QUALITY OF LIFE IN PATIENTS RECEIVING DYSPHAGIA OPTIMIZED INTENSITY MODULATED RADIOTHERAPY (DO-IMRT) IN HEAD AND NECK CANCERS

Thesis

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AIIMS, Jodhpur **Dr.Mukul Choubisa**

All India Institute of Medical Sciences, Jodhpur

DECLARATION

I hereby declare that the thesis titled "**Quality of life in patients receiving dysphagia optimized intensity modulated radiotherapy (Do-IMRT) in head and neck cancers**." embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

Dr. Mukul Choubisa

Department of Radiation Oncology,

All India Institute of Medical Sciences,

Jodhpur, India

All India Institute of Medical Sciences, Jodhpur

CERTIFICATE

This is to certify that the thesis titled "**Quality of life in patients receiving dysphagia optimized intensity modulated radiotherapy (Do-IMRT) in head and neck cancers**." is a record of the bonafide research work of Dr. Mukul Choubisa carried out under our guidance and supervision in the Department of Radiation Oncology, Department of Surgical Oncology and Department of Otorhinolaryngology , All India Institute of Medical Sciences, Jodhpur, Rajasthan. Dr Mukul Choubisa has learned and performed all the clinical and analytical procedures involved in the study under guidance and supervision.

Guide

Dr. Puneet Pareek

Additional Professor

Department of Radiation Oncology,

All India Institute of Medical Sciences, Jodhpur

Co-Guides

Dr. Amit Goyal

Professor and Head

Department of Otorhinolaryngology

AIIMS, Jodhpur

Dr. Jeewan Ram Vishnoi

Associate Professor

Department of Surgical Oncology,

AIIMS, Jodhpur

Dr. Darwin

Associate Professor

Department of Otorhinolaryngology

AIIMS, Jodhpur

All India Institute of Medical Sciences, Jodhpur

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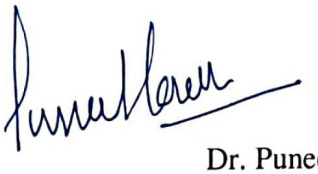
Forwarded and Recommended by

Guide



Dr. Puneet Pareek

Additional Professor

Department of Radiation Oncology,

All India Institute of Medical Sciences, Jodhpur

DEDICATED

TO

MY GRANDMOTHER

SURAJ DEVI

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Mukul Choubisa

LIST OF ABBREVIATIONS

HNSCC	HEAD AND NECK SQUAMOUS CELL CANCER
HPV	HUMAN PAPPILOMA VIRUS
HNSCC	HEAD AND NECK SQUAMOUS CELL CANCER
QOL	QUALITY OF LIFE
RT	RADIATION THERAPY
RR	RELATIVE RISK
3D CRT	3 DIMENSIONAL CONFORMAL RADIOTHERAPY
NACT	NEO ADJUVANT CHEMOTHERAPY
EORTC	EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER
HRQOL	HEALTH RELATED QUALITY OF LIFE
TOLM	TRANS ORAL LASER MICROSURGERY
TORS	TRANS ORAL ROBOTIC SURGERY
GY	GRAY
IV	INTRAVENOUS
RCT	RANDOMISED CONTROLLED TRIAL
IMRT	INTENSITY MODULATED RADIOTHERAPY
IGRT	IMAGE GUIDED RADIOTHERAPY
Do-IMRT	DYSPHAGIA OPTIMIZED INTENSITY MODULATED RADIOTHERAPY

DARS	DYSPHAGIA AND ASPIRATION RELATED STRUCTURES
MDADI	MD ANDERSON DYSPHAGIA INVENTORY
UW-QOL	UNIVERSITY OF WASHINGTON – QUALITY OF LIFE
OPC	OROPHARYNGEAL CANCER
VF	VIDEOFLUOROSCOPY
TD	TOXIC DOSE
S-IMRT	STANDARD INTENSITY MODULATED RADIOTHERAPY
PFS	PROGRESSION FREE SURVIVAL
OS	OVERALL SURVIVAL
GLOBOCAN	GLOBAL CANCER OBSERVATORY
GTV	GROSS TUMOUR VOLUME
CTV	CLINICAL TUMOUR VOLUME
PTV	PLANNING TUMOUR VOLUME
WHO	WORLD HEALTH ORGANISATION
OAR	ORGAN AT RISK
μDD /MDD	MEAN DARS DOSE
NCDC	NON COMMUNICABLE DISEASE CONTROL
ICT	INDUCTION CHEMOTHERAPY
RTOG	RADIATION THERAPY ONCOLOGY GROUP
HBCR	HOSPITAL BASED CANCER REGISTRIES
PBCR	POPULATION BASED CANCER REGISTRIES

CTRT	CONCURRENT CHEMORADIOTHERAPY
BOT	BASE OF TONGUE
SPCM	SUPERIOR PHARYNGEAL CONSTRICTOR MUSCLE
MPCM	MIDDLE PHARYNGEAL CONSTRICTOR MUSCLE
IPCM	INFERIOR PHARYNGEAL CONSTRICTOR MUSCLE
CPM	CRICOPHARYNGEUS MUSCLE
CE	CERVICAL ESOPHAGUS
EIM	ESOPHAGUS INLET MUSCLE
SGL	SUPRA GLOTTIC LARYNX
GL	GLOTTIC LARYNX
LFT	LIVER FUNCTION TEST
KFT	KIDNEY FUNCTION TEST
CBC	COMPLETE BLOOD COUNT
CECT	CONTRAST ENHANCED COMPUTED TOMOGRAPHY
IEC	INSTITUTE ETHICS COMMITTEE
OPD	OUTPATIENT DEPARTMENT
PR	PARTIAL RESPONSE
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
PK	PAIN KILLERS
WL	WEIGHT LOSS
OM	MOUTH OPENING

SS	STICKY SALIVA
SP	SPEECH
SO	SOCIAL EATING
PA	PAIN
DR	DRY MOUTH
SW	SWALLOWING
TE	TEETH
FI	FELT ILL
SC	SOCIAL CONTACT
SE	SENSES
(NU	NUTRITIONAL SUPPLEMENTS
CO	COUGH
SX	SEXUALITY
FE	FEEDING TUBE
WG	WEIGHT GAIN

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INTRODUCTION

INTRODUCTION

The Burden of Head and Neck Cancers

The term '*Head and Neck Cancers*' refers to cancers of upper aerodigestive tract, including the lips, oral cavity, oropharynx, Sino nasal cavities, larynx, hypopharynx and salivary glands(1). Head and Neck Squamous Cell Cancer (HNSCC) is the leading cause of mortality among cancers in India and takes the toll of the young human resource of the country (2,3). More than 75% of HNSCC are attributable to the use of tobacco and alcohol and a minority to infections with HPV or EBV. As per Global Cancer Observatory of International Agency, WHO report GLOBOCAN-2020, there are 219,722 new patients diagnosed with HNSCC every year with 121,906 deaths per year due to same(3). Almost 66.6% of HNSCC patients are diagnosed in locally advanced stage(4).

The Risk Factors and Carcinogenesis

The risk factors most frequently associated with head and neck cancer include smoking, alcohol consumption, human papillomavirus (HPV) infection (especially for oropharyngeal cancers), and Epstein-Barr virus (EBV) infection (especially for nasopharyngeal cancers in Asia), Smoking tobacco products (cigarettes, cigars, pipes) is an important risk factor for the development of head and neck cancer. In heavy cigarette smokers, there is a 5- to 25-fold increased risk of cancer compared with non-smokers(1). Smokeless tobacco (both chewing tobacco and snuff) is associated with an increased risk of cancer of the oral cavity and pharynx.

