HYPOFRACTIONATED RADIOTHERAPY IN EARLY STAGE GLOTTIC CANCER

A SINGLE ARM PROSPECTIVE STUDY

INSTITUTION

DEPARTMENT OF RADIOTHERAPY

MADRAS MEDICAL COLLEGE

&

GOVERNMENT GENERAL HOSPITAL

CHENNAI- 600 003

Dissertation submitted in partial fulfillment of

MD BRANCH IX (RADIOTHERAPY)

EXAMINATION

APRIL 2018

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI-600 032

APRIL 2018

CERTIFICATE

This is to certify that Dr. SHIRLEY T. LEIVON has been posted as a Post Graduate MD student during the period from May 2015 to May 2018 in the Department of Radiotherapy, Madras Medical College &Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled "**HYPOFRACTIONATED RADIOTHERAPY IN EARLY STAGE GLOTTIC CANCER"** is a bonafide work done by her during the study period and is being submitted to the Tamil Nadu Dr. M. G. R. Medical University in partial fulfillment of the MD branch IX Radiotherapy examination.

Prof. Dr. Narayana Babu, MD, DCh.,
DEAN,
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai.

CERTIFICATE

This is to certify that Dr. SHIRLEY T. LEIVON has been posted as a Post Graduate MD student during the period from May 2015 to May 2018 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled "**HYPOFRACTIONATED RADIOTHERAPY IN EARLY STAGE GLOTTIC CANCER"** is a bonafide work done by her during the study period and is being submitted to the Tamil Nadu Dr. M. G. R. Medical University in partial fulfillment of the MD branch IX Radiotherapy examination.

Prof. Dr. N. V. Kalaiyarasi, MDRT, DCH,
Professor and Head,
Deapartment of Radiotherapy,
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai.

ACKNOWLEDGEMENT

I thank **THE LORD ALMIGHTY**, for his eternal grace and guidance in helping me finish this study.

I express my sincere gratitude to **Prof. Dr NARAYANA BABU M.D., DCh,** 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. SUDHA SESAIYAN M.D**., 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 Ethical Committee Council 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 his valuable suggestions.

I express my gratitude to **Prof. Dr.M.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.N.V.Kalaiyarasi**, MDRT, DCH, Professor & Head, Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai - 03 for bringing out an attitude of questioning everything and not accepting anything at face value.

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, his

dedication, sincerity, the way he guides everyone are lessons I would like to inculcate for life.

I am gratified to **Prof. Dr.Giridharan., M.D,DMRD,** Additional Professor **,** for his practical understanding of the subjects, the assignments he gave which helped me to improve my knowledge about the subject and he plays a major role in instituting the habit of daily reading. The feedback what he gives for the assignment and project paved way to explore many areas of the subject.

I am grateful to **Prof.,MUTHUVEL**., Professor & HOD, Department of Radiological Physics, for the support, encouragement and motivation rendered throughout the study period.

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

Dr.SUNDARESAN, M.D.R.T

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

Dr.VIJAY KARTHICK,M.D.R.T

Dr.POONGODI ,M.D.R.T

Dr. SENTHIL KUMARAN, M.D.R.T

Dr. JAYASHANKAR, M.D.R.T

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

Mrs. A. KOPPERUNDEVI,

Mr. SURENDRAN

My words of appreciation and gratitude also extends to our department radiographers **Mr. PURUSHOTAM, Mr. VIVEK** and their team of radiographers and

students for their sincere execution of the treatment, kind support and service rendered for the patients in this study.

I am grateful to **Dr. C. AJAY and Prof. DR. 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.

I am also indebted to my family for their continuous support throughout my post-graduation.

Last but not least 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 "**HYPOFRACTIONATED RADIOTHERAPY IN EARLY STAGE GLOTTIC CANCER"** 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 **October 2016 to August 2017** under the guidance and supervision of Prof. Dr. N.V. Kalaiyarasi.

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.

Dr. SHIRLEY T. LEIVON,

M.D. Radiotherapy,

Post Graduate Student,

Department of Radiotherapy.

Madras Medical College.

Place: Chennai.

Date:16/10/2017

CONTENTS

Sl. No.	TITLE	PAGE No
1.	INTRODUCTION	9
2.	REVIEW OF LITERATURE	25
3.	AIMS AND OBJECTIVES	45
4.	MATERIALS AND METHODS	46
5.	RESULTS AND ANALYSIS	54
6.	DISCUSSION	73
7.	CONCLUSION	85
8.	BIBILIOGRAPHY	86

INTRODUCTION

INTRODUCTION

Cancers of the head and neck usually refers to neoplasm arising from below the skull base to the region of the thoracic inlet. They are a diverse group of diseases each with distinct epidemiologic, anatomic and pathologic features. They show a wide variety in natural history, prognosis and treatment considerations (1). Head and neck cancer is an area of great importance to researchers and oncologists as it is related to high physical and psychological morbidity.

CANCER SCENARIO

Every year around 5 million new cases of head and neck cancers are diagnosed worldwide (2). Being sixth most common cancer in the world, it causes devastating effect on the individual by way of functional and cosmetic consequences. The incidence of head and neck cancers has reduced in the developed countries with the awareness that smoking being the commonest cause and the subsequent decrease in smokers. Global burden rises to 14.1 million new cases and 8.2 million cancer deaths in 2012(2A). In India, Squamous cell carcinoma of the head and neck is one of the commonest cancers in our country due to the widespread use of tobacco products in its various forms.

Among head and neck cancers, the incidence of laryngeal cancer is (3) the most common and the glottic to supraglottic carcinoma ratio is approximately 3:1.

In Tamil Nadu, MMTR states that most common cancer in men is head and neck cancer (19.23%) followed next by stomach cancer (13.98%) and lung cancer (12.46%).

In women, breast cancer is the most common (20.87%) followed by cervical cancer (11.46%), stomach cancer (8.11%) and head and neck cancer (7.53%).

In our institute Barnard Institute of Radiology & Oncology, head and neck cancers constitute the majority of cases registered in our OPD, out of which laryngeal cancer is the third common head and neck cancer after oral cavity and oropharygeal tumors. Early stage laryngeal cancer is uncommon; the patient presents more commonly in the advanced or later stages. There is a paucity of these early staged cases, which may be due to lack of proper screening methods to detect early lesions or the lack of knowledge of the patient as well as lack of health care. Most cases present in the advanced stages and this can be attributed to the lack of knowledge or education of the common people about the causes and incidence of cancer. Only around 20 to 25% of the cases present in the early stages(5). Most of them belong to poor socioeconomic status, tobacco users either in smoked form such as cigarettes, beedis or non-smoked forms such as pan etc.

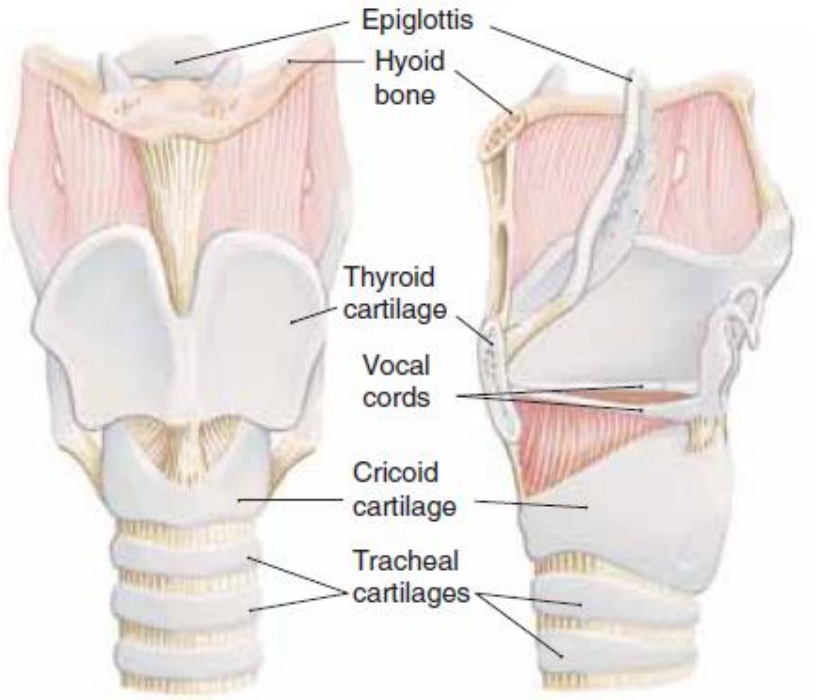
ANATOMY

The larynx is often called the voice box, a name that indicates one of its functions, which is speaking. The other function of the larynx is to be an air passageway between the pharynx and the trachea(6). Air passages must be kept open at all times, and so the larynx is made of nine pieces of cartilage, as shown in the figure below, and is connected by ligaments. The cartilages are listed as below-

Paired-	Unpaired-
1. Arytenoids	1. Epiglottis
2. Corniculate	2. Thyroid
3. Cuneiform	3. Cricoid

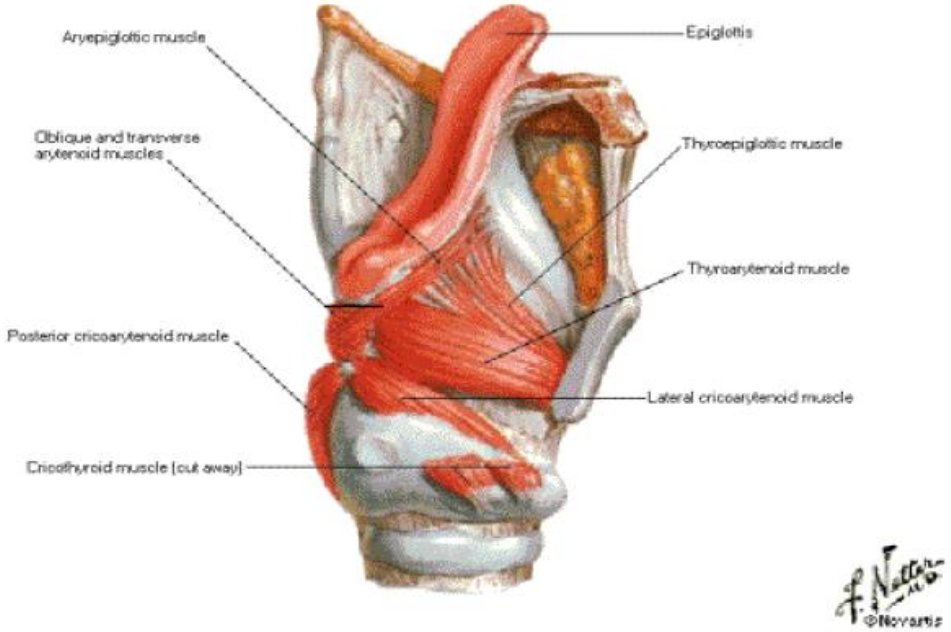
There are laryngeal muscles and the laryngeal membrane around which all these structures lie. These intrinsic muscles of the larynx are –

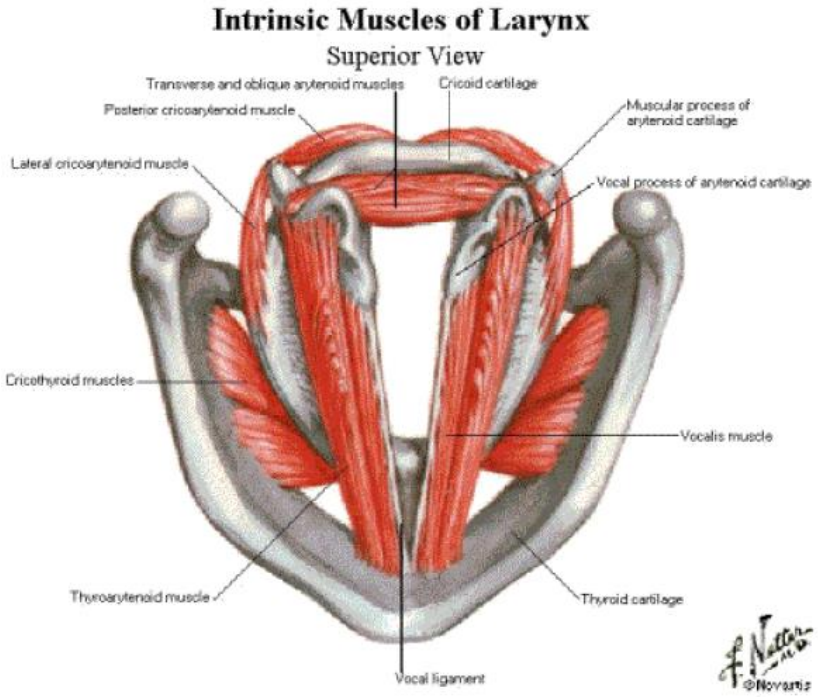
1. Posterior cricoarytenoid
2. Lateral cricoarytenoid
3. Transverse arytenoids
4. Thyroarytenoid
5. Cricothyroid
6. Vocalis



Intrinsic Muscles of Larynx

Lateral Dissection



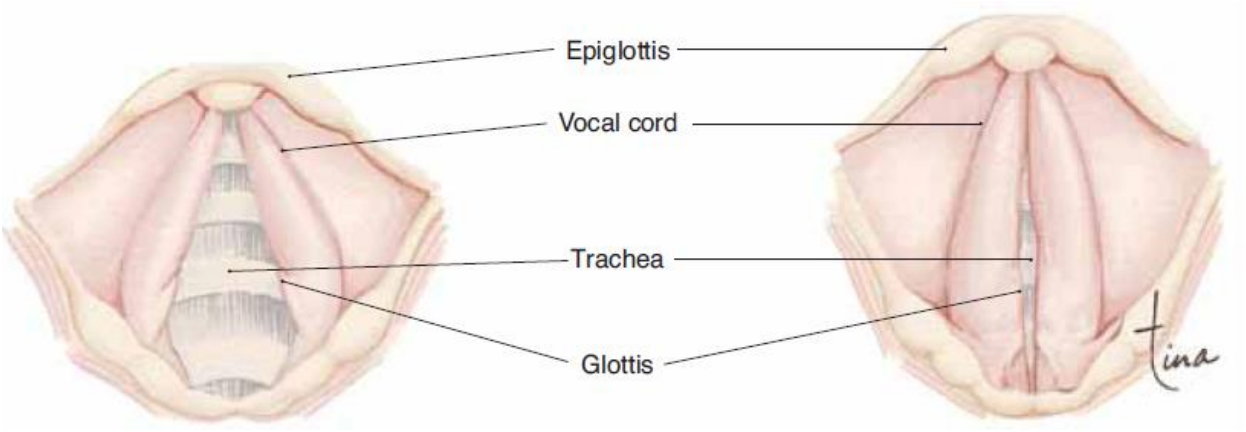


The larynx is subdivided into three main parts- supraglottis, glottis and subglottis. The supraglottis extends from the tip of the epiglottis upto the laryngeal ventricle. It is further made up of subsites which are namely, epiglottis, false cords, aryepiglottic folds, arytenoids cartilages, preepiglottic space and vestibule.

The glottis extends from the laryngeal ventricle to an imaginary plane 1 cm below this level. It is made up of true vocal cords, anterior commisure and posterior commisure as seen in the figure below. The vocal cords located in the glottis extend from thyroid cartilage to the arytenoids and is basically a muscular structure, lined by mucosa. The anterior $3/5^{th}$ of the vocal cord is called the intermembranous part which is responsible

for phonation. The posterior 2/5th of the vocal cord is called the inter-cartilagenous part, which is responsible for respiration.

The subglottis extends from the undersurface of the true vocal cords up to the inferior surface of cricoids cartilage.



