regimen for incurable primary or metastatic cancers, Lok BH et al.
42. Br J Radiol. 2015 May;88(1049):20140646. doi: 10.1259/bjr.20140646. Epub 2015 Feb 19, hypofractionated palliative radiotherapy: an effective treatment for advanced head and neck cancers. Nguyen NT et al
43. Head Neck. 2013 Dec;35(12):1683-8. doi: 10.1002/hed.23219. Epub 2013 Jan 29., Hypofractionated palliative radiotherapy for advanced head and neck cancer: the IHF2SQ regimen, Monnier L et al
44. Int J Radiat Oncol Biol Phys. 1984 May;10(5):695-712. Hypoxic fractions of solid tumors: experimental techniques, methods of analysis, and a survey of existing data. Moulder JE, Rockwell S.
45. J Clin Oncol. 2007 Sep 10;25(26):4066-74, Hypoxic radiosensitization: adored and ignored. Overgaard J.
46. ISRN Otolaryngology, Volume 2012 (2012), Article ID 708974, 8 pages, http://dx.doi.org/10.5402/2012/708974 Review Article, Hypoxia in Head and Neck Squamous Cell Carcinoma. John Zenghong Li

47. Toxicity of Nitro Compounds toward Hypoxic Mammalian Cells In Vitro: Dependence on Reduction Potential, G. E. Adams
48. Br. J. Cancer (1981) 44, 741, Interaction of Nitroimidazole Drugs with DNA In Vitro: Structure-Activity Relationships, R. J. Knox,
49. Oncol Res. 1994;6(10-11):509-18. Clinical evaluation of nitroimidazoles as modifiers of hypoxia in solid tumors. Overgaard J.
50. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85, 1997, Jens Overgaard
51. Journal of radiation research, PubMedID: 16394636, Sugie C, Shibamoto Y, Ito M, Ogino H, Suzuki H, Uto Y, Nagasawa H, Hori H. Reevaluation of the radiosensitizing effects of sanazole and nimorazole in vitro and in vivo. J Radiat Res.2005;46(4):453-9.
52. Ann Acad Med Singapore. 1996 May;25(3):397-404. Hypoxic sensitizer and cytotoxin for head and neck cancer. Lee DJ et al.
53. J Clin Oncol. 2010 Jun 20;28(18):2989-95. doi: 10.1200/JCO.2009.27.4449. Epub 2010 May 17, Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): a phase III trial of the Trans-Tasman Radiation Oncology Group, Rischin D
54. Acta Oncol. 2009;48(4):562-70. doi: 10.1080/02841860902740899, Hypofractionated radiotherapy denoted as the "Christie scheme": an effective means of palliating patients withhead and neck cancers not suitable for curative treatment, Al-mamgani A
55. Acta Oncologica, 2014; 53: 654–661 Compliance and toxicity of the hypoxic radiosensitizer nimorazole in the treatment of patients with head and neck squamous cell carcinoma (HNSCC) Mohamed A. Hassan Metwally et al
56. Radiother Oncol. 2011 Jul;100(1):22-32. doi: 10.1016/j.radonc.2011.03.004. Epub 2011 Apr 19, Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck--a systematic review and meta-analysis, Overgaard J.
57. http://www.npcrc.org/content/25/Measurement-and-Evaluation-Tools.aspx, national palliative care research center

LIST OF TABLES

LIST OF FIGURES

ANNEXURE I

RTOG ACUTE TOXICITY GRADING

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 doesn't need treatment	Persistent hoarseness, Cough requiring antitussive	Whispered speech, throat pain requiring narcotics	Dyspnea/ stridor, hemoptysis with tracheostomy

HEMATOLOGICAL TOXICITY

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

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

(CTCAE) version 4.03

Definition of nausea: A disorder characterized by a queasy sensation and/or the urge to vomit.

Definition of vomiting: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.

Definition of flushing: A disorder characterized by episodic reddening of the face.