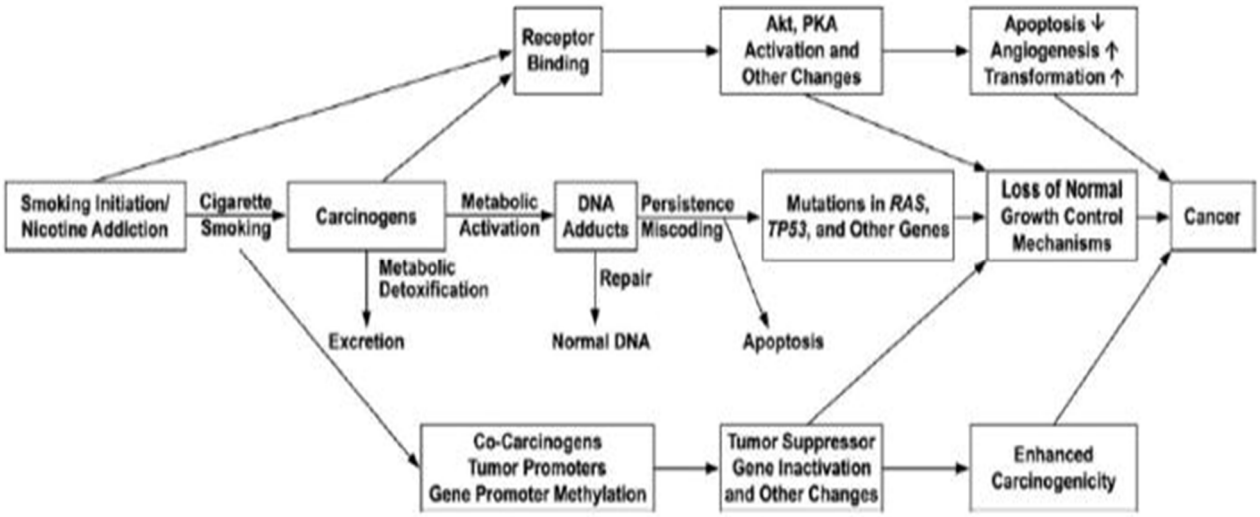


FIGURE 1: ROLE OF SMOKING IN ETIOPATHOGENESIS OF CANCER

Alcohol consumption independently increases the risk of cancer in the upper aerodigestive tract, although it is often difficult to separate the effects of smoking and alcohol. The RR of developing head and neck cancer due to alcohol appears to be dose dependent. Alcohol intake and tobacco smoking appear to have an interactive and multiplicative effect on the risk of developing head and neck cancer. The use of opium has been associated with an increased risk of laryngeal cancer, Betel nut chewing, which is widespread in certain regions of Asia, is an independent risk factor for the development of squamous cell head and neck cancer. The effects appear to be synergistic with tobacco and alcohol interacting with the genome of the host(5–7).

Clinical Signs and Symptoms

HNSCC is predominantly a locally invasive disease which metastasizes to distant organs only less than 5% of time. The exception is nasopharyngeal cancers which have high propensity of metastasis. Thus, most of the signs and symptoms of HNSCC are produced as a result of local disease.

Otalgia – Otalgia as a presenting symptom is significant. Cranial nerves 5, 7, 9, and 10 contribute afferents to the external and middle ear. Referred otalgia is considered a "red flag" in the evaluation of a patient with a possible head and neck malignancy.

Oral cavity tumours – Patients may present with mouth pain or nonhealing mouth ulcers, loosening of teeth, ill-fitting dentures, dysphagia, odynophagia, weight loss, bleeding, or referred otalgia. Up to 66 percent of patients with primary tongue lesions have cervical lymph node involvement, depending on T stage and depth of invasion, while the incidence is substantially lower in patients with hard palate cancers.

Tongue cancer may grow as an infiltrative and/or exophytic lesion. The presenting symptom is often pain, with or without dysarthria. Dysarthria implies deep muscle invasion of advanced tumour stage. There may be a history of longstanding leukoplakia or erythroplakia.

Lip cancer usually presents as an exophytic or ulcerative lesion of the lower lip, occasionally associated with bleeding or pain. Some patients complain of numbness of the skin of the chin due to involvement of the mental nerve

Oropharyngeal tumours – Presenting complaints can include dysphagia, pain (odynophagia, otalgia), obstructive sleep apnoea or snoring, bleeding, or a neck mass. Patients with human papillomavirus (HPV) positive oropharyngeal cancers often present with neck masses

Hypopharyngeal tumours – Patients with these tumours often remain asymptomatic for a longer period and are therefore more likely to be seen in the later stages of the disease. Dysphagia, odynophagia, otalgia, weight loss, haemoptysis, dyspnoea, and neck mass are common presenting symptoms.

Laryngeal Cancers – The symptoms associated with cancer of the larynx depend upon location. Persistent hoarseness may be the initial complaint in glottic cancers; later symptoms may include dysphagia, referred otalgia, chronic cough, haemoptysis, and stridor. Supraglottic cancers are often discovered later and may present with airway obstruction or palpable metastatic lymph nodes. Primary subglottic tumours are rare. Affected patients typically present with stridor or complaints of dyspnoea on exertion.

Treatment and Survival

Localized (early stage) disease — Approximately 30 to 40 percent of patients with head and neck squamous cell carcinomas present with stage I or II (early stage) disease. In general, these patients are treated with either primary surgery or definitive radiation therapy (RT). Patients with carcinoma in situ usually are managed surgically in the same way as those with T1 disease.

Five-year overall survival in patients with stage I or II disease is typically from 70 to 90 percent. Careful observation and follow-up after initial treatment are required both to detect a potentially curable recurrence and to identify and treat second primary tumours. RT and surgery result in similar rates of local control and survival for many sites; the choice of therapy is typically based upon the specific site and its requirements, the surgical accessibility of the tumour, and the functional outcomes and morbidity associated with each modality. Oral cavity cancers are a notable exception and are usually best treated with surgery, based upon generally better cure rates and toxicity profile compared with radiation-based therapy. Traditional surgical approaches through skin incisions to gain access to the primary (ie, wide local excision) are usually used for salivary and thyroid cancers, which are easily accessible. At other sites, minimally invasive techniques, such as transoral laser microsurgery (TOLM)

for larynx and hypopharynx cancers and transoral robotic surgery (TORS) for oropharynx cancers, have improved transoral access

Definitive RT approaches include external beam RT and brachytherapy. Curative RT treatment requires a three-dimensional conformal technique at a minimum. Highly conformal RT techniques, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), have demonstrated reduced morbidity and represent the current standard of care.

For patients initially treated with surgery for clinically early-stage head and neck cancers, postoperative RT, with or without concurrent chemotherapy, is indicated for those that are pathologically locoregionally advanced and have close or positive margins and other factors that increase the risk of local recurrence, including perineural invasion, lymph vascular invasion, and extra nodal extension. Locoregionally advanced (stage III/IV) squamous cell carcinoma of the head and neck is associated with a high risk of both local recurrence and distant metastases. Combined modality approaches (surgery, RT, and/or chemotherapy) are generally required to optimize the chances for long-term disease control. These combined modality approaches include primary surgery followed by either postoperative RT or concurrent chemoradiotherapy, induction chemotherapy (the addition of chemotherapy prior to surgery and/or RT), concurrent chemoradiotherapy without surgery, and sequential therapy (induction chemotherapy followed by concurrent chemoradiotherapy) without surgery.

In oral cavity, surgery is generally preferred for since most cases are easily accessible, and simultaneous resection and reconstruction can be accomplished with acceptable functional outcomes. However, oral cavity tumours are aggressive cancers with high rates of locoregional recurrence; thus, postoperative radiation therapy (RT), with or without chemotherapy, is generally used. Definitive RT, concurrent chemoradiotherapy, and sequential therapy are typically reserved for patients who are medically inoperable, who have unresectable disease, or who have resectable disease where surgical resection cannot be accomplished with acceptable long-term functional consequences (e.g., total glossectomy that may require total laryngectomy to prevent aspiration).