Head and neck cancers of squamous cell type make up 25% of the cancer burden in some developing countries like India (7). Laryngeal cancer make up 2% of the total cancer risk, most of them being squamous cell carcinoma and its variants on histology as they arise from surface epithelium. Other histologies include verrucous carcinoma, small cell neuroendocrine tumors. Minor salivary gland tumors arise from the mucous glands in the supraglottic and subglottic larynx, but they are rare. Paragangliomas, carcinoids, soft-tissue sarcomas, malignant lymphomas, and plasmacytomas are rare as well. Benign chondromas and osteochondromas are also reported, although rare (8).

RISK FACTORS

The etiological factors of glottic cancer point to the impact that lifestyle changes in past century had on our health. The principle risk factors are tobacco and alcohol (9).

TOBACCO:

SMOKING:

According to National Cancer Institute reports 85% of patients with head and neck cancers have a history of tobacco usage (10). There exists a dominant and strong relationship between tobacco usage and squamous cell carcinoma of the head and neck (SCCHN), same is true for cancer of the glottis. Development risk of SCCHN is directly correlated to duration and intensity of smoking (11).Smoking tobacco in the form of beedis, cigarettes, cigars, chutta/cheroot, dhumti, hookah and chillum is prevalent in India. Certain populations especially in coastal areas practice reverse smoking .About 50% men and 11% women between 15 – 49 years of age practice smoking in India (12,13)

Cigarettes are the main form of consumable tobacco worldwide. *Beedis* which consist of a small amount of tobacco flakes wrapped in temburni leaf with a colored string at one end are very famous in India. The puff` rate per minute of a beedi is higher than that of an unfiltered cigarette which is responsible for the more carcinogenic load of beedis.

Nicotine is the major psycostimulant in tobacco. It increases the dopamine levels in nucleus accumbens and causes an incentive value and makes the habit to be repeated again and again causing addiction. Major carcinogens in tobacco causing cancer are PAH (polycyclic aromatic hydrocarbons), NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol] and NNN (N1-nitroso nor nicotine).

SMOKELESS TOBACCO:

Globally there is a 60% increase in alternative nicotine delivery systems like snuff, lozenges. Betel quid is extensively used in India. It is also called as *pan* which consists of pieces of areca nut, tobacco and slaked lime. Added tothis are spices, cardamom, cloves, according to the local preferences and are varyingly called as gutkha, zarda, mawa, khaini(9)

ALCOHOL:

Alcohol has a synergistic effect with tobacco. Duration, intensity and concentration of alcohol consumption directly correlates with oral cavity cancer (14,15)

A meta-analysis from 26 studies of oral and pharyngeal cancers found that consumption of 25, 50, or 100 g pure alcohol/day was associated with a pooled relative risk (RR) of 1.75, 2.85, and 6.01, respectively, of oral and pharyngeal cancer(13,14) Alcohol consumption also leads to immunosuppression, alcohol related diseases, altered behavior, unhealthy dietary pattern, and unstable emotional balance. All these factors have impact on cancer treatment and survival.

HUMAN PAPILLOMA VIRUS:

HPV infection, although not an established cause in glottis cancer specifically, it is proved to be one of the causative factor in SCCHN (16). HPV prevalence is about 30-35% observed in head and neck cancers, with HPV-16 being detected in 60- 90% of infected cancer cases (14, 15). HPV prevalence has been found to be highest in oropharynx tumors(palatine tonsil),less common in the oral cavity(17-19).

The oncogenesis of SCCHN by HPV is by transformation of epithelial cells by viral oncoproteins E6 and E7 which inactivate the tumor suppressor genes p53 and Rb respectively in the host cell leading on to increased cell proliferation and inhibition of apoptosis (20-22).

HPV positive oropharyngeal cancers have characteristic features like

- Young patients,
- Nonsmokers
- Non alcoholics
- Present with locally advanced disease with large T and N stage
- Often with basaloid histology
- Poorly differentiated
-Sexually transmitted cancer due to oral sexual activity
- Better prognosis due to sensitivity to radiotherapy and chemotherapy as compared HPV negative SCCHN

OTHER RISK FACTORS

Genetic susceptibility and gastroesophageal reflux, diet lacking green leafy vegetables, fruit and fibre are also causes for the development of laryngeal cancer. Occupations which expose workers to paint, gasoline fumes, asbestos and radiation are considered hazardous for the development of laryngeal cancer.

HISTOLOGICAL CLASSIFICATION

Most vocal cord carcinomas are well or moderately well differentiated. In a few cases, an apparent carcinoma and sarcoma occur together, but most of these are actually a spindle-cell carcinoma (i.e., squamous cell carcinoma with a spindle-cell stromal reaction). Verrucous carcinoma occurs in 1% to 2% of patients with carcinoma of the vocal cord. Small-cell neuroendocrine carcinoma is rarely diagnosed in the supraglottic larynx, but it should be recognized because of its biologic potential for rapid growth, early dissemination, and responsiveness to chemotherapy.

Minor salivary gland tumors arise from the mucous glands in the supraglottic and subglottic larynx, but they are rare. Even rarer are paragangliomas, carcinoids, soft-tissue sarcomas, malignant lymphomas, and plasmacytomas.

SYMPTOMS

Early stage laryngeal cancer confined to the glottis presents as hoarseness of voice and lesions as early as in situ lesions produce significant voice change . More advanced lesions present with dyspnea, stridor, hemoptysis and/ or referred otalgia. There are no lymphatics in the vocal cords and nodal metastasis is rarely seen unless the disease spreads beyond the region of the membranous cords. Therefore, these cancers are usually regarded to have good prognosis as they present in the early onset of the disease and nodal/local spread occurs late due to sparse lymphatics.

Head and neck lodges the most crucial physiological functions like respiration, nutrition, language and expression most of which are unique to mankind. The oncologist would do well to keep in mind the possibility of preserving these functions in the treatment of early glottic cancer, which are amenable to preservation of the patients voice.

PROGNOSTIC FACTORS

The major determinants of prognosis are the stage of the primary lesion when diagnosed as well as the level of neck disease involved. Local control is more difficult in cases where there is increased neck disease burden. T and N stage according to AJCC(23) both affect Cause Specific survival as well. In general, women tend to have a better prognosis than men.

GENERAL TREAMENT OF LARYNGEAL CANCER

Laryngeal cancers should be managed by a multi-disciplinary team comprising of a head and neck surgeon, a radiotherapist/ oncologist, nurse, speech and swallowing therapist.

There are various treatment options for early stage glottis cancer and they include laser excision, endoscopic submucosal resection, partial laryngo-pharyngectomy, total laryngo-pharyngectomy and definitive radiotherapy (24). T1a tumors of the glottis can be treated effectively with laser excision. Local control and organ preservation is first priority in these cases and so tumors that are not controllable with these light burden treatment or with treatment affecting voice quality make good candidates for definitive radiotherapy.

1. CARCINOMA IN SITU

CIS is the replacement of the full depth of the epithelium by malignant cells, without the breach of the basement membrane. This stage should be considered as an early lesion and should be managed as T1 carcinoma. Treatment options include trans-oral endoscopic C02 laser and microlaryngeal cord stripping. Regular follow up is essential.

2. T1N0

Early lesions of glottis confined to one vocal cord is treated with either radical radiotherapy using a small field, measuring 4cmX4 cm, 5cmX5cm or 6cmX6cm or surgery using voice conservation techniques.

Type of surgery depends on the location of the lesion.

a. Mid-cord lesion

i. Transoral endoscopic cordectomy/ CO2 cordectomy- This method gives >90% cure rates with advantages of good voice quality preservation, very short treatment time and tracheostomy is avoided.

ii. Laryngofissure with cordectomy- also produces >90% cure rates with slightly inferior voice quality and temporary tracheostomy is required.

b. Cord lesion extending to the anterior commisure

i. Radical radiotherapy

ii. Vertical fronto-lateral laryngectomy

iii. Endoscopic CO2 laser excision for which experience is required

c. Pure anterior commisure lesion

These lesions may cause early cartilage invasion and may involve base of epiglottis or cricothyroid membrane without causing cord fixity. Therefore, the possibility that T3/T4 lesions may be clinically understaged as T1/T2 cannot be over-looked. In these cases, cure rates will be drastically compromised if only radical radiotherapy is given and hence, surgery is the preferred modality.

4. **T2N0**

These lesions include superficial tumors where vocal cords are freely mobile but the surface extension is beyond the glottis (T2a) or infiltrative tumors causing impaired cord mobility (T2b).

a. **T2a lesions**- radiotherapy is the treatment of choice. Voice quality is preserved near normal and surgery is reserved for salvage on failure of radiotherapy.
b. **T2b lesions**- these lesions are more infiltrative. The best treatment is VPL (Vertical Partial Laryngectomy) or supracricioid laryngectomy with CHEP (Crico-hyoido-epiglottopexy). Voice quality is partially preserved with hoarseness common after surgery.

RADIOTHERAPY FOR EARLY STAGE GLOTTIC CARCINOMA

The concept of organ preservation as emerged ever since the Radiotherapy as proven its role in the treatment of cancer. Mainly in the Head and neck tumors it provides the major effect of organ preservation.

X-Rays were discovered by William Roentgen in 1985. The first head and neck cancer to be cured by Fractionated Radiotherapy was in 1928 and since then various modalities and combinations with chemotherapy have been tried to increase the cure rate in these cancers.

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

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

The fractionation of radiotherapy can be of different types as follows-

CONVENTIONAL FRACTIONATION:

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

ALTERED FRACTIONATION:

Accelerated Radiotherapy:

Decreases the overall treatment time so that the tumor cells regenerate less during the treatment and hence better loco regional control is achieved (36).

Pure accelerated radiotherapy:

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

Hybrid accelerated fractionation: There are three types.

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

Type B: Treatment time is decreased, total dose remains the same with an added break in between treatment (67.2 Gy in 42 fractions of 1.6 Gy twice daily over 6 weeks, including a 2-week break).

Type C(Accelerated concomitant boost): Total dose is same; overall treatment time is reduced with concomitant boostregimen (72 Gy in 42 fractions over 6 weeks, with 1.8 Gy daily for the first 3.6 weeks and 1.8 Gy [large field] plus 1.5 Gy [boost field], 6 hours apart, for the last 2.4 weeks)(36).

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

PALLIATIVE RADIOTHERAPY:

In patients who presents with very advanced stage, such cases cure is not possible as effort to alleviate the symptoms. In these cases, radiation is mostly given in hypofractionated schedules.

For the treatment of early stage glottic carcinoma, the standard treatment has been to give radical radiation in standard fractionation of 1.8-2 Gy per fraction, upto 70 Gy, treating a small field of 4cmX 4 cm, 5cm X 5 cm, or upto a maximum of 6cm X 6 cm. The five-year local control rates have been reported to be 85-94% in T1 larynx (24) and 69-80% in T2 larynx (25). These results are however, not satisfactory and there has been some attempt at trying to improve local control using different strategies. Such strategies

include higher total dose, hyperfractionated radiotherapy, concurrent chemotherapy and hypofractionated radiotherapy. Some reports have shown improved results with higher dose per fraction than the standard 2 Gy per fraction or lower (26). While the advantage of higher dose per fraction is attractive, issues that deal with normal tissue toxicity needs to be addressed, like acute mucositis, dermatitis, late laryngeal edema and cartilage necrosis. Higher dose per fraction treatment also require plans that give better dose distribution. This can be achieved by using plans that include parallel opposed wedged techniques.

LITERATURE

REVIEW

REVIEW OF LITERATURE

BIOLOGICAL BASIS OF FRACTIONATION

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

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

In general repair and repopulation will tend to make the tissue more resistant whereas reassortment and reoxygenation tend to make it more sensitive (27). Tumour, Early responding tissue and Late responding tissues are having different cell kinetics, so they are affected by these 4 factors in different ways.

The **Strandquist plot** is the relation between the total dose and overall treatment time.The extra dose required to counteract tumour proliferation in a fractionated treatment is a sigmoidal function of time. The **Ellis NSD system** made the important contribution of separating the effects of number of fractions and overall time.

THE LINEAR – QUADRATIC MODEL

The L.Q model (28) explains that the radiation cell kill has 2 components. The initial linear component (αD) is due to single track events and quadratic component (βD^2) is due to two track events.

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

S is the fraction of cells surviving a dose D.

This model explains why there are different responses between tumor, early responding tissues and late responding tissues; this is due to difference in repair capacity or shoulder shape of underlying dose-response curve. The dose response curve of late responding tissue is more curved than that of tumor and early responding tissue.

In terms of linear quadratic relationship between effect and dose, this translates into a larger α/β ratio for early, tumor than for late effects, α/β ratio is the dose at which linear and quadratic components are equal. So, by dividing total number of doses, preferentially reduces the late effects. The early responding tissue and tumor tissue, particularly, squamous cell carcinoma in head & neck have a large α/β ratio. It is usual in radiotherapy to compare different fractionation regimens using **BIOLOGICAL EFFECTIVE DOSE** or equivalent doses (BED). Using L.Q. Model, as suggested by Jack Fowler at ASTRO and ESTRO Tutorials,

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

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

d - Dose per fraction.

According to the linear quadratic Model, Biological Effective Dose for a dose 66Gy, delivered in 5.3 weeks in 6 fractions per week is 72.4Gy. The α/β ratio for glottic tissue is 9.9.

RATIONALE FOR USING HYPOFRATIONATED RADIOTHERAPY

Hypofractionation is defined as the use of doses per fraction higher than 2.0Gy. The total number of fractions is reduced, hence the prefix 'hypo-'.

In the developmental days of radiotherapy, it was believed that fractionated radiotherapy was thought to be inferior to the conventional fractionation and was judged to be a primitive method. The importance of hypofractionated radiotherapy was established in the early 1950s where Lars Leksell and Borge Larasson worked together to create the first Gamma Knife (Elekta AB) in Stockholm. Thus, its use and popularity became more common, making it a technique to be exploited in the use of treating cancer.

The rationale behind using hypofractionated radiotherapy is that with increased dose per fraction, there is an increase in cell kill. When this method is employed, it

results in a shorter treatment time, which is beneficial for the patient in spending less days for treatment as well as to decrease the work burden on the centre providing treatment.

Another factor to take into account is tumor repopulation. This is the phenomenon by which treatment with any cytotoxic agent, including radiation, can trigger surviving cells (clonogens) in a tumor to divide faster than before. This is known as accelerated repopulation. During the time that the tumor is overtly shrinking and regressing, the surviving clonogens are dividing and increasing in number more rapidly than ever. Withers and colleagues surveyed the literature on radiotherapy for head and neck and estimated the dose to achieve local control in 50% of cases as a function of overall duration of fractionated treatment. The analysis suggests that clonogen repopulation in this human cancer accelerated at about 28 days after the initiation of radiotherapy in a fractionated regime. A dose increment of about 0.6 Gy per day is required to compensate for this repopulation. Such a dose increment is consistent with a 4-day clonogen doubling rate, compared with a median of about 60 days for unperturbed growth.

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

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

To overcome these problems **altered fractionations** schedules have been studied in various trials.

However, the disadvantage with hypofractionation is the increased chances of toxicity to late responding tissues due to the fall in the iso-effective dose for the same. Radiobiology explains that hypofractionation will lower the therapeutic ratio between tumors and late-responding normal tissues, compared with conventional fractionation, in the same overall time. This expectation depends on the α/β ratio for the tumor being considerably higher than for late-responding normal tissues; exceptions could therefore occur for tumors that have low α/β ratios, for example some melanomas, liposarcomas and potentially early-stage prostate and breast cancer. Hypofractionation is considered to be superior to conventional fractionation in these cases based on studies (29).

The therapeutic gain factor for any dose per fraction is derived from the relative isoeffect doses for the tumor and the normal tissues. However, short intensive schedules compare favorably to protracted lengthy schedules in terms of tumor and late responding tissues.