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Flushing	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL		

ANNEXURE II

INFORMATION TO PARTICIPANTS

Title: "Palliative radiotherapy along with Nimorazole as hypoxic radio sensitizer in locally advanced head and neck squamous cell carcinoma"

Principle Investigator: Dr. Ragavendra A.

Name of Participant:

Site: Department of Radiotherapy, Madras Medical College & RGGGH, Chennai-3

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

What is the purpose of this study? The incidence of head and neck cancers has been increasing worldwide. As many cases present only in advanced stage, curative surgery or curative chemo radiation is not possible. Among the many palliative treatment options available, with our treatment methodology we are aiming to give a better palliation for the disease by achieving a better immediate loco regional response, better symptom control and less treatment related toxicity.

We have **obtained permission from the Institutional Ethics Committee**.

The study design: Single arm Prospective study.

Study Procedures: Patients will need to undergo blood investigations, CT scan neck, X-ray chest, dental prophylaxis and Smoking cessation counselling, if smoker, which were done routinely in all head and neck cancer patients. These tests are essential to assess the status of the disease. Patients are treated with palliative radiotherapy in hypofractionated regimen over 3 weeks along with tablet nimorazole daily. This is followed by assessment for toxicity and response and after 6 weeks. Patients will undergo clinical examination, laryngoscopy and CT scan neck for this. These tests are essential to assess the efficacy of treatment.

Possible risks to you: None greater than patients receiving standard radiotherapy. Possible benefits to you: Better response at the tumor and less toxicity from treatment.

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

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

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

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

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

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

Signature of Investigator	Signature of Participant
Date	Date

ANNEXURE III

INFORMED CONSENT FORM

TITLE OF THE STUDY: "Palliative radiotherapy along with Nimorazole as hypoxic radio sensitizer in locally advanced head and neck squamous cell carcinoma"

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPLE INVESTIGATOR: Dr.Ragavendra A.

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 this study

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.*
8. I have not participated in any research study within the past 12month(s). *
9. I agree to undergo complete blood count, renal and liver function test, CT scan neck and X-ray chest
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.*
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.*
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understood that my identity will be kept confidential, if my data are publicly presented.

14. I have had my questions answered to my satisfaction.

15. I have decided to be in the research study.

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

ANNEXURE IV

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு

தலை மற்றும் கழுத்துப் பகுதியில் மிகவும் முற்றிய புற்றுநோய்க்கு நோய்க்குறி தனிப்பு கதிர்வீச்சு சிகிச்சையுடன் கதிர்வீச்சின் பயனை அதிகரிக்கக் கூடிய நிமரசோல் என்னும் மாத்திரை உட்கொள்ளல்.

ஆய்வாளர் :

பங்கேற்பாளர் :

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

இந்த ஆய்வின் நோக்கம்:

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

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

ஆய்வின் செயல்முறை:

நோயாளிகள் இரத்தப் பரிசோதனை, முகம் மற்றும் கழுத்துப்பகுதி சி.டி.ஸ்கேன், நெஞ்சுப்பகுதி எக்ஸ்-ரே, பல் சுத்தம் மற்றும் பாதுகாப்பு, புகைப்பழக்கத்தை கைவிட ஆலோசனை முதலியவற்றை மேற்கொள்ள வேண்டும். இவை அனைத்தும் வழக்கமாக எல்லா புற்றுநோயாளிகளிடமும் நோயின் நிலையை அறிய மேற்கொள்பவையே. நோயாளிகளுக்கு வாரத்திற்கு ஐந்து நாட்கள் 3 வாரங்களுக்கு நோய்க்குறி தனிப்பு கதிர்வீச்சுடன் தினமும் நிமரசோல் என்னும் மாத்திரை கொடுக்கப்படும்.

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

ஆய்வினால் ஏற்படும் நன்மைகள்

சிறந்த நோய்க்குறி தனிப்பும், குறைவான பின்விளைவுகளும் கிடைக்க அதிக வாய்ப்புகள் உள்ளன.

ஆய்வினால் ஏற்படும் தீமைகள்

வழக்கமான கதிர்வீச்சுகளில் வரும் விளைவுகளைவிட அதிகம் ஏதுமில்லை.