In pharyngeal tumours of Oro-Laryngo-Hypo Pharynx, Organ-sparing and, more importantly, function-sparing approaches (TORS, TOLM, chemoradiotherapy) rather than large ablative primary surgery are preferred for most patients with cancers of the oropharynx, hypopharynx, and larynx. Concurrent chemoradiotherapy is often a standard option for functional organ

preservation, either as upfront definitive treatment or in a postoperative setting. Definitive RT alone, often using an altered fractionation schedule, remains a treatment option for older adult patients and those with a poor performance status, as a meta-analysis showed a lack of benefit for concurrent chemotherapy in those in their 70s and a potential detrimental for those in their 80s

Thus radiation therapy becomes an inevitable part of the standard of treatment of head and neck malignancies.

Intensity modulated radiotherapy (IMRT)

Intensity modulated radiotherapy (IMRT) is a special form of three-dimensional conformal radiotherapy (3D-CRT). In contrast to conventional 3D-CRT, where only the beam apertures are shaped to the irregular form of the target, IMRT is based on the use of x-ray beams with individually optimized, non-uniform photon fluencies across the beam area. The treatment criteria for plan optimization are specified by the planner and the optimal fluence profiles for a given set of beam directions are determined through inverse planning. The patient input data for the inverse planning is same as that for forward planning. For each target the user will enter the plan criteria: maximum dose, minimum dose and a dose volume histogram. For critical structures the program requires the desired limiting dose and a dose volume histogram, before proceeding to optimizing intensity profiles and calculating the required dose distribution(8).

The treatment related toxicity and Quality of Life (QOL)

The World Health Organization has defined Quality of Life (QOL) as *"An individual's perception of their position in life, in the context of culture and value system in their life and in relation to their goals, expectations, standards and concern"*(9). Ionizing Radiations cause plethora of radiation induced changes in the normal tissues of the head and neck region. These adverse effects produce significant changes in the QOL, which may / may not resolve completely with time. Cancers arising in the head and neck sites are in close proximity to several critical structures such as the spinal cord, brainstem, parotid glands, optic apparatus (eyes, optic nerves, and chiasma), lacrimal glands, cochlea, and mandible that makes its treatment difficult and challenging. Each of these organs can manifest different reactions to radiation ranging from acute side effects during the treatment which may last for as long as 6 to 12 weeks after the completion of treatment. Most important of these acute toxicities is

mucositis which may limit treatment tolerance of most patients. Common acute toxicities include mucositis, dysphagia, dysgeusia, and dermatitis(10). The most common and debilitating late toxicity is xerostomia – gross reduction in salivary output – leading to persistent dryness of mouth, oral discomfort, difficulty in speech and swallowing, impairment of taste, and deterioration of dental hygiene(11,12). Some other late effects include subcutaneous fibrosis, hoarseness, and mucosal atrophy resulting in chronic dysphagia and increased risk of aspiration. Thus, both the disease (H & NSCC) and its treatment (radiation therapy or chemoradiation) can significantly affect disease- specific health-related QOL domains such as speech, salivary, and swallowing functions as well as more general QOL domain such physical, mental, and social health(13,14). The measurement of such QOL parameters are often done using questionnaires with likert like scales which are further transformed and grouped in domains of various QOL(15).

In cases where dysphagia is present, it is often attributed to an array of functional characteristics, such as reduced retraction of base of tongue, poor epiglottic retroflexion, reduced laryngeal elevation, delay in pharyngeal transit, and/or poor coordination of swallowing muscles. In many cases, these functional characteristics are accompanied by oral mucositis, causing continuous pain, resulting in difficulty with oral eating, malnutrition, and/or weight loss; systemic fatigue and nausea may also play a role diminishing motivation to eat. Of note, mucositis is also strongly related to other cofactors including smoking, infection, oral hygiene, and nutritional status

Onset of post-radiation dysphagia has been linked to both consequential and generic late effects. Early inflammatory damage to mucosa (i.e., xerostomia, mucositis) and radiation dose have been significantly correlated with dysphagia at 6–12 months post-treatment, indicative of consequential effects. However, dysphagia can also present years (>2) after treatment with no appreciable early symptoms, which may be due to fibrosis and/or atrophy and is suggestive of a generic effect.

The distinct outer neuromuscular compartment of pharynx is thought to be responsible for coarse movement of bolus through the lumen might be at greater risk of radiation injury. Clinically, irradiated HNSCC survivors often present with difficulties attributed to pharyngeal dysmotility including impaired bolus movement during swallow and post-swallow residue in the posterior pharyngeal wall, laryngeal vestibule and preform sinus.

With the advent of IMRT, doses were escalated to achieve better tumour control while attempts to reduce xerostomia was made by sparing the parotid glands. MACH-NC meta-analysis clearly demonstrated that concomitant cisplatin based chemoradiation therapy regimes achieve best results with clear survival advantages. However, the high doses of Chemoradiation are associated with more mucositis, need for feeding tubes, difficulty in swallowing and feeding tube dependencies. The structures of Superior, Middle and Inferior Constrictors, Base of Tongue, Superior Glottis, Glottic Larynx, Cricopharyngial Muscles, Cervical Oesophagus and Oesophageal Inlet Muscles have been found to play maximum roles in dysphagia produced by radiation therapy and are collectively called as Dysphagia Aspiration Related Structures (DARS)(16) Eisburch et. al. in their article describing DARS, proposed dose constraints for DARS equal to 50 Gy or lower, as this was the lowest dose at which they could observe stricture in the pharynx(16). On the basis of these studies a randomized controlled trial evaluating standard IMRT without DARS constraints and Do-IMRT (Dysphagia optimised IMRT) with constraint of DARS < 50 Gy prescribed during IMRT planning was conducted. As per preliminary results of 'DARS' (CRUK/14/014) trial published by Nutting et. al. in 2020, they could achieve mean dose to Superior and Middle Pharyngeal Constrictor Muscles around 49.7 Gy in the Do-IMRT arm. This mean dose was as high as 57 Gy in standard IMRT arm in which there was significantly inferior outcomes in swallowing(17). Despite the advantage in QOL and non-inferiority in survival shown in the randomized clinical trial of DARS, there is cautiousness in most of the centres to give spare the DARS as they are located in the vicinity of target volumes, and it takes time to properly delineate them without encroaching the target volumes and compromising the treatment outcomes.

Rationale for the Study

The evidence created from the (CRUK/14/014) trial and the proposed dose constraints have created an opportunity to explore the applications of same in the real-world scenario in a busy high volume Radiation Oncology practise in India, where the H & NSCC incidence is highest. The prospective study was designed to examine same with objective measurements of treatment, QOL and outcome parameters.

AIM & OBJECTIVES

AIM AND OBJECTIVES

Aim of the study:

To evaluate Quality of Life in patients receiving Dysphagia Optimized Intensity Modulated Radiotherapy (Do-IMRT) in Head and Neck cancers.

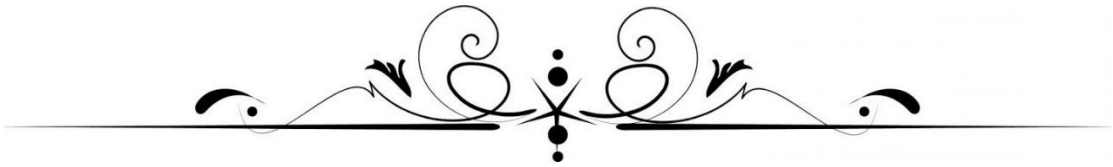
Objectives:

Primary Objective:

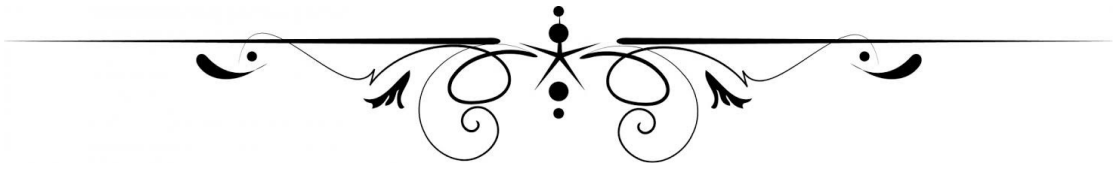
To determine whether reducing the radiation dose to DARS using IMRT improves quality of life in patients with carcinoma of the oral cavity, oropharynx, larynx and hypopharynx treated with radical chemo-radiation or radiation alone.