The linear quadratic equation can be used to calculate the isoeffect relationships of radiotherapy. The simplest method to compare the iso-effectiveness of different doses per

fraction and different total doses is to convert the schedule into an equivalent schedule with 2 Gy per fraction to give the same biologic effect.

Another reason for the feasibility of hypofractionated radiation therapy in early glottic cancer is due to the fact that squamous cell carcinoma of the glottis is usually well differentiated and a slowly growing lesion (30).

In a study done by **Krzysztof Skladowski et al**., the dose along with the overall treatment time was established. They also took into account the pretreatment hemoglobin level of the patient. In this study, 235 patients with T1N0M0 glottic cancer were recruited and treated by radiation therapy alone given in a conventional schedule with 5 fractions each week. The individual total dose, dose per fraction, and overall treatment time (*OTT*) ranged from 51–70 Gy, 1.5–3.0 Gy, and 24–79 days, respectively. The median follow-up was 48 months. Patient data—total dose, dose per fraction, Overall Treatment Time and hemoglobin level measured before the radiation treatment—were fitted by the mixed LQ/log-logistic model. They concluded that the dose–response curve for 235 patients with T1 glottic cancer was well defined and steep, and showed significant decrease in tumor control probability (*TCP*) when total doses were below 61 Gy. The 10-day prolongation of *OTT*, from 45 to 55 days, decreased the *TCP* by 13%. The dose of 0.35 Gy/day, compensated repopulation during the 1 day of prolongation, which indicates a **potential doubling time (Tpot) for glottic T1 tumor clonogens of 5.5 days.** The drop of Hb level of 1 g/dl (from 13.8 g/dl to 12.8 g/dl) gave a 6% decrease of *TCP*, provided that *OTT* was 45 days. Therefore, dose per fraction, above 2Gy and overall treatment

time to around 6 weeks proves to be a schedule where acceptable tumor control is achieved.

In another study where growth rate of laryngeal cancer was studied, there was a variable range of the rate of growth. The rate of tumor growth seemed to be an important factor for Disease Free Survival and Overall Survival. This tumor growth rate is independent of age, differentiation and tumor volume associated with DFS, but N-stage seems to be a more important risk factor (31). There are sparse lymphatics in the laryngeal glottis, hence, the major risk factor can be taken into less consideration when analyzing the factors that affect the growth rate of the tumor, which in turn, affect the DFS and OS. This study showed that tumors that grow rapidly had a worse outcome in the form of decreased DFS.

Tumor location	**Number**	**N%**	**Slow Growth Rate**	**Fast Growth Rate**
Glottic	64	48.9	49	15
Supraglottic	66	50.4	34	32
Subglottic	1	0.7	0	1
T 1	2	1.6	2	0
T 2a	37	28.2	27	10
T 2b	38	29	26	12

Table showing the incidence of fast and slow growing tumors in laryngeal carcinoma

As not many studies have been done to correlate the tumor growth rate and its association to DFS or OS, we take this study into account for the number of patients and the number of tumors which show either fast or slow growth rate. The statistics in this study show that most of the early staged laryngeal tumors show slow growth pattern. In a subset analysis of the glottis, 49out of 64 glottic cancer patients showed slow growth rate in the tumor, while the other 14 showed faster growth rate. Hence, we can conclude that not only for most early laryngeal cancer but for early stage glottis cancer, most of the tumors are slow growing. The method of the study was done as follows.

In this study they delineated the tumor according to abnormal contrast enhancement, soft tissue thickening, presence of a mass lesion, infiltration of fatty tissue, or a combination of these. Delineation on both scans was performed using 3-D delineation software (in-house developed). This software package (VolumeTool) includes image quantification tools such as volumetry and 3D visualization. The delineation package is based on a combined Java/C+ library and includes a (in-house developed) DICOM server for storing image data-sets as well as delineated structures sets. Tumor growth rate was then calculated by taking the interval (in days) between the two CT scans and recording the findings. Tumor growth was based on the volume difference between the diagnostic and planning CT-scans. Exponential growth was assumed (32).

Tumor Growth Rate (TGR) = ln(Vplan- Vdiagn) / T

Vdiagn= tumor volume on dCT; Vplan

=tumor volume on pCT; T

= days between dCT and pCT

(Where dCT is diagnostic CT scan and pCT is planning CT scan)

The end point was Disease Free Survival. The mean time between the dCT- and pCT scans was 25.7 days (SD 11.6). The mean tumor growth rate was _0.3 ln(cc/day) and, therefore, this was used as cut-off point . In a subset analysis taking only glottic cancers into account, 49 out of the 64 patients showed a slow growth rate and the rest showed a fast tumor growth rate. This study found a significant association with DFS (HR 2.4; 95% Confidence Interval (CI) 1.3–4.4) and OS (HR 1.9; CI 1.2–3.2).

Fast growing tumors (n = 48) had a 5 year DFS and OS of 56% and 40% respectively compared with 78% and 65% in slow growing tumors (n = 83).

Thus, slow growing tumors can be taken as a more common phenomenon in a population of early glottic cancer. From the general idea we have of slow growing tumors, it can be safe to say that there are multiple studies showing the efficacy of hypofractionated radiation therapy over standard fractionation. Therefore, the patient population in this study has been assumed to be amenable to hypofractionated radiation therapy as all, except one patient are of squamous cell carcinoma and all patients are

early stage, without lymph node metastases, which would have otherwise influenced the outcome independent of tumor growth (33).

The glottis is a structure devoid of lymphatics. Lymph node metastases become apparent only when there is extension into the supraglottis or subglottis.

The incidence of lymph nodes metastases is given as follows:

STAGE	LYMPH NODE METASTASIS
T1	≤ 2%
T2	5%
T3	20%-30%
T4	40%

In early stage glottic carcinoma, i.e, T1 & T2 tumors, there is very minimal lymph node spread and therefore the prophylactic or therapeutic treatment of the neck or its echelon lymph node stations are not required unless there is obvious involvement of the lymph nodes. Hence, the standard of treatment in early stage glottic cancer consists of a small field, shaped like a box, with a margin wide enough to cover the entire glottis, keeping in mind the change in position of the structure in case of swallowing and to make up for set up errors. This small treatment field allows us to treat the tumor in an increased dose per fraction, taking into account toxicity to normal tissues.

Thus, taking all these factors into account, hypofractionation seems like not only a feasible approach, but also advantageous in terms of tumor biology and patient factors.

RATIONALE OF USING BEAM MODIFICATION TECHNIQUES

TYPES OF BEAM MODIFICATION

- **Shielding**: To eliminate radiation dose to some special parts of the zone at which the beam is directed.
- **Compensation**: To allow **normal** dose distribution data to be applied to the treated zone, when the beam enters a or obliquely through the body or where different types of tissues are present.
- **Wedge filtration**: Where a special tilt in isodose curves is obtained.
- **Flattening**: Where the spatial distribution of the natural beam is altered by reducing the central exposure rate relative to the peripheral.

TYPES OF BEAM MODIFICATION DEVICES

- Field blocking and shaping devices:
  - Shielding blocks.
  - Custom blocks.
  - Asymmetrical jaws.
  - Multileaf collimators.
- Compensators.
- Beam spoilers
- Wedge filters.

- Beam flattening filters.
- Bolus
- Breast cone
- Penumbra trimmers.
- Electron beam modification

In this study, wedge filters and bolus were used for every patient during treatment.

WEDGE FILTERS

This is the most commonly used beam modifying device. It is mounted into the tray and placed 15 cm away from the skin surface. Wedges come in 4 angles 15,30,45 and 90 degrees. Wedge filters offer dose homogeneity for irregular surfaces(34).

As the angle increases-

-Attenuation produced by the thicker end (heel)increases .

- Dose transmission from thinner end(toe) thus tilting of isodose curve increases.

Wedge Field Techniques (hinge angle and wedge angle)

ϕ=hinge angle

θ=wedge angle

$\theta = 90^{\circ} - \frac{\phi}{2}$

BOLUS

A tissue equivalent material used to reduce the depth of the maximum dose (D_{max}). It is better called a "build-up bolus". A bolus can be used in place of a compensator for kilovoltage radiation to even out the skin surface contours. In megavoltage radiation bolus is primarily used to bring up the **buildup zone** near the skin in treating superficial lesions. The thickness of the bolus used varies according to the energy of the radiation.

In megavoltage radiation:

- **Co^{60}** : 2 - 3 mm
- **6 MV** : 7- 8 mm
- **10 MV** : 12 - 14 mm
- **25 MV**: 18 - 20 mm

Properties of an ideal bolus are that it should have the same electron density and atomic number as the tissue being irradiated, it should be pliable to conform to surface with a usual specific gravity of 1.02 -1.03.

- Commonly used materials are:
  - Cotton soaked with **water**.
  - Paraffin wax.
- Other materials that have been used:
  - Mix- D (wax, polyethylene, mag oxide)
  - Temex rubber (rubber)
  - Lincolnshire bolus (sugar and mag carbonate in form of spheres)
  - Spiers Bolus (rice flour and soda bicarb)

- Commercial materials:
  - **Superflab**: Thick and doesn't undergo elastic deformation. Made of synthetic oil gel.
  - **Superstuff**: Add water to powder to get a pliable gelatin like material.

Bolx Sheets: Gel enclosed in plastic sheet.

SUPPORTING STUDIES

KROG-0201- the aim of this trial was to prospectively investigate the effect of fraction size of radiotherapy and its outcome in early glottic carcinoma. This trial compared two arms- one that of conventional fractionation 66 Gy in 33 fractions for T1 disease, 70 Gy in 35 fractions for T2 disease and a hypofractionation arm 63 Gy in 28 fractions for T1 disease and 67.5 Gy in 30 fractions for T2 disease. All patients were followed up for 67 months and the primary objective was local progression free survival. **The 5-year local progression free survival for the conventional arm was 77.8% and 88.5% for the hypofractionated arm**(35). There was no difference in toxicity in both the arms. This study established the fact that hypofractionation is not inferior to conventional radiation in terms of local control and toxicity. This method of treatment proved that hypofractionated radiotherapy can be given for early T1 and T2 lesions in carcinoma of glottis with advantages of potential better local control and shortened treatment time.

A Japanese study by **Onimaru et al** was done in 200 patients with T1-T2 glottic cancers to investigate the importance of the overall treatment time by giving hypofractionated radiation therapy 2.5 Gy per fraction for a total dose of 65 Gy, four fractions a week. It was found that patients who completed the treatment within 46 days had a significantly better local control (91.9±2%) than those (36) who completed treatment in 47 or more days (82.6±6%).

Ermis et al conducted a retrospective analysis with hypofractionated radiotherapy with 55Gy in 20fractions at 2.75Gy per fraction in 132 patients**. Five year local control and overall control rates were 85.6 % and 97.3 % respectively, with T1a having 91.8 % and 100 %, T1b - 81.6 and 93.8 %, and T2 - 80.9 % and 95.8 % (37).**Only one patient needed tracheostomy due to a non-functioning larynx while on long term follow up. This study concluded that hypofractionated radiation therapy for early stage glottic cancer shows high rates of local control with acceptable toxicity.

Another study from Japan done by **Karasawa et al** evaluated the effect of hypofractionated radiation therapy in 69 patients of early glottic cancer with 2.25 Gy per fraction upto a total dose of 63 Gy treated within a median time of 41 days. One case of T2 glottic cancer could not reach complete response , but all other cases achieved complete response. **The 5-year LC rates in larynx T1 and larynx T2 were 97.6%, and 70.1%, respectively (38).** No acute adverse effects more than Grade 2 toxicity (CTCAE 3.0) were seen. They concluded that this treatment was safe and valuable in treating early glottic cancer, with T1 showing a better outcome compared to historical data. For T2, local control did not show any improvement compared to

historical data and treatment strategy that involves dose escalation is needed for these tumors.

Khan et al conducted a retrospective analysis to evaluate the patient, tumor and treatment characteristics in patients with early glottic carcinoma in 141 patients. Therapy consisted of 2.2 Gy per fraction for 25 fractions upto a total dose of 55 Gy within 5 weeks with the help of 6 MV linear accelerator. **The 5-year local control rates were as follows:T1a, 94%; T1b, 83%; T2a , 87%; T2b, 65% (39).**The 10-year local control rates were as follows: T1a, 89%;T1b, 83%; T2a, 87%; T2b, 56%. This study highlighted the **improvement in voice quality post radiation therapy in those patients who initially had poor voice quality.** 73% out of the 92% of patients experienced an improvement, and none of the patients suffered severe or fatal complications. They concluded that definitive radiotherapy offered excellent local control in T1-T2a, N0 glottic carcinoma along with good voice preservation and minimal long term toxicity. T2b tumors had an inferior response and alternative strategies may be considered.

Mendenhall et al described a local control of 94%, 93%, 80%, 72% for T1a, T1b, T2a and T2b respectively for patients treated with 2-2.25 Gy per fraction, one fraction daily. Out of the 519 patients received radiotherapy at the University of Florida (Gainesville, FL) for T1N0–T2N0 glottic carcinoma, six patients developed severe complications, including severe mucositis necessitating hospitalization and a treatment break , total laryngectomy for a suspected local tumor recurrence with a pathologically negative specimen. laryngeal edema, and a pharyngocutaneous fistula after a salvage total laryngectomy (40). Five of these patients had T2N0 disease. None of these patients died.

Laskar et al conducted a retrospective analysis to evaluate the effect of dose and fractionation with respect to tumor characteristics , toxicity and outcome in patients with T1N0 glottic cancer. The records of 652 patients were analyzed. The four hypofractionated schedules were 50 Gy in 15 fractions (3.3 Gy per fraction), 55 Gy in 16 fractions (3.43 Gy per fraction), 60 Gy in 24 fractions (2.5 Gy per fraction) or 62.5 Gy in 25 fractions (2.5 Gy per fraction). The patients were categorized into two groups of < 3 Gy or > 3 Gy. All patients were treated with 6MV photons in linear accelerator. **Local control in 10 years was 84% and overall survival was 86.1% (41)** for T1 glottic carcinoma. Persistent laryngeal edema was seen in 123 patients. This study concluded that hypofractionated radiation therapy offers acceptable local control rates and late toxicity as long field size was restricted to 36 $cm^{2.}$

Short et al conducted yet another study to analyze the effect of dose and fractionation compared to standard fractionation (SFX) in T1, T2 N0 tumors in glottic cancer. This New Zealand study employed Accelerated Hypofractionated Radiation Therapy (AHFX), with 145 patients receiving this treatment. The treatment consisted of 60-66 Gy in 30-33 fractions (SFX) with ^{60}Co and 6 MV beams. AHFX consisted of 52.5-55 Gy in 20 fractions over 4 weeks using ^{60}Co and 6 MV beams. The 5-year overall survival was 78%. The 5-year loco-regional control for T1was higher in AHFX (42) compared to SFX. Locoregional control in T2 was similar in both fractionation schedules. None of the patients had grade 4 or 5 late reactions. These results showed that AHFX is comparable to standard fractionation regimen with equivalent local control and toxicity.

Spector et al evaluated the therapeutic outcome of dose on the voice quality and preservation in patients treated with low dose, high dose radiation therapy and surgery. This retrospective study analyzed 625 patients who were divided into four groups- low dose radiation- 55-65 Gy, in 1.5-1.8 Gy per fraction, high dose radiation with 65-70 Gy in 2-2.25 Gy per fraction daily. 404 patients underwent conservation surgery and 61 underwent endoscopic resection. The overall local control was 89% and the overall unaided laryngeal voice preservation was 90%. Actuarial survival was significantly decreased in the low dose group was compared to the other groups. This study concluded that the four treatments used provide similar rates of survival and ultimate local control (43). The low dose arm was associated with lower actuarial overall survival and unaided voice preservation. Hence, the survival, local control and voice preservation rates were comparable in all groups except for low dose radiation group which showed a lower overall survival and unaided voice preservation.