ஆய்வினால் பிறருக்கு ஏற்படும் நன்மைகள்:

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

மருத்துவ சிகிச்சையின் தகவல்கள் குறித்த விவரங்கள்:

உங்கள் மருத்துவ சிகிச்சை குறித்த தகவல்கள் ரகசியமாக பாதுகாக்கப்படும்.

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

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

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

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

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

ANNEXURE V

சுய ஒப்புதல் படிவம்

ஆய்வு தலைப்பு:

தலை மற்றும் கழுத்துப் பகுதியில் மிகவும் முற்றிய புற்றுநோய்க்கு நோய்க்குறி தனிப்பு கதிர்வீச்சு சிகிச்சையுடன் கதிர்வீச்சின் பயனை அதிகரிக்கக் கூடிய நிமரசோல் என்னும் மாத்திரை உட்கொள்ளல்.

பெயர்: வயது: தேதி: வெளிநோயாளி எண்:

_____ என்பவராகிய நான், இந்த ஆய்வின் விவரங்களும், அதன் நோக்கங்களும் பற்றி முழுமையாக அறிந்து கொண்டேன். எனது சந்தேகங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் பங்குகொள்ள முழு சுதந்திரத்துடன் மற்றும் சுயநினைவுடன் சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் நன்கு புரிந்துகொண்டு எனது சம்மதத்தைத் தெரிவிக்கிறேன். இந்த சுய ஒப்புதல் படிவத்தைப் பற்றி எனக்கு விளக்கப்பட்டது.

இந்த ஆய்வினைப் பற்றிய அனைத்துத் தகவல்களும் எனக்குத் தெரிவிக்கப்பட்டது. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினை அறிந்து கொண்டேன்.

இந்த ஆய்வில் பிறரின் நிர்ப்பந்தமின்றி, என் சொந்த விருப்பத்தின்பேரில்தான் பங்கு பெறுகிறேன். நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும், அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் புரிந்து கொண்டேன்.

இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என்னிடம் பெறப்படும் தகவலை ஆய்வாளர் மருத்துவமனை நெறிமுரைக்குழுவினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வு முடிவுகள் வெளியிடப்படும்போது, எனது பெயரோ, அடையாளமோ வெளியிடப்படாது என அறிந்து கொண்டேன். இந்த ஆய்வின் விவரங்களைக்கொண்ட தகவல் தாளைப் பெற்றுக்கொண்டேன். இந்த ஆய்விற்காக தேவைப்படும் பரிசோதனைகளை செய்துகொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கேற்கும்போது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்பு கொள்ளவேண்டும் என்பதை அறிந்து கொண்டேன்.

இச்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்குத் தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கிறேன் என்று புரிந்து கொண்டேன். இச்சுய ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்று தெரிந்து கொண்டேன்.

ஆய்வாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி: தேதி:

ANNEXURE VI

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

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

CERTIFICATE OF APPROVAL

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

Dear Dr. Ragavendra.A.,

The Institutional Ethics Committee has considered your request and approved your study titled **"Palliative Radio-Therapy Along With Nimorazole as Hypoxic Radio Sensitizer in Locally Advanced Head and Neck Squamous Cell Carcinoma" No.49012015.**