Secondary Objectives

1. Acute and late toxicity
2. Disease free survival and overall survival using Kaplan Meier survival analysis.



REVIEW OF LITERATURE



REVIEW OF LITERATURE

Hyuna Sung et. al. published his data on global cancer statistics in 2020 which provides an update on the global cancer burden using the GLOBOCAN 2020 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer. Worldwide, an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancer) occurred in 2020. Female breast cancer surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10.0 %), prostate (7.3%), and stomach (5.6%) cancers. Lung cancer remained the leading cause of cancer death, with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers. Overall incidence was from 2-fold to 3-fold higher in transitioned versus transitioning countries for both sexes, whereas mortality varied(3).

Mathur et. al. published in 2020, the systematic collection of data on cancer by various population-based cancer registries (PBCRs) and hospital-based cancer registries (HBCRs) across India under the National Cancer Registry Programme–National Centre for Disease Informatics and Research of Indian Council of Medical Research since 1982. This study examined the cancer incidence, patterns, trends, projections, and mortality from 28 PBCRs and also the stage at presentation and type of treatment of patients with cancer from 58 HBCRs (N = 667,666) from the pooled analysis for the composite period 2012-2016. Time trends in cancer incidence rate were generated as annual percent change from 16 PBCRs (those with a minimum of 10 years of continuous good data available) using Joint point regression. The projected number of patients with cancer in India is 1,392,179 for the year 2020, and the common 5 leading sites are breast, lung, mouth, cervix uteri, and tongue. Trends in cancer incidence rate showed an increase in all sites of cancer in both sexes. The majority of the patients with cancer were diagnosed at the locally advanced stage for breast (57.0%), cervix uteri (60.0%), head and neck (66.6%), and stomach (50.8%) cancer, whereas in lung cancer, distant metastasis was predominant among males (44.0%) and females (47.6%)(18).

Chen et. al. did a cross sectional survey study to design a reliable and validated self-administered questionnaire to assess dysphagia's effects on quality of life of patients with head and neck cancers. Focus group were called for questionnaire development and design.

the MD Anderson dysphagia inventory included global, emotional, functional and physical subscales. speech pathologist evaluated performance status of all the patients. they concluded that MDADI is the first validated and and reliable self-administered questionnaire for evaluating the impact of dysphagia on the QOL of patients with head and neck cancers(19).

Hutcheson et. al. studied 1,136 HNC patients in a retrospective cross-sectional analysis. The global, composite, and subscale scores of the MD Anderson Dysphagia Inventory were computed. They discovered that a 10-point difference in composite MDADI scores across groups was linked to clinically significant changes in swallowing performance(20)

Wilson et. al. studied 167 patient of head and neck cancer to assess patients perspective on the severity, time course and relative importance of swallowing deficit before and after chemoradiotherapy by using MD Anderson Dysphagia Index (MDADI) and the University of Washington Quality of Life Questionnaire (UWQOL) before treatment and at 3, 6, and 12 months. They found that there was a sharp deterioration in swallowing on average by 18%, from before treatment to 3 months post treatment (mean difference in MDADI score = 14.5; $P < .001$). Treatment schedule, pre-treatment score, and age accounted for 37% of the variance in 3-month posttreatment MDADI scores. There was then little improvement from 3 to 12 months. Patients treated with only 50-Gy radiotherapy reported significantly less dysphagia at 1 year than patients receiving higher doses or combined chemoradiation ($P < .001$). Swallowing as the most commonly prioritized domain of the 12 UWQOL domains among treated patients both before and after therapy. They concluded that swallowing is a top priority before and after treatment for the vast majority of patients with head and neck cancer. Swallowing deteriorates significantly posttreatment ($P < .001$). Treatment intensity, younger age, and lower pre-treatment scores predict long-term dysphagia. After chemoradiation, there is little improvement from 3 to 12 months(21).

Mazumdar et. al. studied 103 patients of LAHNSCC treated with IMRT to analyse the cumulative incidence of late xerostomia, dysphagia, and aspiration at an interval of 6-month, 1-year, 2-year, and 3-year from the start of IMRT. They concluded that the cumulative incidence of grade ≥2 xerostomia, dysphagia, and aspiration at 1 year were 5.4%, 5.4%, and 3.6%, respectively. A Dmean of ≥26 Gy to the parotids was associated with a higher risk of xerostomia. Dysphagia was found to be significantly associated with Dmean of ≥45 Gy to the PC, ≥55 Gy to the larynx, and a patient receiving adjuvant RT. The risk of aspiration is

associated with Dmean of ≥45 Gy to larynx and patients having late dysphagia(mention the percentage of complication for the given Dmean)(22)

Montejo et. al. studied 747 patients with advanced head and neck squamous cell carcinoma to evaluate the efficacy and toxicity of accelerated radiotherapy with concurrent chemotherapy. They found that Grade 3 mucositis and dermatitis occurred in 13 patients (30.2%) and 3 patients (6.9%), respectively. Grade 2 xerostomia occurred in 12 patients (27.9%). In patients with adequate follow-up, 82% were feeding tube free by 6 months after therapy; 13% remained feeding tube dependent at 1 year(23).

Margot et. al. studied 60 patients for very late xerostomia , dysphagia after head and neck radiotherapy .They observed a decreasing trend in severity of late dysphagia during 1 to 5 years post treatment and but a significant increase in severity was again noted after the 5 year period .Even though dysphagia severity decreases after radiotherapy until 5 years of follow-up, a large portion of patients with HNC still present with dysphagia years after radiotherapy , with almost half (48%) of the patients showing dysphagia after 8 years of follow-up (34% grade 1, 9% grade 2, 5% grade 3)(24).

Roe et. al. studied 61 patients of H NC to evaluate patient-reported swallowing outcomes and how swallowing is prioritised following parotid-sparing IMRT. They concluded that despite the significant improvements in radiation delivery techniques and encouraging results emerging in the literature, patients continue to experience significant HR-QoL and swallowing-related QoL difficulties up to 12 months following H & NC treatment. Patients consistently rate dysphagia as a high priority up to one year following treatment. Ongoing improvement is evident at 12 months and future studies should record longer-term, patient-reported swallowing outcomes in these patients(25)

Cristopher et. al. did a randomised controlled trial, that compared conventional radiotherapy (control) with parotid sparing IMRT. The primary endpoint of the study was the proportion of patients with grade 2 or worse xerostomia at 12 months, as assessed by the Late Effects of Normal Tissue (LENT SOMA) scale. Analyses were done on an intention-to-treat basis, with all patients who had assessments included. They found that grade 2 or worse xerostomia at 12 months was significantly lower in the IMRT group than in the conventional radiotherapy group. The only recorded acute adverse event of grade 2 or worse that differed significantly between the treatment groups was fatigue, which was more prevalent in the IMRT. At 24 months, grade 2 or worse xerostomia was significantly less common with IMRT than with

conventional radiotherapy. At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry-mouth-specific and global quality of life scores. At 24 months, no significant differences were seen between randomised groups in non-xerostomia late toxicities, locoregional control, or overall survival(17).