Quynh-Thu X. Le et al performed a prospective study in the University of California to assess the significance of fraction size, total dose and overall treatment time in the control of T1-T2, N0 glottic carcinoma. A total of 398 patients were recruited and treatment was delivered in 5 days per week. Minimum tumor dose ranged from 46.6-77.6 Gy , with a median dose of 63 Gy. The fraction size was <1.8 Gy in 146 patients, 1.8-1.99 Gy in 128, 2-2.24 Gy in 62 and 2.25 Gy in 62 patients. All patients were treated within a median of 50 days. **5 year control was 85% for T1 and 70% T2 glottic carcinomas (44).** For the T1 lesions, there was no apparent relationship between the fraction size, overall time and total dose with respect to local control on multivariate

analysis. For T2 lesions, local control rate was 100% for the patients treated with 43 days overall time, 2.25 Gy per fraction. Local control was 44% for those treated with fractions size <1.8 Gy, 78% for those treated with a total >65 Gy. This study concluded that factors like total dose and overall treatment time were significant factors when considering the treatment and local control of T2 but not T1 glottic carcinomas. Anterior commisure involvement was also associated with lower local control rates for T1 but not T2 lesions.

Gowda et al. conducted a study in T1 glottic tumors with invasive squamous cell carcinoma. All patients were treated with definitive radiotherapy with a total tumor dose of 50-52.5 Gy in 16 fractions over 21 days. The fraction size ranged from 3.12 to 3.28 Gy. This study **achieved 5-year local control rates of 93%; there were 14 recurrences of which seven were successfully salvaged by surgery, giving an ultimate local control of 96% (45).** The 5-year overall survival was 80% and cause specific survival was 97% at 5 years.

AIM

AIM AND OBJECTIVES

The aim of this study was to evaluate the influence of dose per fraction in early glottic carcinoma.

Primary objective: To assess the immediate loco regional response rates of hypofractionated radiation in early glottic carcinoma.

Secondary objective: To assess the early toxicity of hypofractionated radiation in early glottic carcinoma.

MATERIALS

AND

METHODS

MATERIALS AND METHODS

STUDY DESIGN: this was a single arm prospective study with a Phase II design.

STUDY DURATION: October 2016– August 2017.

STUDY CENTRE:

This study was conducted in Department of Radiotherapy, Barnard Institute of Radiology & Oncology, Madras Medical College, Chennai.

SAMPLE SIZE:

30 consecutive patients with histo-pathologically proven squamous cell carcinoma of who fulfilled early stage glottic carcinoma who fit into the inclusion criteria were recruited in the study from the outpatient department.

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

ETHICAL COMMITTEE APPROVAL: Approval from the institute ethical committee was obtained on 4/10/2016.

INFORMED PATIENT CONSENT:

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

INCLUSION CRITERIA:

- Biopsy proven newly diagnosed squamous cell carcinoma of the glottis.
- Stage T1 and T2 , N0M0 disease
- Age 20 - 70 years
- ECOG 0-1 performance status
- No major life threatening comorbidities

EXCLUSION CRITERIA:

- Patient who did not consent for radiation at any point of time during treatment.
- Patients with history of any malignancy previously and received treatment for the same.
- Recurrent tumors.
- Previous history of radiation or surgery to the area planned for treatment.
- Patients with collagen vascular disease
- Pregnant females

PRE TREATMENT WORK UP:

1. Detailed history elucidation.

2. Complete physical examination by inspection, palpation.

3. Upper aerodigestive tract evaluation by direct and indirect laryngoscopy, anterior and posterior rhinoscopy and endoscopy if indicated to know the extent of disease and rule out a second primary.

4. Biopsy from the primary tumor

5. Blood grouping and typing.

6. Complete blood count.

7. Renal function test.

8. Liver function test.

9. CT scan of the head and neck, plain and contrast, before initiating treatment and also after treatment for response assessment.

10. Chest X ray postero-anterior view.

11. Cardiac evaluation and fitness.

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

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

PATIENT PREPARATION DURING TREATMENT:

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

Quitting alcohol and tobacco

The harmful effects of tobacco, both in smoking and nonsmoking form, and alcohol were explained to the patient and their addictions as inferior outcome after treatment. Also has increased risk of second malignancy due to field cancerization effect.

Mucositis

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

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

Studies show that daily dose, cumulative dose and volume of irradiated tissue determine the severity of mucositis. This pain produced by mucositis can lead to nutrition compromise thereby lack of proper hydration and oral hygiene. The

desquamated epithelium, fibrin, and polymorphonuclear leukocytes in a moist background provide a favorable environment for opportunistic infections such as candidiasis.

Radiation to a small field in case of early glottic cancer can cause mucositis of the esophageal and pharyngeal mucous membranes. According to studies, when radiation therapy is the only treatment used, esophagitis usually has its onset at about 20-30 Gy, or two to three weeks after treatment. This condition usually begins to subside 10 days to 2 weeks after radiation therapy is completed. This is best accomplished if the patient's nutritional status is maintained at an optimal level. Immunocompromised patients can have persistent symptoms and the patient needs to be assessed for candidiasis.

NUTRITIONAL CARE:

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

All patients enrolled in this study were given dietary advice and encouraged to take easily available, nutritionally rich local foods, dairy products and fresh fruits and juices (avoid citrus fruits, acidic and spicy foods). Everyone was encouraged to take supplemental calories before treatment consisting of two raw eggs and milk daily.

Homemade preparation of health mix with milk which is rich in protein is given to regenerate tissue protein. Pureed or soft meals preparation at room temperature is also a preparation that has found to be well accepted. All patients were monitored for weight loss every week and special meals were designed for individual patients.

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

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

TREATMENT PROTOCOL:

30 cases of early staged glottic cancer patients were selected consecutively from the outpatient department, who then underwent the pre treatment work up as mentioned before.

RADIATION THERAPY:

All patients were treated with a accelerated dose schedule of 2.25 Gy per fraction with a Theratron Phoenix Tele Cobalt-60 machine, using wedges of either 30° or 60° to achieve dose homogeneity along with bolus on the surface of the patient to be treated to achieve adequate dose to the anterior commisure, especially if it is involved.

Patient Position:

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

Patient Immobilization:

Strict immobilization was practiced while irradiating the patient.

Radiation Portals:

Patients were treated with opposing lateral radiation portals

Verification:

X-ray simulation was done with the patient in treatment position to verify the treatment field.

Radiation Dose:

Patients were treated with a dose of 2.25 Gy per fraction, with 6 fractions per week, up to a total dose of 63Gy. Aim was to complete radiation within 5.6 weeks. Appropriate shielding was done to limit the spinal cord dose to 40 Gy as per the institutional policy.

ASSESSMENT DURING RADIATION:

Toxicity Assessment:

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

Hematological and renal parameters were assessed on a weekly basis. Hemoglobin less than 10 mg/dl was corrected by packed red cell transfusion. WBC and platelet counts were kept under regular monitoring.

RESPONSE EVALUATION:

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

Response to treatment was described based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1 version) Criteria.

- **COMPLETE RESPONSE**: Disappearance of all target lesions; malignant nodes <10 mm.
- **PARTIAL RESPONSE:** At least 30% reduction in the sum of the longest diameter of target lesions, taking as reference the baseline study; confirmed at 4 weeks.
- **STABLE DISEASE**: Neither partial response nor progressive disease criteria are met, in a minimum time set by the protocol.
- **PROGRESSIVE DISEASE:** At least 20% increase in the sum of the diameter, with a minimum absolute increase of 5 mm, taking as reference the smallest sum in the study or appearance of new lesions.

FOLLOW UP:

- Patients after completion of concurrent radiation were discharged from the hospital. Response evaluation was done based on RECIST criteria after 4-6 weeks.
- Chest imaging was done when indicated clinically. Continued smoking cessation, counseling to the patient and their attendee, rehabilitation, speech and swallowing therapy.

STATISTICAL ANALYSIS:

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

CASE ANALYSIS

AND

RESULTS

RESULTS AND ANALYSIS

The total 30 patients recruited completed their entire treatment protocol and all of them were available for analysis of results.

PATIENT CHARACTERISTICS:

AGE DISTRIBUTION:

43% of the patients belonged to the age group 51- 60yrs, followed by 41 -50yrs. The mean age of presentation was 55.5yrs. The youngest patient age was 35yrs and the oldest was 64yrs.

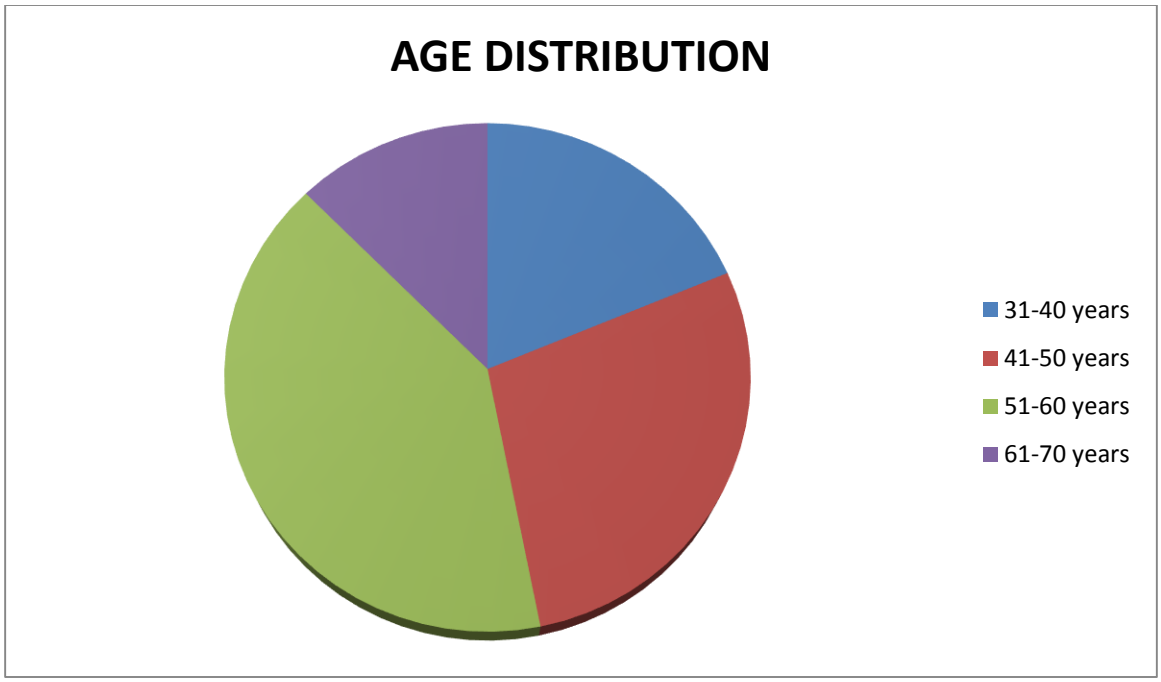


Figure No: 1, AGE DISTRIBUTION

AGE GROUP	NUMBER	PERCENTAGE
31- 40yrs	6	20%
41 -50yrs	9	30%
51-60yrs	13	43%
61- 70 yrs	4	7%

Table No: 1, AGE DISTRIBUTION

Table no: 2, GENDER DISTRIBUTION OF THE STUDY POPULATION

SEX	NO. OF PATIENTS	PERCENTAGE
MALE	24	80%
FEMALE	6	20%

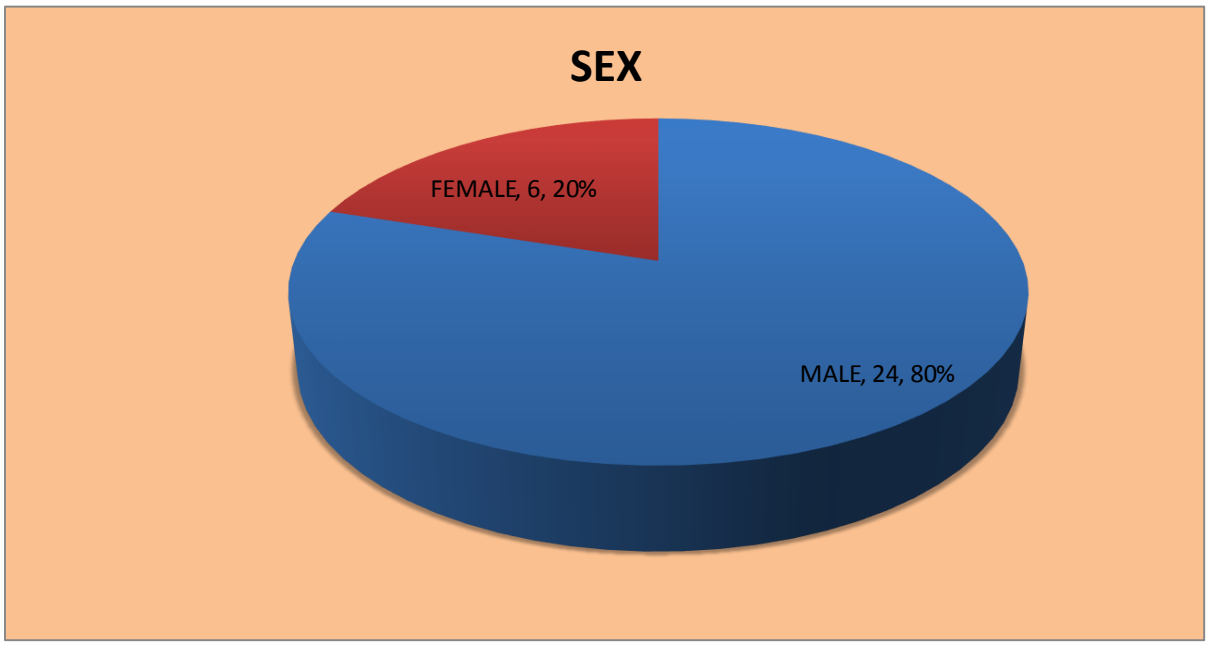


Figure no: 2, Gender distribution of the study population

PERFORMANCE STATUS:

All patients in this study had a general performance status of

ECOG (Eastern Cooperative Oncology Group)grade 0 or 1.(figure no:3)

Table no:3, ECOG performance status

ECOG	NO.OF PATIENTS	PERCENTAGE
ECOG 0	18	60%
ECOG 1	12	40%

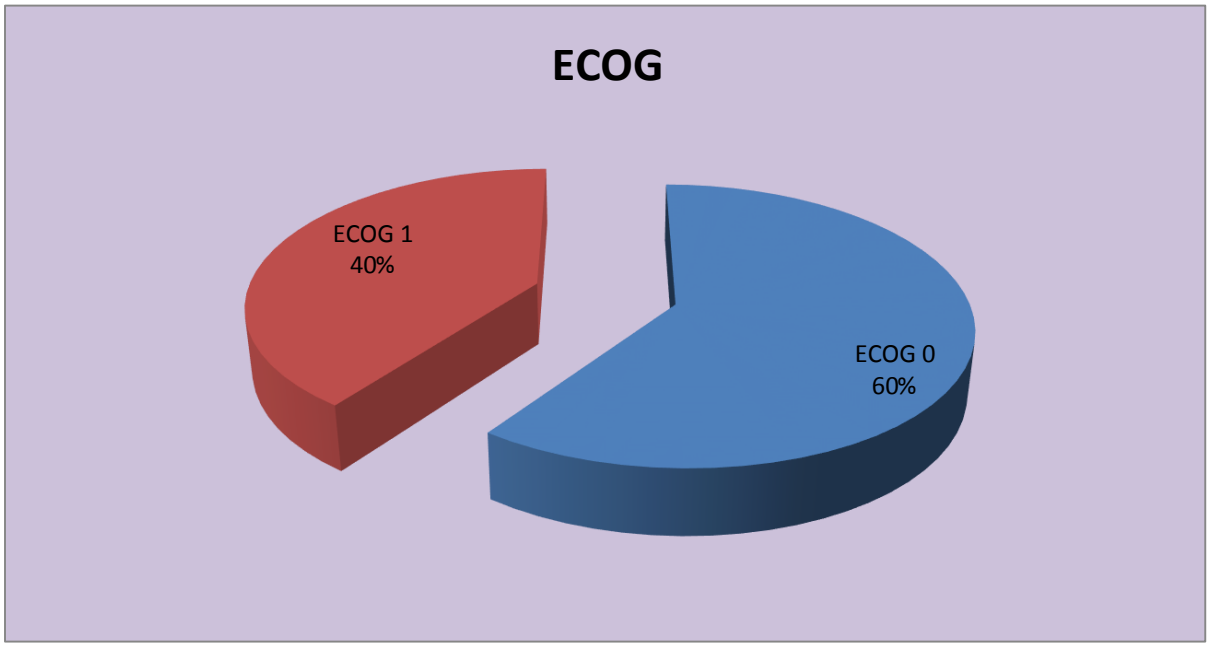


Figure no:3, ECOG performance status

HABITS:

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

Table no: 4, Habits / addictions in the study population.