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

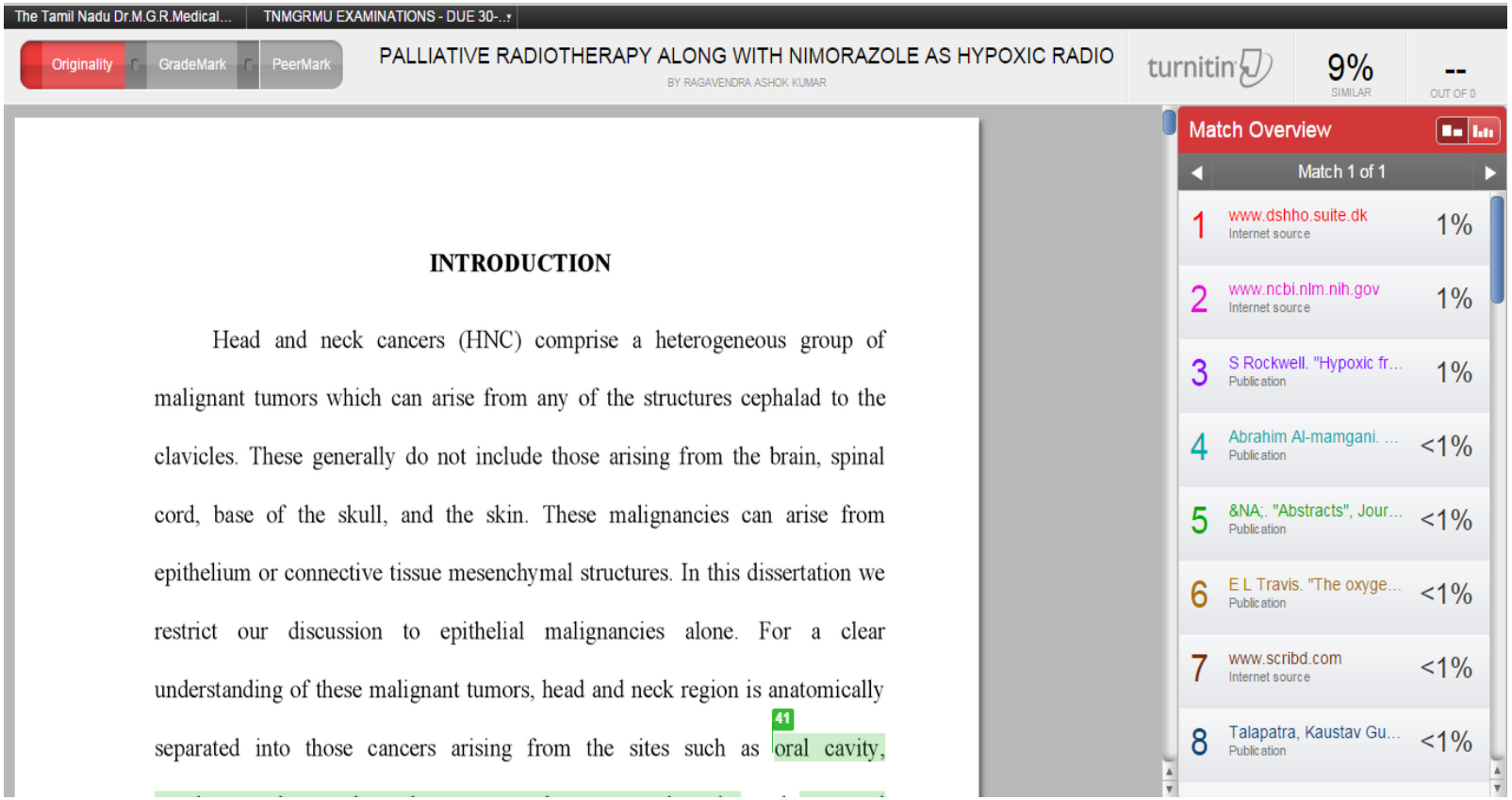
1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6.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