From this they concluded that sparing the parotid glands with IMRT significantly reduces the incidence of xerostomia and leads to recovery of saliva secretion and improvements in associated quality of life, and thus strongly supports a role for IMRT in squamous-cell carcinoma of the head and neck.

Hunter et. al. - The salivary glands and swallowing structures were spared in 72 individuals with Stage III-IV oropharyngeal cancer who received final chemo-IMRT. Summary scores from the Head Neck QOL (H & NQOL) and University of Washington QOL (UWQOL) questionnaires, as well as the H & NQOL "Overall Bother" item, were used to determine overall QOL. Pre-therapy to two years post-therapy, QOL, observer-rated toxicities (CTCAE v2), and objective assessments (video fluoroscopy for dysphagia and saliva flow rates for xerostomia) were all documented. All observer-rated toxicities and QOL ratings deteriorated 1-3 months after treatment and improved over the next 12 months, with small improvements over the next 24 months. Dysphagia grades 0-1, 2, and 3 were seen in 95 percent, 4%, and 1% of patients after 12 months, respectively. Observer-rated dysphagia was substantially connected with all overall QOL measures using all post-therapy observations, whereas xerostomia, mucosal, and voice toxicities were significantly correlated with some, but not all, overall QOL measures, with lower correlation values than dysphagia. Observer-rated dysphagia and, to a lesser extent, xerostomia were linked with late overall QOL (6 or 12 months post-therapy)(26).

While late dysphagia was on average modest after chemo-IMRT, it was remained the most important predictor of QOL. Ongoing improvements in QOL are anticipated to result from additional attempts to minimize swallowing difficulty(26).

Popovzter et. al. compared the MRI finding in 12 patients with stage III–IV head and neck cancer before and 3 months after completing chemo-irradiation. (11) They found that T1-weighted signals decreased in the pharyngeal constrictor muscle which received >50 Gy .The T2-weighted signals in the PCs also increased significantly as the dose increased and increased thickness was noted in all PCs receiving >50 Gy. They concluded that the

underlying causes of PC dysfunction were inflammation and oedema, consequential to acute mucositis post radiation and reducing mean PC doses to <50 Gy, can improve long-term dysphagia(27).

Eisbruch et. al. looked at the dosimetric correlates of long-term dysphagia after oropharyngeal cancer (OPC) was treated with concurrent chemo-intensity-modulated radiation (IMRT) sparing sections of the swallowing organs(16). The pharyngeal constrictors (PC), glottic and supraglottic larynx (GSL), oesophagus, oral cavity, and major salivary glands were recognised as swallowing-related organs(16).

Patient-reported Swallowing and Eating Domain scores, Observer-based (CTCAEv.2) dysphagia, and video fluoroscopy (VF) were used to assess dysphagia before and after treatment over a period of two years. All dysphagia outcomes were substantially linked with mean doses to PC, GSL, and oesophagus. All dysphagia outcomes were substantially linked with mean doses to PC, GSL, and oesophagus. All dysphagia metrics were substantially linked with mean dosages to each portion of the PCs (superior, middle, and inferior), with superior PCs showing the strongest correlations. Toxic doses (TDs) 50 and TD25 for elevated VF-based aspirations scores were 63 Gy and 56 Gy for PC, and 56 Gy and 39 Gy for GSL, respectively. **Schwartz et al.** studied 21 patients to see if there were any dosimetric predictors of long-term swallowing impairment following oropharyngeal intensity-modulated radiation. Univariate and multivariate analyses revealed dose–volume restrictions (V30 65 percent and V35 35 percent for anterior oral cavity and V55 80 percent and V65 30 percent for high superior pharyngeal constrictors) that were predictive of objective swallowing failure(28).

In 141 patients treated with concurrent intensity-modulated radiation treatment and chemotherapy for locally advanced head and neck cancer, **Vlacich et. al**. discovered that a dosage to the inferior pharyngeal constrictor predicts protracted gastrostomy tube reliance. The authors found that keeping the mean inferior constrictor dosage at 41 Gy and V40 at 41% might help reduce the need for a gastrostomy tube(29). In 56 patients who underwent intensity modulated radiotherapy, **Mazolla et** colleagues discovered dose volume predictors of late dysphagia(30)

Cagler et. al. studied 96 patients to evaluate early swallowing after intensity-modulated radiotherapy for head and neck squamous cell carcinoma and determine factors correlating with aspiration and/or stricture. the found that of the 96 patients, 32% had clinically

significant aspiration and 37%developed a stricture. The radiation dose–volume metrics, including the volume of the larynx receiving ≥50 Gy and volume of the inferior constrictor receiving ≥50 Gy were significantly associated with both aspiration and stricture. The mean larynx dose correlated with aspiration. Smoking history was the only clinical factor to correlate with stricture but not aspiration. Hence they concluded that Aspiration and stricture are common side effects after intensity-modulated radiotherapy for head-and-neck squamous cell carcinoma. The dose given to the larynx and inferior constrictors correlated with these side effects(31).

They've proposed the following limits for PCs, with PTV coverage as a secondary concern: Dmax60Gy for superior PC; Dmax60Gy for cricopharyngeal muscle. D-mean50Gy, Dmax60, V5070% for middle PC; Dmax60Gy, V5070% for superior PC; Dmax60Gy for cricopharyngeal muscle. They also discovered that D-mean>26Gy and V30 >50% to the parotid were statistically linked to acute and late xerostomia, both of which can exacerbate dysphagia.

One of the issues with sparing DARS is the tumour's proximity to these structures. As a result, there's always the chance that the tumour may be spared accidently while aiming to spare DARS. **Feng et. al.** performed a prospective trial of IMRT in 73 patients with oropharyngeal malignancies, with the goal of sparing non-involved areas of the swallowing structures, such as the pharyngeal constrictors, glottic and supraglottic larynx, oesophagus, oral cavity, and major salivary glands. They found that IMRT for oropharyngeal malignancies that aims to minimise dysphagia may be done safely and has good loco-regional tumour control rates.

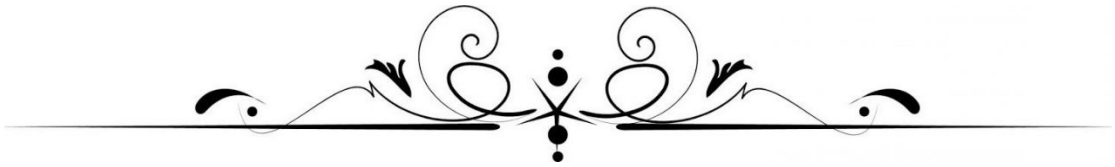
Rathod et. al. from Tata Memorial Hospital, Mumbai prospectively evaluated and compared health-related quality-of-life (QOL) outcomes in patients with head–neck squamous cell carcinoma randomized to either intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiotherapy (3D-CRT) and assess serial longitudinal change in QOL over time. QOL outcomes were assessed using the European Organization for Research and Treatment of Cancer (EORTC) QOL questionnaire (QLQ-C30) and Head-Neck module (H & N-35) at baseline (pre-treatment) and subsequently periodically on follow-up. Mean scores of individual domains/scales of 3D-CRT and IMRT were compared using 't' test at each time point, while longitudinal change in mean scores of both groups over time was evaluated by repeated measurement analysis of variance. They found that fifty eight of the 60 randomized

patients who filled the QOL questionnaire at least at one time point were included in the analysis. Several general (emotional functioning, role functioning, social contact) as well as head and neck cancer-specific (dry mouth, opening mouth, sticky saliva, pain, senses) QOL domains were better preserved with IMRT compared to 3D-CRT at different time points. Importantly, none of the QOL domains were worse with IMRT at any time point. There was substantial deterioration in QOL scores immediate post-treatment (3-months) in both arms. However, QOL scores gradually but definitely improved over time for most domains. Global QOL, emotional/role functioning, nausea/vomiting, pain, swallowing, speech, social contact/eating, insomnia showed rapid recovery (<6 months) while physical/cognitive functioning, dry mouth, sticky saliva, fatigue, senses showed delayed recovery (>6 months). There were no significant differences in loco-regional or survival between the two arms. They concluded that there is substantial deterioration in QOL after curative-intent head–neck irradiation that gradually improves over time. IMRT results in clinically meaningful and statistically better QOL scores for some domains compared to 3D-CRT at several time points with comparable disease outcomes that could support its widespread adoption in routine clinical practice(14).