HABITS	NO.OF PATIENTS	PERCENTAGE
TOBACCO(SMOKING)	19	63%
TOBACCO(SMOKELESS)	11	36%
ALCOHOL	16	53%
NONE	4	13%

SYMPTOMS AND SIGNS:

The most common symptom of presentation among the patients in this study was a change in voice or hoarseness of voice.

Some complained of sore throat, but none complained of pain, or difficulty in swallowing or any palpable neck nodes.

PRESENTING SYMPTOMS/SIGNS	NUMBER	PERCENTAGE
VOICE CHANGE	26	87%
SORE THROAT	4	13%
PAIN	5	16%
DYSPHAGIA	2	7%
NECK SWELLING	0	0%

Table No:5, Presenting Signs and Symptoms

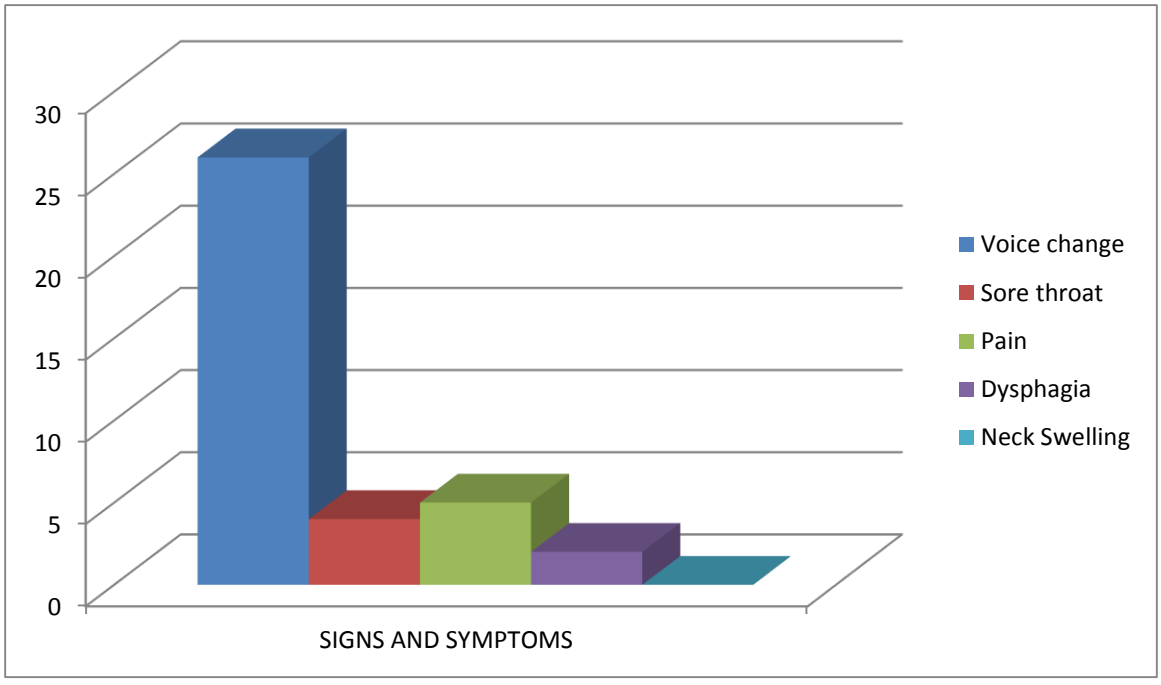


Figure No:5, Presenting Signs and Symptoms

PRIMARY SITE:

Table no:6, Primary site

PRIMARY SITE	NUMBER	PERCENTAGE
RIGHT VOCAL CORD	17	56%
LEFT VOCAL CORD	14	46%
ANTERIOR COMMISURE INVOLVEMENT	13	43%
SUPRAGLOTTIS/SUBGLOTTIS EXTENSION	3	10%

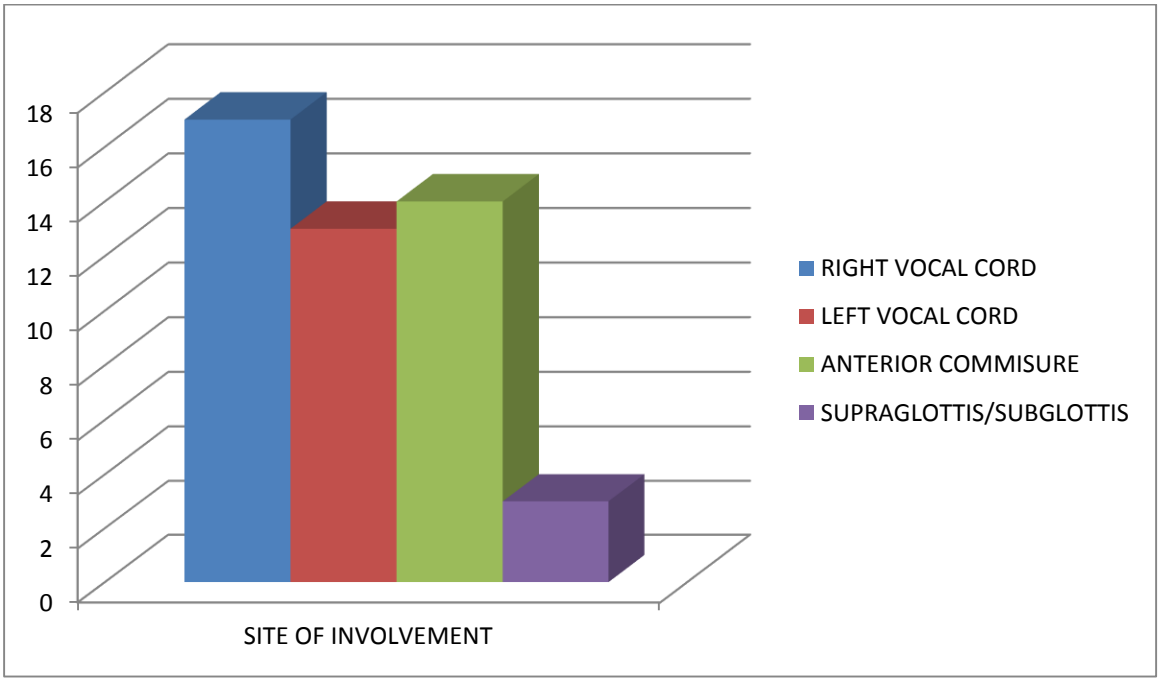


Figure No:6, Site of Involvement

In the subset analysis, the involvement of the right vocal cord was only slightly more common than the left vocal cord and the incidence of the anterior commisure was 43%, i.e, in 13 patients. There was extension to supraglottis or subglottis in 3 patients.

TUMOR STAGE:

This study included only early stage glottic cancer, i.e, T1 and T2 with no nodal involvement, N0. Thirteen patients had T1N0M0 and 12 had T2N0M0 disease. Out of the 18 patients who were staged as T1, 8 had T1a and 10 patients had T1b disease.

TUMOR STAGE	No. OF PATIENTS	% OF PATIENTS
T1a	8	26.6%
T1b	10	33.33%
T2	12	40%

Table No:7, Tumor Stage

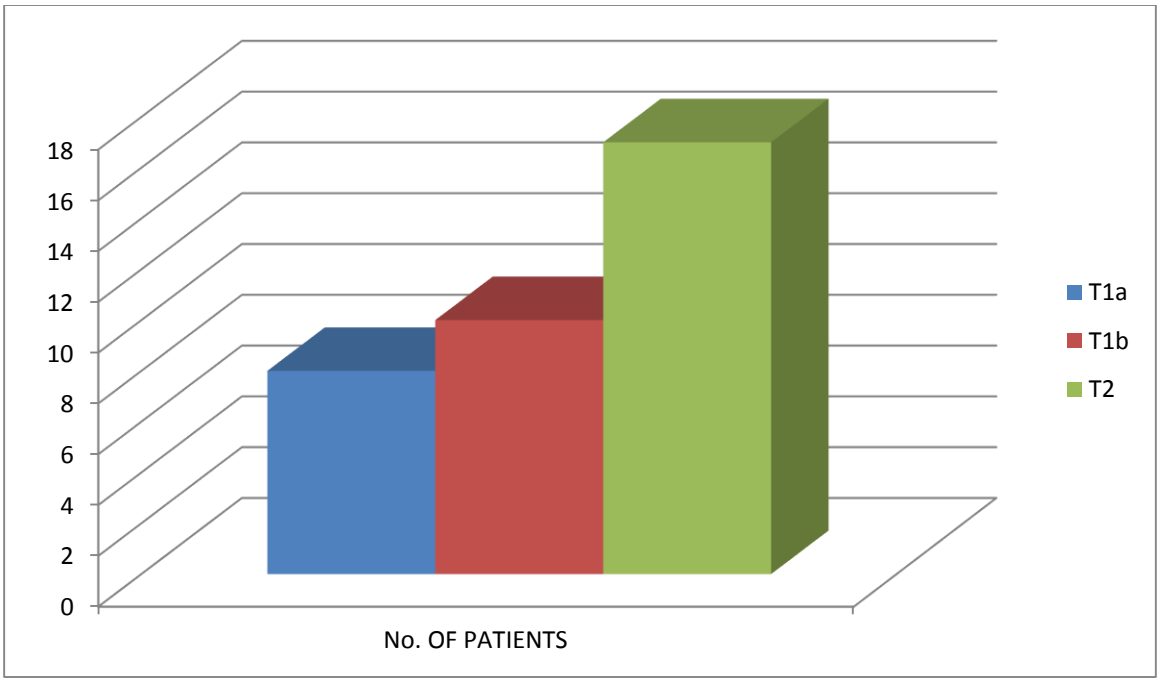


Figure No:7, Tumor Stage

STAGE GROUPING OF THE STUDY SAMPLE:

The staging grouping was done according to AJCC 7th edition. Patients were staged either stage I or stage II. None of the patients had nodal disease.

STAGE GROUPING	NUMBER	PERCENTAGE
STAGE I	18	60%
STAGE II	12	40%

Table No:8, Stage Grouping

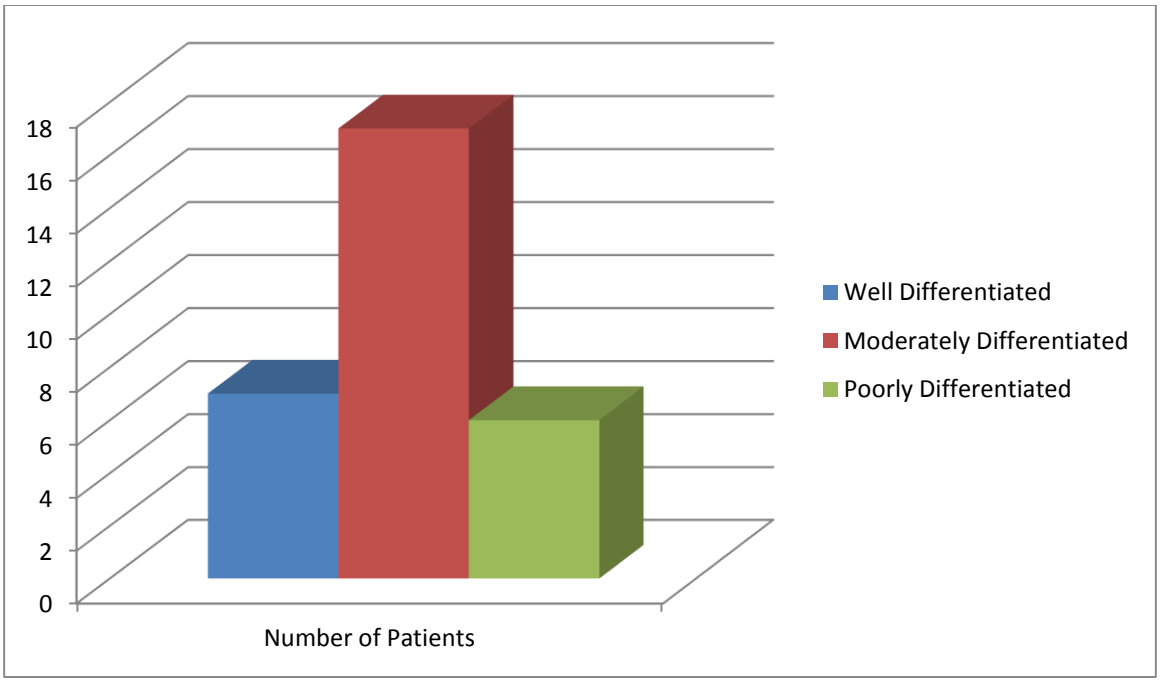
HISTOLOGICAL DIFFERENTIATION:

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

Table No:9, Histological Differentiation

HISTOLOGICAL DIFFERENTIATION	NUMBER	PERCENTAGE
WELL DIFFERENTIATION	7	23.33%
MODERATELY DIFFERENTIATED	17	56.66%
POORLY DIFFERENTIATED	6	20%

Figure No:9, Histological Differentiation



TREATMENT RESULTS:

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

RESPONSE RESULTS:

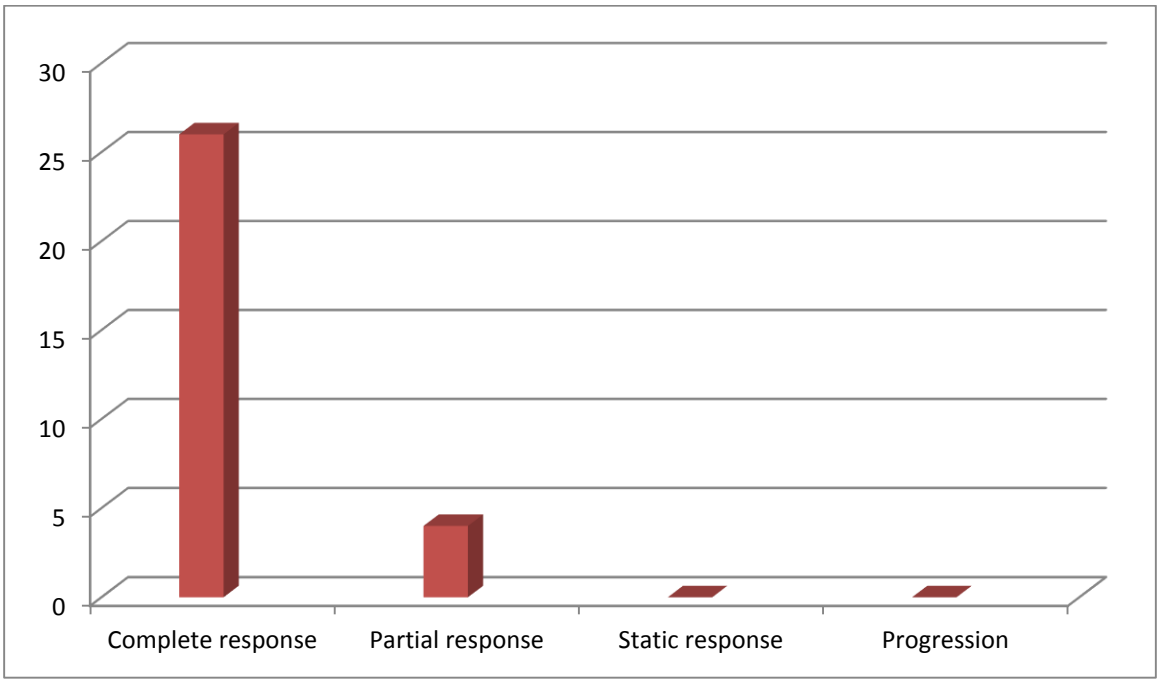


Figure no:10, Response results

RESPONSE	NUMBER	PERCENTAGE
COMPLETE RESPONSE	26	87%
PARTIAL PRESPONSE	4	13%
STATIC RESPONSE	0	0
PROGRESSION	0	0

Table no:10, Response results

SUBSET ANALYSIS:

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

TUMOR STAGE Vs RESPONSE:

Out of the 18 T1 lesions, 17 patients had complete response whereas out of the 12 T2 patients 9 had complete response.