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

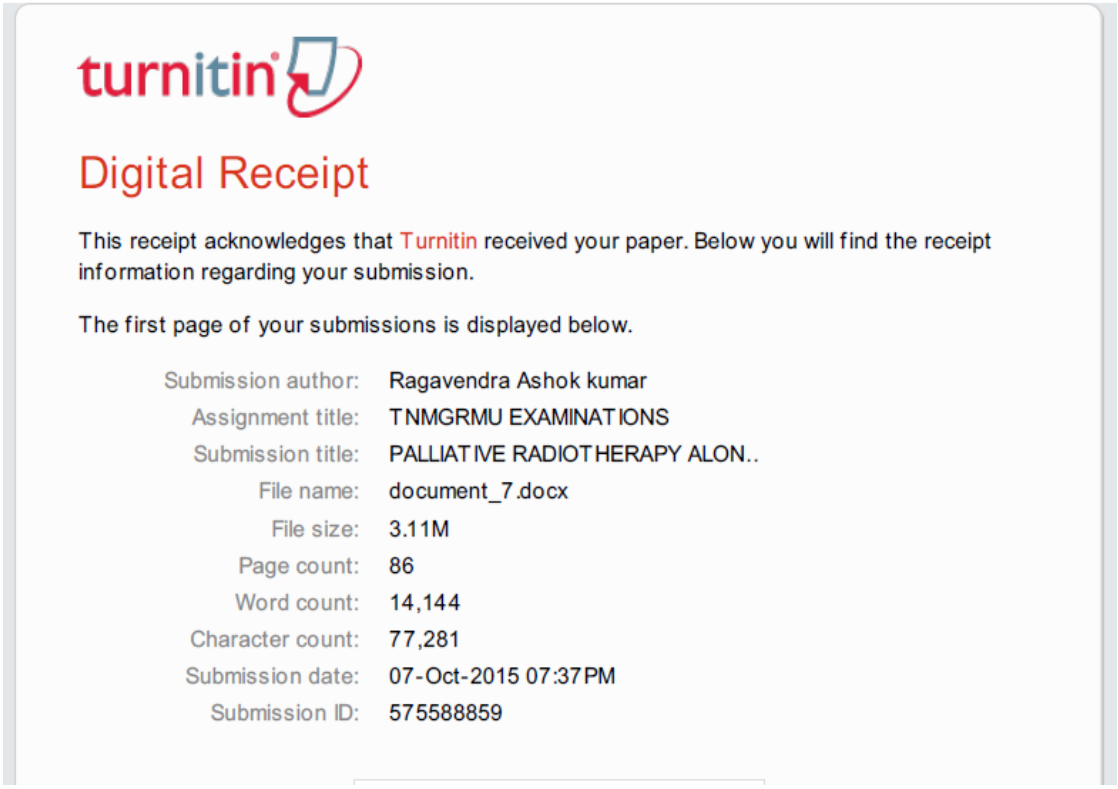
The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

22/1/15

Member Secretary, Ethics Committee
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLE - -
CHENNAI-600 003


The Tamil Nadu Dr.M.G.R.Medical...
TNMGRMU EXAMINATIONS - DUE 30-..
Originality
GradeMark
PeerMark
PALLIATIVE RADIOTHERAPY ALONG WITH NIMORAZOLE AS HYPOXIC RADIO
BY RAGAVENDRA ASHOK KUMAR
turnitin
9%
SIMILAR
--
OUT OF 0
INTRODUCTION
Head and neck cancers (HNC) comprise a heterogeneous group of malignant tumors which can arise from any of the structures cephalad to the clavicles. These generally do not include those arising from the brain, spinal cord, base of the skull, and the skin. These malignancies can arise from epithelium or connective tissue mesenchymal structures. In this dissertation we restrict our discussion to epithelial malignancies alone. For a clear understanding of these malignant tumors, head and neck region is anatomically separated into those cancers arising from the sites such as
41
oral cavity,
Match Overview
Match 1 of 1
1 www.dshho.suite.dk Internet source 1%
2 www.ncbi.nlm.nih.gov Internet source 1%
3 S Rockwell. "Hypoxic fr... Publication 1%
4 Abrahim Al-mamgani. ... Publication <1%
5 &NA;. "Abstracts", Jour... Publication <1%
6 E L Travis. "The oxyge... Publication <1%
7 www.scribd.com Internet source <1%
8 Talapatra, Kaustav Gu... Publication <1%

ANNEXURE VIII



turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Ragavendra Ashok kumar
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	PALLIATIVE RADIOTHERAPY ALON..
File name:	document_7.docx
File size:	3.11M
Page count:	86
Word count:	14,144
Character count:	77,281
Submission date:	07-Oct-2015 07:37PM
Submission ID:	575588859