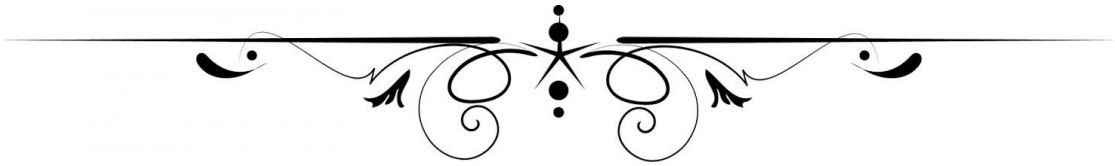
Petkar et.al. described the protocol of a randomized clinical trial of standard IMRT vs Do-IMRT They described that persistent dysphagia following primary chemoradiation (CRT) for head and neck cancers can have a devastating impact on patients' quality of life. Single arm studies have shown that the dosimetric sparing of critical swallowing structures such as the pharyngeal constrictor muscle and supraglottic larynx can translate to better functional outcomes. However, there were no current randomised studies to confirm the benefits of such swallow sparing strategies. The aim of Dysphagia/Aspiration at risk structures (DARS) trial was to determine whether reducing the dose to the pharyngeal constrictors with dysphagia-optimised intensity- modulated radiotherapy (Do-IMRT) will lead to an improvement in long- term swallowing function without having any detrimental impact on disease-specific survival outcomes. The DARS trial (CRUK/14/014) was a phase III multicentre randomised controlled trial (RCT) for patients undergoing primary (chemo) radiotherapy for T1-4, N0-3, M0 pharyngeal cancers. Patients were randomised (1:1 ratio) to either standard IMRT (S-IMRT) or Do-IMRT. Radiotherapy doses were same in both groups; however, in patients allocated to Do-IMRT, irradiation of the pharyngeal musculature was reduced by delivering IMRT identifying the pharyngeal muscles as organs at risk. The primary endpoint of the trial was the difference in the mean MD Anderson Dysphagia Inventory (MDADI) composite

score, a patient-reported outcome, measured at 12 months post radiotherapy. Secondary endpoints include prospective and longitudinal evaluation of swallow outcomes incorporating a range of subjective and objective assessments, quality of life measures, loco-regional control and overall survival. It was the first RCT that investigates the effect of swallow sparing strategies on improving long-term swallowing outcomes in pharyngeal cancers(32).

Nutting et.al. in their results of DARS trial narrated that most newly diagnosed oro- & hypopharyngeal cancers (OPC, HPC) are treated with (chemo)RT with curative intent but at the consequence of adverse effects on quality of life. CRUK/14/014 investigated if using Do-IMRT to reduce RT dose to the dysphagia/aspiration related structures (DARS) improved swallowing function compared to S-IMRT. in their study patients with T1-4, N0-3, M0 OPC/HPC were randomised 1:1 to S-IMRT (65 Gray (Gy)/30 fractions (f) to primary & nodal tumour; 54Gy/30f to remaining pharyngeal subsite & nodal areas at risk of microscopic disease) or Do-IMRT. The volume of the superior & middle pharyngeal constrictor muscle (PCM) (OPC) or inferior PCM (HPC) lying outside the high-dose target volume was set a mandatory mean dose constraint in Do-IMRT. Treatment allocation was by minimisation balanced by centre, use of induction/concomitant chemotherapy, tumour site & AJCC stage. Primary endpoint was mean MD Anderson Dysphagia Inventory (MDADI) composite score 12 months after RT with 102 patients needed to detect a 10-point improvement (assuming S-IMRT score of 72, standard deviation (SD) 13.8; 90% power, 2-sided 5% alpha). Patients were blind to treatment allocation. Secondary endpoints included local control. They reported that 112 patients (56 S-IMRT, 56 Do-IMRT) were randomised from 22 UK centres from 06/2016 to 04/2018. Mean age was 57 years; 80% were male; 97% had OPC; 90% had AJCC stage 3&4 disease; 86% had concomitant chemotherapy only, 4% induction & concomitant and 10% no chemotherapy. 111/112 had RT doses as prescribed (1 patient died before RT). Median of the mean inferior PCM dose was S-IMRT 49.8Gy (IQR 47.1-52.4) vs. Do-IMRT 28.4Gy (21.3–37.4), $p < 0.0001$; superior & middle PCM dose was S-IMRT 57.2Gy (56.3–58.3) vs. Do-IMRT 49.7Gy (49.4–49.9), $p < 0.0001$. Do-IMRT had significantly higher MDADI scores: S-IMRT 70.3 (SD 17.3) vs. Do-IMRT 77.7 (16.1), $p = 0.016$. 3 local recurrences (1 S-IMRT, 2 Do-IMRT) have been reported. They concluded that Do-IMRT reduced RT dose to the DARS and improved patient reported swallowing function compared with S-IMRT. This is the first randomised study to demonstrate functional benefit of swallow-sparing IMRT in OPC(17).



MATERIALS & METHODS



MATERIALS AND METHODS

Study design: Single arm prospective study

Eligibility criteria:

Inclusion criteria:

1. Age >18 and<80
2. Carcinoma in the oral cavity oropharynx, larynx or Hypopharynx.
3. Stage T1-4, N0-3, M0
4. Histologically confirmed squamous cell carcinoma
6. ECOG score 0,1 or 2.
7. Available to attend long term follow- up.

Exclusion criteria:

1. Pre-existing swallowing dysfunction not related to head and neck cancer.
2. Previous radiotherapy to the head and neck region.
3. Posterior pharyngeal wall, retropharyngeal lymph node involvement
4. Major Head and neck surgery (excluding biopsies/tonsillectomy)
5. Tracheostomy tube
6. Co-morbidities which would interfere with completion of therapy and follow-up
7. Patients not willing for follow up
8. Nasopharyngeal carcinoma

A. Sampling

a. Sampling population : All patients with cancers of the oral cavity, oropharynx larynx and hypopharynx attending Radiation oncology OPD

b. Sample size calculation-

Open EPI software from the internet was used for the sample size calculation (33). Based on literature review it was estimated that at least 50% of patients will have events during the study period affecting the quality of life and progression free survival

Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(*N*):	1000000
Hypothesized % frequency of outcome factor in the population (*p*):	50%+/-15
Confidence limits as % of 100(absolute +/- %)(*d*):	15%
Design effect (for cluster surveys-*DEFF*):	1

Sample Size(*n*) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	43
80%	19
90%	31
97%	53
99%	74
99.9%	121
99.99%	169

Equation

Sample size $n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$

Results from OpenEpi, Version 3, open source calculator--SSPropor
Print from the browser with ctrl-P
or select text to copy and paste to other programs.

FIGURE 2: SAMPLE SIZE CALCULATION

B. Study procedure:

After the approval from the Institute Ethics Committee ,patient accrual was done starting from the department of radiation oncology beginning from May 2020 and continued till August 2021 based on the inclusion criteria. All study cases satisfying inclusion criteria were enrolled after obtaining proper informed consent. Hemogram, biochemical tests including liver function tests and renal function tests were done at the start of treatment and thereafter as indicated as per the current standard protocol of treating patients with chemoradiation in the department.