Figure no: 11,Tumor Stage Response

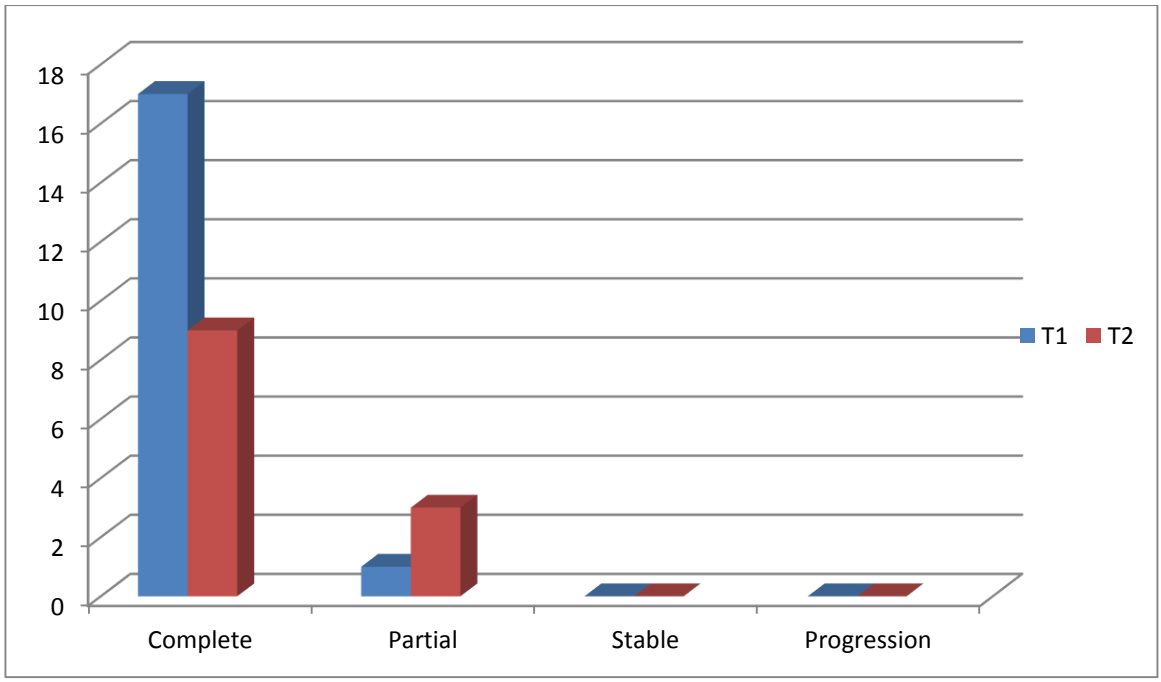


Table no:11, Tumor Stage Response

TUMOR STAGE	COMPLETE RESPONSE	PARTIAL RESPONSE
T1	17 (56.66%)	1(3.3%)
T2	9 (30%)	3 (10%)

HISTOLOGICAL DIFFERENTIATION Vs RESPONSE:

As already mentioned maximum numbers of the patients in our study were moderately differentiated, which accounted for 17 patients; in which 16 patients had complete response and 1 had partial response. Among the poorly differentiated cancer, 5 had complete response and 1 had partial response. Out of 7 well differentiated tumors only 5 had complete, this is lower than patients with moderately differentiated tumors but almost equal to the poorly differentiated category.

Figure no:12, Histological Differentiation Vs. Response

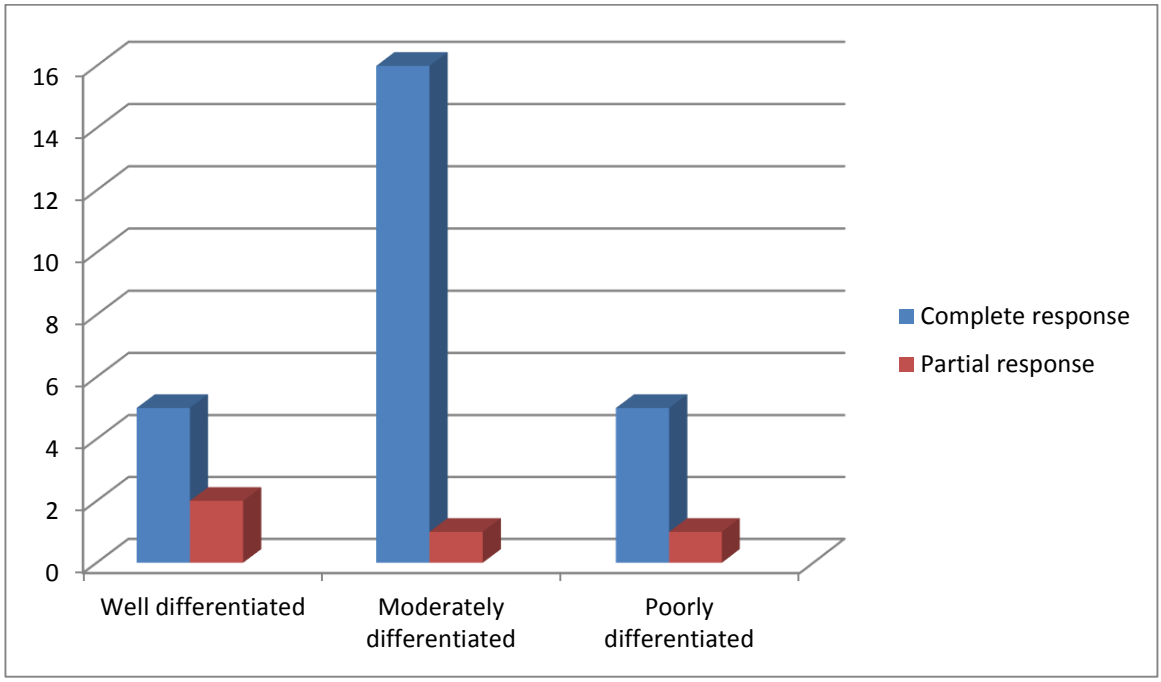


Table no: 12, Histological differentiation Vs. response

HISTOLOGIC DIFFERENTIATION	COMPLETE RESPONSE	PARTIAL RESPONSE
WELL DIFFERENTIATED	5 (16.6%)	2 (6.66 %)
MODERATELY DIFFERENTIATED	16 (53.3%)	1(3.33 %)
POORLY DIFFERENTIATED	5 (16.6%)	1 (3.33%)

These were the patients who presented with Squamous cell Carcinoma histology. One patient presented with Sarcomatoid histology of well differentiated category who showed partial response to treatment.

PERFORMANCE STATUS Vs RESPONSE:

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

Table no: 13, ECOG Vs Response

ECOG	COMPLETE RESPONSE	PARTIAL RESPONSE
0	14 (46.6%)	4 (13.33%)
1	10 (33.3%)	1 (3.33%)

AGE:

In this study people aged less than 50yrs were 15 patients out of them 12(80%) had complete response. In case of above 50yrs there were

15 patients, in which only 66% had complete response.

Table no: 14, Age Vs Response

AGE GROUP	COMPLETE RESPONSE	PARTIAL RESPONSE
31-40Yrs	3(10%)	3(10%)
41-50Yrs	5(16.66%)	1(3.33%)
51-60Yrs	13(43.33%)	1(3.33%)
61-70Yrs	3(10%)	1(3.33%)

TREATMENT RELATED ACUTE TOXICITIES:

ACUTE LOCAL TOXICITY:

` Acute local toxicity is done by RTOG Acute morbidity scoring criteria.(Table 15, figure no:15)

SKIN REACTION:

In this study 77% of the patients had Grade 1 skin reactions in the form of dry desquamation, decreased sweating. Another 23% had patchy moist desquamation whereas none of the patients had Grade 3 or 4 reactions. For those patients with grade 2 reactions, i.e, patchy moist desquamation, hydrogel dressing was given if needed.

Instructions were given to maintain clean and dry skin over the irradiated area. None of the patients had treatment breaks due to these toxicities.

MUCOSITIS:

Nearly 40% of the study population developed grade 2 reactions in the form of dysphagia and pharyngitis. Most of their diet consisted of bland, puréed food and liquids. None required nasogastric tube feeding or intravenous fluid with hospital stay. Supportive measures with analgesics, strict oral hygiene, mouth-wash with alcohol free antibacterial solution was adviced if needed. Also T. Dexamethasone 8mg PO bid was given for 4-5 days.

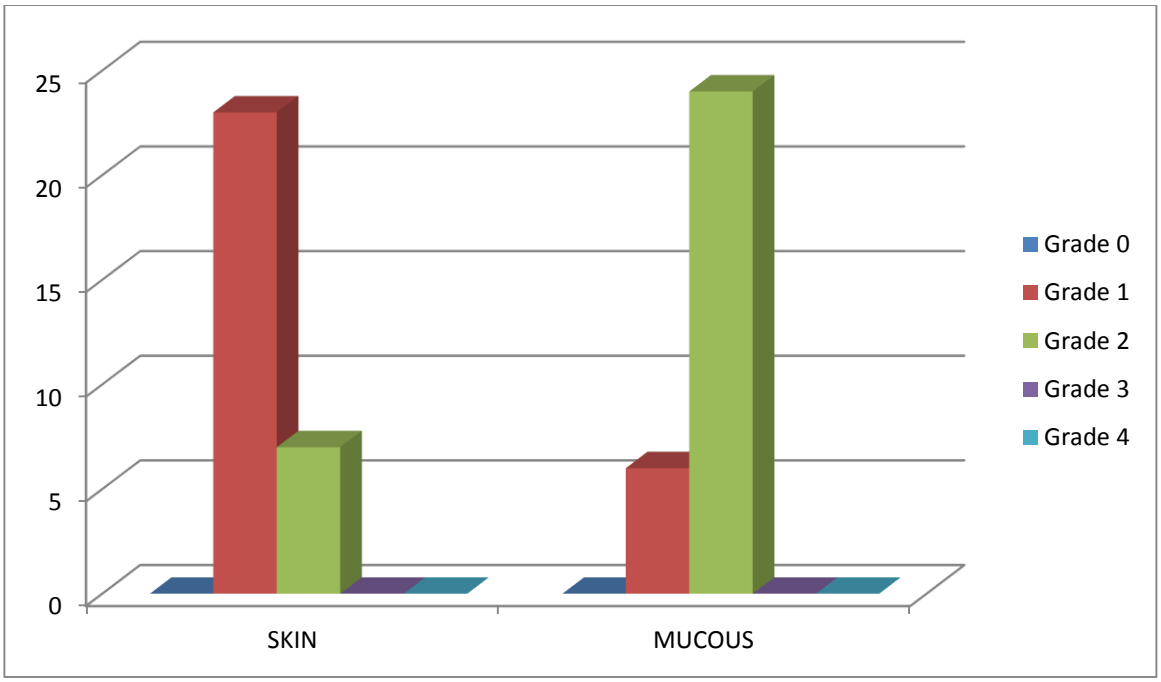


Figure No:15, Acute Toxicities

ACUTE TOXICITY	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
SKIN REACTIONS	0	23 (76.66%)	7 (23.33%)	0	0	0
MUCOSITIS	0	6 (20%)	24 (80%)	0	0	0

Table No:15, Acute Toxicities

OTHER TOXICITIES:

One patient had grade 1 laryngeal edema, which did not require hospitalization or tracheostomy. None of the patients had grade 3 or 4 toxicities. None of the patients had cartilage necrosis. None of the patients had systemic or hematological toxicity.

DISCUSSION

DISCUSSION

The head and neck cancer census incidence is increasing in the present decade. Mainly in India, due to the habit and addiction towards tobacco in smoked form like cigarettes or beedi also in smokeless forms like pan, kurkha etc plays a major causative effect. As the youngster's exposure to these agents increase, there is rise in cancer incidence, mainly head and neck cancer.

As the head and neck cancer affects the quality of life in patients due to disfigurement, dysphagia, hoarseness of voice etc. Patients also in our country present in advanced stage due to lack of awareness, illiteracy, poor socioeconomic status. This gives them very limited treatment options.

Cases of early glottic carcinoma commonly experience a change in voice, maybe associated with hoarseness and/ or sore throat. The priority of the treatment should be to achieve good local control and preserve the function and structure of the vocal cords and laryngeal structures as it is in its early. There are various options to achieve good local control , which include laser excision, endoscopic submucosal resection, partial laryngo-pharyngectomy, and total laryngo-pharyngectomy. Superior organ preservation with better voice quality has been reported in use of radiation therapy alone when compared to surgery.

Good local control can be achieved by radiation therapy alone as shown in these studies. Dose and dose per fraction schedule differs from institution to institution and the standard dose is usually a total of 70 Gy in 35 fractions, given five days per week. The local control rates using this dose prescription have been good in achieving local control

and delaying DFS. More studies have sought to achieve higher control rates by using higher dose per fraction. A higher dose per fraction can be used in these tumors owing to several factors.

Radiobiology explains that **hypofractionation will lower the therapeutic ratio between tumors and late-responding normal tissues, compared with conventional fractionation, in the same overall time.** This expectation depends on the α/β ratio for the tumor being considerably higher than for late-responding normal tissues; exceptions could therefore occur for tumors that have low α/β ratios, for example some melanomas, liposarcomas and potentially early-stage prostate and breast cancer. Hypofractionation is considered to be superior to conventional fractionation.

Overall treatment time affects both acute effects and tumor control. It is now well documented for head and neck cancer, that, local control is reduced by about 0.4 -2.5% for each day that overall treatment time is prolonged. **Hypofractionation is advantageous in this regard as it administers the same dose (BED value of the dose or EQD2) to complete it in a shorter time period.** The BED (Biologically Effective Dose) for this dose regimen is calculated to be 77.17 Gy, which is slightly higher than the prescribed dose for the standard early stage glottic carcinoma, but is by no means lesser or inadequate compared to the former.