Radiation therapy planning and treatment details

CT Simulation -After counselling and explaining about the procedure each patient was immobilized in head first supine position with neck neutral and resting on a suitable headrest using 5 clamp thermoplastic mask of Medtronic, USA. Contrast enhanced CT scan images with slice thickness of 2.5 mm was obtained using GE optima 580, 16 slice CT simulator.

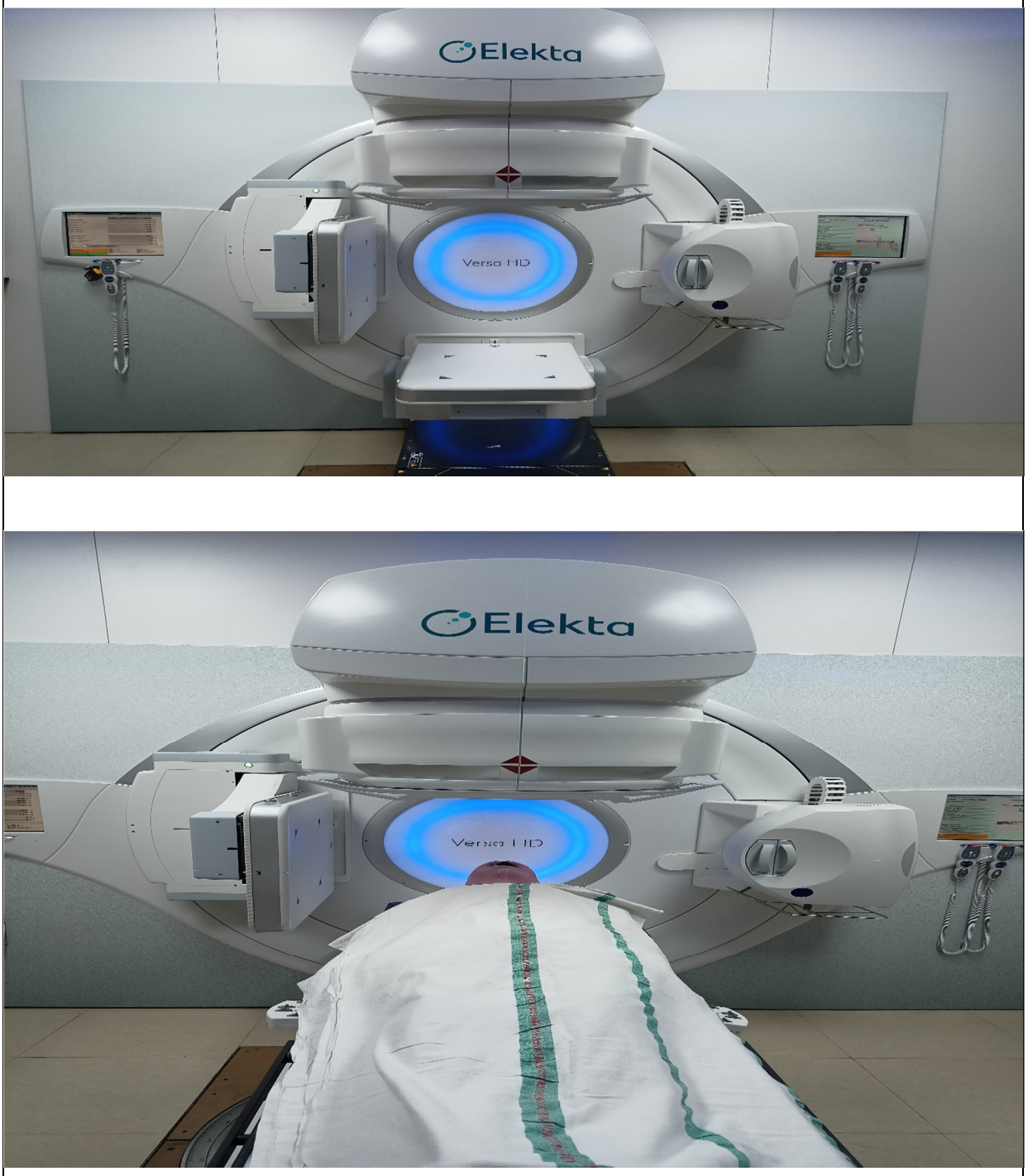


FIGURE 3: TREATMENT SETUP ON VERSA HD

FIGURE 4: 5 CLAMP THERMOPLASTIC MASK USED FOR IMMOBILIZATION

Details of Radiotherapy- Patients received 66Gy in 30 fractions to the high-risk area [primary tumour and involved nodes (PTV_6600)] and 54Gy in 30 fractions (PTV_5400) to low-risk areas. Treatment was delivered using IMRT.

Target volume delineation and planning

The planning CT images were transferred to the MONACO treatment planning system of Elekta, UK. Any radiologically visible and clinically marked disease was contoured as Gross tumour volume (GTV). Two clinical target volumes (CTV) were defined and edited to exclude natural barriers to disease spread. CTV_6600 included in the primary and nodal gross tumour volume (GTV) with a suitable isotropic margin while the prophylactic CTV_5400 included remainder of the involved subsite and nodal levels at risk of microscopic disease. Corresponding planning target volumes (PTVs) were grown with 5 mm margins according to the Institutional practice. All PTVs were restricted to 5 mm within the skin surface for the purpose of dose optimization and evaluation. Thus, all target volumes were drawn on the TPS using standard guidelines for the IMRT of H & NSCC. Standard organs at risk (OAR) such as spinal cord, parotid glands, lens, cochlea, orbits, optic nerve, brain stem and lips etc were drawn.

The contouring of DARS

The Superior, Middle and Inferior Constrictors, Base of Tongue, Superior Glottis, Glottic Larynx, Cricopharyngial Muscles, Cervical Oesophagus and Oesophageal Inlet Muscles were contoured as mentioned in published contouring guidelines defined by Christianen et al(34). For oropharyngeal primaries, mandatory mean dose constraints of <50 Gy to the volume of SMPCM lying outside PTV_6600 (Plan-SMPCM) together with an optimal mean dose constraint of <20 Gy to the volume of IPCM lying outside PTV_6600 (Plan-IPCM) have been defined. Likewise, for hypopharyngeal tumours, mandatory and optimal mean dose constraints of <50 Gy and <40 Gy have been set for Plan-SMPCM and Plan-IPCM respectively. 95 % of PTV was covered by 95% or more of the dose prescribed. The maximum plan dose was not exceeded 7260cGy Gy and the volume receiving 7260cGy Gy did not exceed 2 cm^3. Crucially, was taken care that there will be no sparing of the constrictor muscles that lie within the PTV_6600.

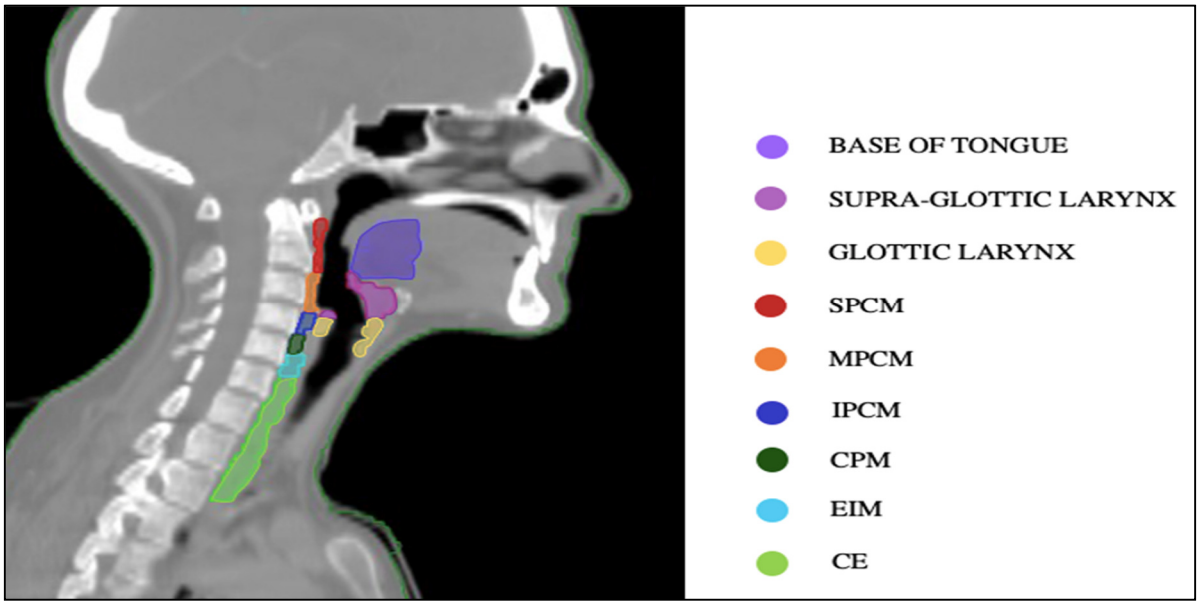


FIGURE 5: DELINEATION OF DARS STRUCTURE

(Image Source: Monaco TPS image of actual study patient)