Another factor to take into account is **tumor repopulation**. This is the phenomenon by which treatment with any cytotoxic agent, including radiation, can trigger surviving cells (clonogens) in a tumor to divide faster than before. This is known

as accelerated repopulation. During the time that the tumor is overtly shrinking and regressing, the surviving clonogen are dividing and increasing in number more rapidly than ever. Withers and colleagues surveyed the literature on radiotherapy for head and neck and estimated the dose to achieve local control in 50% of cases as a function of overall duration of fractionated treatment. The analysis suggests that clonogen repopulation in this human cancer accelerated at about 28 days after the initiation of radiotherapy in a fractionated regime. A dose increment of about 0.6 Gy per day is required to compensate for this repopulation. Such a dose increment is consistent with a 4-day clonogen doubling rate, compared with a median of about 60 days for unperturbed growth. This problem of accelerated repopulation of the tumor clonogens is circumvented by a shorter treatment time duration and yet achieving the same tumoricidal dose to achieve excellent local control.

Another reason for the feasibility of hypofractionated radiation therapy in early glottic cancer is due to the fact that **squamous cell carcinoma of the glottis is usually well differentiated and a slowly growing lesion.**

In a study done by **Krzysztof Skladowski et al**., the dose along with the overall treatment time was established. They also took into account the pretreatment hemoglobin level of the patient. In this study, 235 patients with T1N0M0 glottic cancer were recruited and treated by radiation therapy alone given in a conventional schedule with 5 fractions each week. The individual total dose, dose per fraction, and overall treatment time (*OTT*) ranged from 51–70 Gy, 1.5–3.0 Gy, and 24–79 days, respectively. The median follow-up

was 48 months. Patient data—total dose, dose per fraction, Overall Treatment Time and hemoglobin level (Hb) measured before the radiation treatment—were fitted by the mixed LQ/log-logistic model. They concluded that the dose–response curve for 235 patients with T1 glottic cancer was well defined and steep, and showed significant decrease in tumor control probability (*TCP*) when total doses were below 61 Gy. The 10-day prolongation of *OTT*, from 45 to 55 days, decreased the *TCP* by 13%. The dose of 0.35 Gy/day, compensated repopulation during the 1 day of prolongation, which indicates a **potential doubling time (Tpot) for glottic T1 tumor clonogens of 5.5 days.** The drop of Hb level of 1 g/dl (from 13.8 g/dl to 12.8 g/dl) gave a 6% decrease of *TCP*, provided that *OTT* was 45 days. Therefore, dose per fraction, above 2Gy and overall treatment time to around 6 weeks proves to be a schedule where acceptable tumor control is achieved.

In another study where growth rate of laryngeal cancer was studied, there was a variable range of the rate of growth**. The rate of tumor growth seemed to be an important factor for Disease Free Survival and Overall Survival**. This tumor growth rate is independent of age, differentiation and tumor volume associated with DFS, but N-stage seems to be a more important risk factor. There are sparse lymphatics in the laryngeal glottis, hence, the major risk factor can be taken into less consideration when analyzing the factors that affect the growth rate of the tumor, which in turn, affect the DFS and OS. This study showed that tumors that grow rapidly had a worse outcome in the form of decreased DFS and that slow growing tumors shows better DFS and OS. This

pertains to slowly growing early stage glottic cancers which are slow growing and are amenable to fractions sizes above 2.0 Gy i.e., the standard dose per fraction.

Other studies that have shown increased benefit in terms of local control by using a dose higher than the standard fraction have been successful and have proven that hypofractionated radiation therapy is the preferred treatment in early stage glottic cancer.

. This trial compared two arms- one that of conventional fractionation 66 Gy in 33 fractions for T1 disease, 70 Gy in 35 fractions for T2 disease and a hypofractionation arm 63 Gy in 28 fractions for T1 disease and 67.5 Gy in 30 fractions for T2 disease. All patients were followed up for 67 months and the primary objective was local progression free survival. **The 5-year local progression free survival for the conventional arm was 77.8% and 88.5% for the hypofractionated arm**. There was no difference in toxicity in both the arms. This study established the fact that hypofractionation is not inferior to conventional radiation in terms of local control and toxicity. This method of treatment proved that hypofractionated radiotherapy can be given for early T1 and T2 lesions in carcinoma of glottis with advantages of potential better local control and shortened treatment time.

A Japanese study by **Onimaru et al** was done in 200 patients with T1-T2 glottic cancers to investigate the importance of the overall treatment time by giving hypofractionated radiation therapy 2.5 Gy per fraction for a total dose of 65 Gy, four fractions a week. It was found that patients who completed the treatment within 46 days had a significantly better local control (91.9±2%) than those who completed treatment in 47 or more days (82.6±6%).

Ermis et al conducted a retrospective analysis with hypofractionated radiotherapy with 55Gy in 20fractions at 2.75Gy per fraction in 132 patients**. Five year local control and overall control rates were 85.6 % and 97.3 % respectively, with T1a having 91.8 % and 100 %, T1b - 81.6 and 93.8 %, and T2 - 80.9 % and 95.8 %.** Only one patient needed tracheostomy due to a non-functioning larynx while on long term follow up. This study concluded that hypofractionated radiation therapy for early stage glottic cancer shows high rates of local control with acceptable toxicity.

Another study from Japan done by **Karasawa et al** evaluated the effect of hypofractionated radiation therapy in 69 patients of early glottic cancer with 2.25 Gy per fraction upto a total dose of 63 Gy treated within a median time of 41 days. One case of T2 glottic cancer could not reach complete response, but all other cases achieved complete response. **The 5-year LC rates in larynx T1 and larynx T2 were 97.6%, and 70.1%, respectively.** No acute adverse effects more than Grade 2 toxicity (CTCAE 3.0) were seen. They concluded that this treatment was safe and valuable in treating early glottic cancer, with T1 showing a better outcome compared to historical data. For T2, local control did not show any improvement compared to historical data and treatment strategy that involves dose excalation is needed for these tumors.

Khan et al conducted a retrospective analysis to evaluate the patient, tumor and treatment characteristics in patients with early glottic carcinoma in 141 patients. Therapy consisted of 2.2 Gy per fraction for 25 fractions upto a total dose of 55 Gy within 5 weeks with a 6 MV linear accelerator. **The 5-year local control rates were as follows: T1a, 94%; T1b, 83%; T2a , 87%; T2b, 65%.** The 10-year local control rates were as

follows: T1a, 89%;T1b, 83%; T2a, 87%; T2b, 56%. This study highlighted the **improvement in voice quality post radiation therapy in those patients who initially had poor voice quality.** 73% out of the 92% of patients experienced an improvement, and none of the patients suffered severe or fatal complications. They concluded that definitive radiotherapy offered excellent local control in T1-T2a, N0 glottic carcinoma along with good voice preservation and minimal long term toxicity. T2b tumors had an inferior response and alternative strategies may be considered.

Mendenhall et al described a local control of 94%, 93%, 80%, 72% for T1a, T1b, T2a and T2b respectively for patients treated with 2-2.25 Gy per fraction, one fraction daily. Out of the 519 patients received radiotherapy at the University of Florida (Gainesville, FL) for T1N0–T2N0 glottic carcinoma, six patients developed severe complications, including severe mucositis necessitating hospitalization and a treatment break , total laryngectomy for a suspected local tumor recurrence with a pathologically negative specimen, laryngeal edema, and a pharyngo-cutaneous fistula after a salvage total laryngectomy . Five of these patients had T2N0 disease. None of these patients died.

Laskar et al conducted a retrospective analysis to evaluate the effect of dose and fractionation with respect to tumor characteristics, toxicity and outcome in patients with T1N0 glottic cancer. The records of 652 patients were analyzed. The four hypofractionated schedules were 50 Gy in 15 fractions (3.3 Gy per fraction), 55 Gy in 16 fractions (3.43 Gy per fraction), 60 Gy in 24 fractions (2.5 Gy per fraction) or 62.5 Gy in 25 fractions (2.5 Gy per fraction). The patients were categorized into two groups of < 3 Gy or > 3 Gy. All patients were treated with 6MV photons in linear accelerator. **Local**

control in 10 years was 84% and overall survival was 86.1% for T1 glottic carcinoma.

Short et al conducted yet another study to analyze the effect of dose and fractionation compared to standard fractionation (SFX) in T1, T2 N0 tumors in glottic cancer. This New Zealand study employed Accelerated Hypofractionated Radiation Therapy (AHFX), with 145 patients receiving this treatment. The treatment consisted of 60-66 Gy in 30-33 fractions (SFX) with ^{60}Co and 6 MV beams. AHFX consisted of 52.5-55 Gy in 20 fractions over 4 weeks using ^{60}Co and 6 MV beams. The 5-year overall survival was 78%. The 5-year loco-regional control for T1was higher in AHFX compared to SFX. Locoregional control in T2 was similar in both fractionation schedules. None of the patients had grade 4 or 5 late reactions. **These results showed that AHFX is comparable to standard fractionation regimen with equivalent local control and toxicity.**

Spector et al evaluated the therapeutic outcome of dose on the voice quality and preservation in patients treated with low dose, high dose radiation therapy and surgery. This retrospective study analyzed 625 patients who were divided into four groups- low dose radiation- 55-65 Gy, in 1.5-1.8 Gy per fraction, high dose radiation with 65-70 Gy in 2-2.25 Gy per fraction daily. 404 patients underwent conservation surgery and 61 underwent endoscopic resection. The overall local control was 89% and the overall unaided laryngeal voice preservation was 90%. Actuarial survival was significantly decreased in the low dose group was compared to the other groups. This study concluded that the four treatments used provide similar rates of survival and ultimate local control.

The low dose arm was associated with lower actuarial overall survival and unaided voice preservation. **Hence, the survival, local control and voice preservation rates were comparable in all groups except for low dose radiation group which showed a lower overall survival and unaided voice preservation**.

Quynh-Thu X. Le et al performed a prospective study in the University of California to assess the significance of fraction size, total dose and overall treatment time in the control of T1-T2, N0 glottic carcinoma. A total of 398 patients were recruited and treatment was delivered in 5 days per week. Minimum tumor dose ranged from 46.6-77.6 Gy , with a median dose of 63 Gy. The fraction size was <1.8 Gy in 146 patients, 1.8-1.99 Gy in 128, 2-2.24 Gy in 62 and 2.25 Gy in 62 patients. All patients were treated within a median of 50 days. **5 year control was 85% for T1 and 70% T2 glottic carcinomas.** For the T1 lesions, there was no apparent relationship between the fraction size, overall time and total dose with respect to local control on multivariate analysis. For T2 lesions, local control rate was 100% for the patients treated with 43 days overall time, 2.25 Gy per fraction. Local control was 44% for those treated with fractions size <1.8 Gy, 78% for those treated with a total >65 Gy. This study concluded that factors like total dose and overall treatment time were significant factors when considering the treatment and local control of T2 but not T1 glottic carcinomas. Anterior commisure involvement was also associated with lower local control rates for T1 but not T2 lesions.

Gowda et al. conducted a study in T1 glottic tumors with invasive squamous cell carcinoma. All patients were treated with definitive radiotherapy with a total tumor dose

of 50-52.5 Gy in 16 fractions over 21 days. The fraction size ranged from 3.12 to 3.28 Gy. **This study achieved 5-year local control rates of 93%**; there were 14 recurrences of which seven were successfully salvaged by surgery, giving **an ultimate local control of 96%. The 5-year overall survival was 80% and cause specific survival was 97% at 5 years.**

SUBSET ANALYSIS

Most of the patients were males, which might be due to the associated risk factors like smoking and alcohol. The response rate was also higher in males when compared to females.

Well differentiated tumors showed a poorer response when compared to moderately or poorly differentiated tumors. The results of this study showed poorly differentiated high CR > moderately > well differentiated histology. One patient with sarcomatoid histology showed poor response.

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

The secondary objective of this study is the toxicity assessment. Most of the patients had grade 1 or 2 skin reactions and mucositis. None of the patients required parenteral feeding or nasogastric tube feeding. None of the patients experienced grade 3

or 4 toxicity. There was one case of grade 1 laryngeal edema. The patient was treated conservatively and didn't require hospitalization.

There were no treatment related deaths in this study.

MERITS OF THIS STUDY:

- All patients had early stage glottic cancer squamous cell carcinoma, except one patient, and the treatment of choice is primary radiation therapy, was given.
- Optimal tumoricidal dose of 63Gy in hypofractionated RT, BED value of 77 Gy, was given for all patients.
- Treatment time was shorter than the time taken by standard fractionation.
- Toxicities were manageable. No treatment related death occurred in this study. Toxicity were graded with RTOG Acute radiation morbidity scoring criteria and CTCAE version 4.03
- Response assessment was done after 4-6weeks of completion of radiation, RECIST 1.1 criteria was used for assessment.

DEMERITS OF THIS STUDY:

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

Future perspective:

This study further established the feasibility and efficacy of radiation in early stage glottic cancer. Different fractionation protocol might be needed to compare with to achieve adequate BED/EQD2 , especially for T2 tumor control. Randomized trial using the same protocol is recommended.

CONCLUSION

CONCLUSION

Hypofractionated radiation therapy is valuable and feasible in the definitive treatment by radiotherapy and provides excellent LC and CSS for T1-T2, N0 glottic SCC, with excellent voice preservation outcomes and minimal long term toxicity. Dose fraction sizes above 2.25 Gy have shown excellent local control. For the long term analysis of this study, a longer follow up period is required. Dose fraction sizes of 3.12-3.28 Gy may be required for better local control of T2 tumors. There must be caution while using a large dose per fraction for the prevention of late toxicity in the form of cartilage necrosis or severe laryngeal edema. A dose schedule of 55Gy in 20 fractions over 4 weeks offers high rates of local control with acceptable long term toxicity for both T1 and T2 disease.

Non-SCC histology might be less responsive to radiation therapy alone and dose escalation might be required for good local control.

In general, definitive treatment with radiotherapy of dose per fraction above 2.0 Gy is safe, beneficial and feasible for patients with early glottic cancer, showing excellent local control rates along with preservation of voice quality and minimal toxicity.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. National Notifiable Diseases Surveillance System (NNDSS). Available from http://wwwn.cdc.gov/nndss/script/conditionsummary.aspx CondID=32

2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55:74.

2 (A). International agency for research on cancer, WHO press release. December 2013.

3. Head and neck cancer in India. Availbablehttp ://www.veedaoncology.com/PDF-Document/Head-neck%20Cancer%20In%20India.pdf. (Last assessed on:2011 Dec 26)

4. Franceschi S, Talamini R, Barra S, et al.Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. Cancer Res 1990;50:6502–6507.

5. KulkarniM.R.Indian Journal Of Head and Neck Surgery, January-April 2013;4(1):29-35

6. Tobacco Use In India: An Evil With Many Faces. Available from http://www.cpaaindia.org/infocentre/acs/eng/Tobacco%20Abuse.pdf

7. International Agency for Research on Cancer. Smokeless tobacco and tobacco-specific nitrosamines. In: *IARC monographs on the evaluation of carcinogenic risks to humans*, vol. 89.Lyon: IARC, 2007:57

8. Sinha DN, Gupta PC, Dobe M, Prasad VM.Tobacco control in schools of India: review from Global School Personnel Survey 2006.Indian J Public Health. 2007 Apr-Jun;51(2):101-6.

9. Lee KW, Kuo WR, Tsai SM, et al. Different impact from betel quid, alcohol and cigarette: risk factors for pharyngeal and laryngeal cancer. Int J Cancer 2005;117:831–836.

10. Dal Maso L, La Vecchia C, Polesel J, et al. Alcohol drinking outside meals and cancers of the upper aero-digestive tract. Int J Cancer 2002;102: 435–437.

11. Huang WY, Winn DM, Brown LM, et al. Alcohol concentration and risk of oral cancer in Puerto Rico. Am J Epidemiol 2003;157:881–887.

12. Pöschl G, Seitz HK. Alcohol and cancer.Alcohol Alcohol. 2004;39(3):15565.

13. Bagnardi V., Blangiardo M.,LAVecchia, C., Corrao G. A metaanalysis of alcohol drinking and cancer risk.British Journal of Cancer 85:1700– 1705, 2001. PMID: 11742491

14. Talamini R.; LA Vecchia C.; Levi F.et.al. Cancer of the oral cavity and pharynx in nonsmokers who drink alcohol and in nondrinkers who smoke tobacco. Journal of the N Engl J Med, Vol. 344, No. 15

15. Gillison ML, Koch MW, Capone RB, Spafford M, Westra W, Li Wu et al. Evidence for a Causal Association Between Human Papillomavirus and a Subset of Head and Neck Cancers. Journal of the National Cancer Institute 2000;92

16. Duncan W, MacDougall RH, Kerr GR, Downing D. Adverse effect of treatment gaps in the outcome of radiotherapy for laryngeal cancer. *Radiother Oncol* 1996; **41:** 203-7.

17.Wilczynski SP, Lin BT, Xie Y, Paz IB. Detection of human papillomavirus DNA and oncoprotein overexpression are associated with distinct morphological patterns of tonsillar squamous cell carcinoma. *Am J Pathol* 1998;152:145

18. Fakhry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. *J ClinOncol* 2006;24:2606

19. Munger K, Phelps WC, Bubb V, Howley PM, Schlegel R. The E6 and E7genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. *J Virol* 1989;63:4417.

20. Park NH, Min BM, Li SL, Huang MZ, Cherick HM, Doniger J. Immortalization of normal human oral keratinocytes with type 16 human papillomavirus. *Carcinogenesis* 1991;12:1627

21. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. Nov 2007; 36(10):575-80. 22.Cowan CG, Gregg TA, Napier SS, McKenna SM, Kee F.Potentially malignant oral lesions in northern Ireland: a 20-year population-based perspective of malignant transformation. Oral Dis 2001; 7:18-24.

23. Ai L, Vo QN, Zuo C, et al. Ataxia-telangiectasia-mutated (ATM) gene in head and neck squamous cell carcinoma: promoter hypermethylation with clinical correlation in 100 cases. *Cancer Epidemiol Biomarkers Prev* 2004;13:150.

24. Fortin A, Couture C, Doucet R, Albert M, Allard J,Tetu B. Does Histologic Grade Have a Role in the Management of Head and Neck Cancers?. J ClinOncol 2001;19:4107-4116

25. A.K. Agarwal, AswiniSethi, deepikasareen and ShruthiDhingra , treatment delay in Oral and oropharyngeal cancer in our population: the role of socioeconomic factors and health seeking behaviour. Indian J otolaryngology, Head and Neck Surgery. 2011 April ; 63(2); 145-150

26. OM Cojocariu, Huguet F, Lefevre M, S Périé.Prognostic and predictive factors of cancer of the upper aerodigestivetract.Bulletin du Cancer 2009;96:4:369-78

27. Krzysztof Skladowski, M.D., Rafal Tarnawski, M.D., Boguslaw Maciejewski, M.D.,Andrej Wygoda, B.M., Krzysztof Slosarek.D.S. Clinic of Radiation Oncology and Departments of Radiotherapy and Radiobiology, Centre of Oncology,Maria Sklodowska-Curie Memorial Institute, 44-101 Gliwice, Poland

28. Mendenhall WM, Parsons JT, Mancuso AA, *et al.* Larynx. In:Perez CA, Brady LW, editors. Principles and practice of radiation oncology. 3rd ed. Philadelphia, PA: Lippincott- Raven; 1997. p. 1069–1093.

29. Sinard RJ, Netterville JL, Garrett CG, *et al.* Cancer of the larynx. In: Meyers EN, Suen JY, editors. Cancer of the head and neck. 3rd ed. Philadelphia, PA: W.B. Saunders Co; 1996.p. 381–421.

30.Corvo R, Giaretti W, Sanguineti G, et al. Potential doubling time in head and neck tumors treated by primary radiotherapy: preliminary evidence for a prognostic significance in local control. Int J Radiat Oncol Biol Phys 1993;27:1165–72.

31. Jensen AR, Nellemann HM, Overgaard J. Tumor progression in waiting time for radiotherapy in head and neck cancer. Radiother Oncol 2007;84:5–10.
Liselotte W. van Bockel , Gerda M. Verduijn b, Evelyn M. Monninkhof , Frank A. Pameijer ,Chris H.J. Terhaard ,University Medical Centre Utrecht, Department of Radiation Oncology; Erasmus Medical Centre, Department of Radiation Oncology, Rotterdam; University Medical Centre, Utrecht, Julius Center for Health Sciences and Primary Care; University Medical Centre Utrecht, Department of Radiology, The Netherlands

32. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62(1):10–29.

33. Rancati T, Schwarz M, Allen A, et al. Radiation dose-volumeeffects in the larynx and pharynx. *Int J Radiat Oncol Biol Phys*2010;**76**(Suppl.):S64–9.8. 34.Le QT, Fu KK, Kroll S, et al. Influence of fraction size, totaldose, and overall time on local control of T1–T2 glottic carcinoma. *Int J Radiat Oncol Biol Phys* 1997;**39**(1):115–26.9

35. Chera BS, Amdur R, Morris C, et al. T1 N0 to T2 N0 squamouscell carcinoma of the glottic larynx treated with definitiveradiotherapy. *Int J Radiat Oncol Biol Phys* 2010;**78**(2):461–6.10.

36. Yu E, Shenouda G, Beaudet MP, et al. Impact of radiationtherapy fraction size on local control of early glottic carcinoma. *Int J Radiat Oncol Biol Phys* 1997;**37**(3):587–91.11

37. Yamazaki H, Nishiyama K, Tanaka E, et al. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *Int J Radiat Oncol Biol Phys* 2006;**64**(1):77–82.12.

38. Mendenhall W, Amdur R, Morris C, et al. T1–T2 N0 squamouscell carcinoma of the glottic larynx treated with radiationtherapy. *JCO* 2001;**19**(20):4029–36.13.

39. Franchin G, Minatel E, Gobitti C, et al. Radiotherapy forpatients with early-stage glottic carcinoma: univariate andmultivariate analyses in a group of consecutive, unselectedpatients. *Cancer* 2003;**98**:765–72.14.

40. Fein DA, Lee WR, Hanlon AL, et al. Do overall treatment time,field size and treatment energy influence local control ofT1–T2 squamous cell carcinomas of the glottic larynx? *Int JRadiat Oncol Biol Phys* 1996;**34**(4):823–31.15.

41. Reddy SP, Hong RL, Nagda S, et al. Effect of tumor bulk onlocal control and survival of patients with T1 glottic cancer: a30-year experience. *Int J Radiat Oncol Biol Phys* 2007;**69**:1389–94.16

42. Nishimura Y, Nagata Y, Okajima K, et al. Radiation therapyfor T1,2 glottic carcinoma: impact of overall treatment timeon local control. *Radiother Oncol* 1996;**40**:225–32.

43. Gowda RV, Henk JM, Mais KL, Sykes AJ, Swindell R, Slevin NJ. Three weeks radiotherapy for T1 glottic cancer: the Christie and Royal Marsden Hospital

experience. *Radiother Oncol* 2003; **68:** 105-11.

44. Short S, Krawitz H, Macann A, West T, Morton RP, McIvor NP, et al. T1N0/ T2N0 glottic carcinoma: a comparison of two fractionation schedules. *Austr Rad* 2006; **50:** 152-7.

45. Dinshaw KA, Sharma V, Agarwal JP, Ghosh S, Havaldar R. Radiation therapy in T1-T2 glottic carcinoma: influence of various treatment parameters on local control/ complications. *Int J Radiat Oncol Biol Phys* 2000; **48:** 723-35.

APPENDIX 1

TABLE NUMBER	TITLE
1	Cancer trend
2	Head and neck cancer Site (1)
3	Head and neck cancer site (2)
4	Age distribution of study population
5	Gender distribution of study population
6	ECOG performance status
7	Habits/ addiction of the study population
8	Symptoms / Signs
9	Primary site
10	Subsite analysis
11	Tumor Tstage
12	Stage grouping
13	Histological differentiation
14	Response results
15	Site Vs response
16	T stage Vs response
17	Histological response Vs Response
18	ECOG Vs Response
19	Age Vs response
20	Stage Vs response
21	Treatment Vs response
22	Acute Toxicity

APPENDIX 2

FIGURE	TITLE
1,2,3,4	Anatomy of larynx
5	Lymph node incidence
6	Age distribution of the study population
7	Gender distribution of the study population
8	ECOG performance status
9	Symptoms and signs
10	Site distribution of the study population
11	Subsite Analysis
12	T stage in the study population
13	Nodal stage in the study population
14	Stage grouping
15	Treatment results – Response
16	Site Vs Response
17	T stage Vs Response
18	Histologic differentiation Vs Response
19	Response in the Primary
20	Acute toxicity

APPENDIX 3

RTOG ACUTE RADIATION MORBIDITY CRITERIA

SITE	GRADE 0	GRADE1	GRADE2	GRADE3	GRADE 4
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous Membran e	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis

SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste		Acute salivary gland necrosis
Pharynx & Esophagu s	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia / may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pretreatment baseline) requiring N-G feeding tube, I.V. fluids or hyper alimentation	Complete obstruction, ulceration, perforation, fistula

Laryngitis	No change over baseline	Mild or intermittent hoarseness/cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

INFORMATION TO PARTICIPANTS

Title: "HYPOFRACTIONATED RADIATION THERPAY IN EARLY GLOTTIC CARCINOMA"

Name of Participant:
Name of the Principal(co – investigator) :DR.SHIRLEY T.LEIVON
Name of the institution : Department of radiotherapy, RGGGH, MMC.

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

What is the purpose of research?
Carcinoma glottis is mainly caused by lifestyle habits like cigarette smoking and alcohol. Early stage laryngeal cancers are good candidates for definitive radiotherapy. Other treatment options include laser excision, endoscopic submucosal resection, partial laryngo-pharyngectomy, total laryngo-pharyngectomy. Surgical procedures offer good local control but with loss of organ function.
Definitive hypofractionated RT can be given to preserve organ function with equal, if not inferior, local control as conventional RT. The five-year local control rates have been reported to be 85–94% in T1 larynx, 69–80% in T2 larynx with definitive radiotherapy.*
Early glottic tumors(T1,T2, N0 M0) do not spread to regional lymph nodes and are effectively treated by radiation therapy to the primary tumor alone or, in select circumstances, by surgery .A single modality of treatment should suffice. Radiation therapy is generally the preferred option, based on better subsequent voice quality.However, no high-level evidence exists to select between treatment options.
To evaluate tumor response and acute toxic reactions.Treatment response assessment 1 month after completion of treatment by physical examination and CT/MRI of the neck; and toxicity measurement by Common Terminology Criteria for Adverse Events version 3.0 (CTCAE ver. 3.0)

Dose of 2.25 Gy per fraction, for T1 leasions, a total of 63 Gy, 28 fractions, 2.25 Gy per fraction and for T2 lesions, a total of 67.5 Gy, 30 fractions, 2.25 Gy per fraction. Patients are treated 5 days a week, for a total of 5.3 weeks for T1 and 5.5 weeks for T2 disease.
We want to test the efficacy and safety of We have obtained permission from the Institutional Ethics Committee.

The study design
Single arm prospective study

Study Procedures
The study involves evaluation of early stage carcinoma glottis with hypofractionated radiotherapy, each fraction of dose 2.25 Gy. Every week, the physician will examine you for possible toxicities. Some [blood / urine /clinical examination other] tests will be carried out

at each visit. 5 ml of blood will be collected at each visit. Blood collection involves prick with a needle and syringe.] These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.
In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document.
You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible benefits to other people

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

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

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

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

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

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

Signature of Investigator

Date

Signature of Participant

Date

INFORMED CONSENT FORM

TITLE OF THE STUDY **"HYPOFRACTIONATED RADIATION THERAPY IN EARLY STAGE GLOTTIC CARCINOMA"**

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL (Co – Investigator) : **DR.SHIRLEY T. LEIVON**

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising myfree power of choice, hereby give my consent to be included as a participant in "HYPOFRACTIONATED RADIATION THERAPY IN EARLY STAGE GLOTTIC CRACINOMA"

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

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

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

Name _____ Signature_____ Date_____

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

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent

Name _____ Signature_____ Date_____

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு

ஆரம்ப நிலை குரல்வளைய புற்றுநோய்க்கு குறைந்த பின் கதிர்வீச்சு சிகிச்சை கொடுக்கும் ஆய்வு.

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

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்துக்கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனக்கு ஆரம்ப நிலை குரல்வளைய புற்றுநோய் பகுதியில் குறைந்த பின் கதிர்வீச்சு சிகிச்சை எடுத்துக் கொள்ள சம்மதம்.

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

நான் ஆரம்ப நிலை குரல்வளைய புற்றுநோய்க்கு குறைந்த பின் கதிர்வீச்சு குறித்த இந்த ஆய்வுக்கான விவரங்கள் கொண்ட தகவல் தாளைப் பெற்றுக்கொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியின்படி முழு இரத்த பரிசோதனை, சிறுநீரகம் மற்றும் கல்லீரல் பரிசோதனை, நெஞ்சு ஊடுகதிர், தலை மற்றும் கழுத்து பகுதியில் கணினி வழி உடலுறுப்பு ஊடுகதிர்படம் எடுத்துக் கொள்ள சம்மதம். இந்த ஆராய்ச்சிக்கு தேவையான பிற பரிசோதனைகள் செய்துக்கொள்ள சம்மதம்.

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

ஆராய்ச்சியாளர் கையொப்பம்

பங்கேற்பாளர் கையொப்பம்

நாள் :
இடம் :

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ் காந்தி அரசு பொது மருத்துவமனைக்கு வரும் கர்பப்பை வாய் புற்றுநோய் நோயாளிகளிடம் கதிர்வீச்சு சிகிச்சை பற்றிய ஆராய்ச்சி.

ஆரம்ப நிலை குரல்வளைய புற்றுநோய்க்கு குறைந்த பின் கதிர்வீச்சு சிகிச்சை பற்றி ஆராய்வது இந்த ஆராய்ச்சியின் நோக்கம்.

இந்த ஆராய்ச்சியில் தங்களது நோயின் தன்மையை அறிய முழு இரத்த பரிசோதனை, சிறுநீரகம் மற்றும் கல்லீரல் பரிசோதனை, நெஞ்சு ஊடுகதிர், தலை மற்றும் கழுத்து பகுதியில் கணினி வழி உடலுறுப்பு ஊடுகதிர்படம் எடுக்கப்படும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் கதிர்வீச்சு சிகிச்சை மற்றும் புற்றுநோய் மருந்து அளித்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் தன்மையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

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

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

ஆராய்ச்சியாளர் கையொப்பம்

பங்கேற்பாளர் கையொப்பம்

நாள் :
இடம் :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

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

CERTIFICATE OF APPROVAL

To
Dr.Shrley T.Leivon
Post Graduate in MD Radiotherapy
Madras Medical College
Chennai 600 003

Dear Dr.Shrley T.Leivon,

The Institutional Ethics Committee has considered your request and approved your study titled **"HYPOFRACTIONATED RADIATION THERAPY IN EARLY STAGE GLOTTIC CARCINOMA" NO. 10102016.**

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

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

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

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

Member Secretary – Ethics Committee

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

Urkund Analysis Result

Analysed Document: thesis.docx (D31273961)
Submitted: 10/13/2017 3:05:00 AM
Submitted By: thai3orchid@gmail.com
Significance: 1 %

Sources included in the report:

hari thesis 190916 10pm 5.doc (D21833788)

Instances where selected sources appear:

2