Planning objectives were prioritized in the following order:

1. Critical organ constraints (spinal cord and brainstem);
2. PTV_6500 coverage.
3. Constrictor constraints.
4. PTV_5400 coverage.
5. Parotid gland constraints

Treatment verification

Treatment verification included cone beam CT. images were repeated for consecutive 3 days and any recurrent systematic errors in the setup were identified and corrected.

Concomitant Chemotherapy – weekly cisplatin (40 mg/m2) was infused intravenously along with suitable hydration and supportive medications. Haematological and clinical parameters were checked before each cycle of chemotherapy, which was administered if they were under permissible limits as per standard guidelines of the Institute.

Assessments

All patients underwent weekly clinical review, complete blood counts and Kidney function tests as per the Institute guidelines for chemoradiation.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0) was used to grade acute toxicity. Clinical assessments were done at 6 weeks, 3 months ,6 months ,9 months after completion of treatment as a minimum. Additional investigations were requested if clinically indicated.

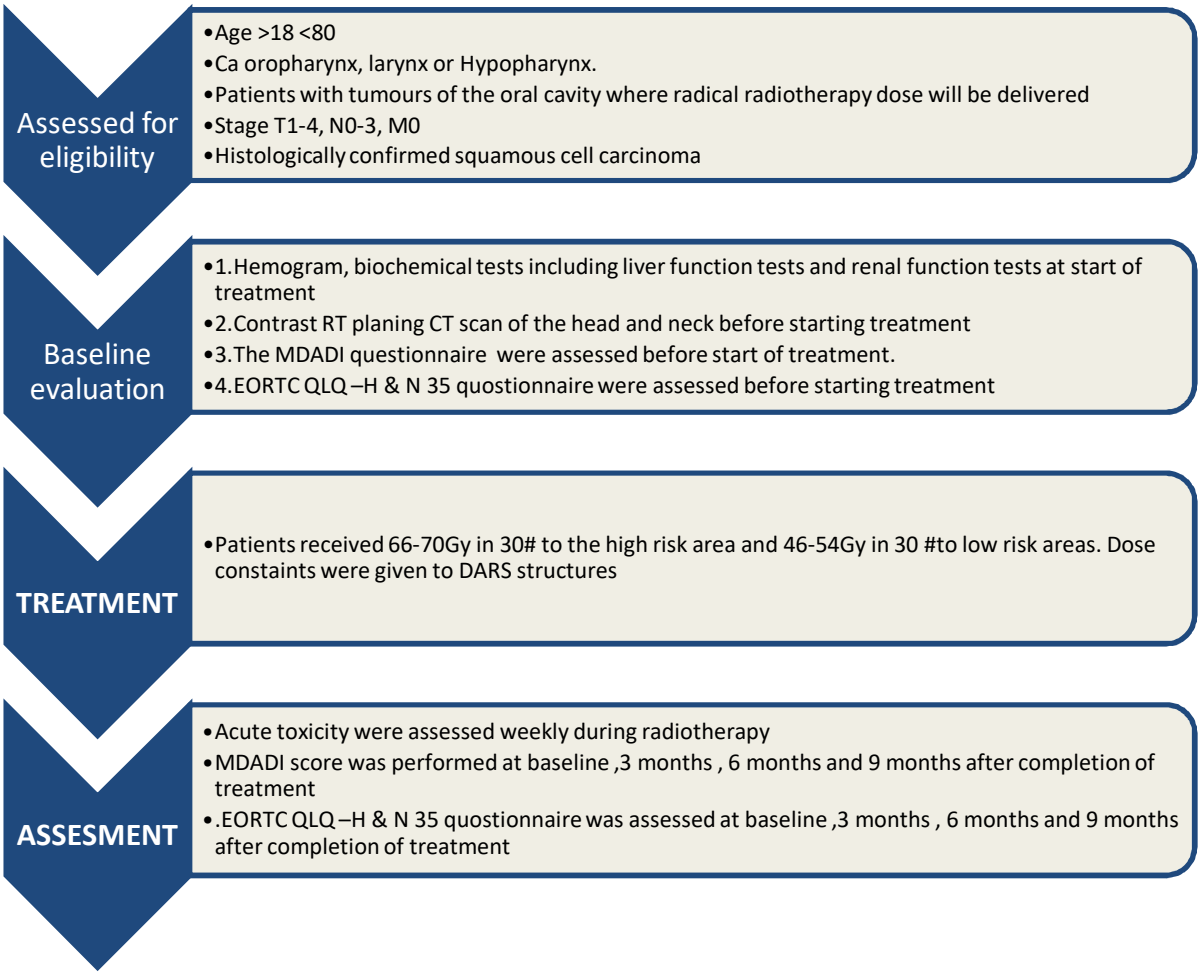


FIGURE 6: SUMMARY OF MATERIALS AND METHODS

Data collection methods including settings & Periodicity:

1. Statistical analysis was done with the use of Python and Microsoft excel
2. MDADI scores of each patient were assessed at baseline and 3 and 6 months after completion of treatment by the primary investigator.
3. EORTC QLQ –H & N 35 questionnaire were assessed at baseline ,3 months , 6 months and 9 months after completion of treatment

Data analysis –

1. Acute and late toxicities as percentage

2 . Disease free survival and overall survival using Kaplan Meier survival curves

QoL SCORES AND CALCULATION

For each patient enrolled in the study we obtained the QoL scores by using EORTC H&N 35 questionnaire which consisted of 35 questions and 4 options under each question scored from 1-4. Option 1 was designated as 'not at all', option 2 as 'A little bit', option 3 as 'quite a bit' and option 4 as 'very much'. For eg: for question no:31. Have you had pain in your mouth, a patient with little bit of pain may mark the option 2 in the questionnaire. And similarly based on the severity of the symptom's patients were allowed to mark the suitable option for all the 35 question sin the questionnaire. This option number is taken as the score from which a Raw score and a linear transformation score is derived with the help of the EORTC H&N 35 scoring manual as given below:

	Scale	Number of items (n)	Item range*	QLQ-H&N35 item numbers ($I_1, I_2, \ldots, I_n$)
Symptom scales / items				
Pain	PA	4	3	31 – 34
Swallowing	SW	4	3	35 – 38
Teeth	TE	1	3	39
Opening mouth	OM	1	3	40
Dry mouth	DR	1	3	41
Sticky saliva	SS	1	3	42
Senses	SE	2	3	43, 44
Coughing	CO	1	3	45
Felt ill	FI	1	3	47
Speech	SP	3	3	46, 53, 54
Social eating	SO	4	3	49 – 52
Social contact	SC	5	3	48, 55 – 58
Sexuality	SX	2	3	59, 60
Pain killers	PK	1	1	61
Nutritional supplements	NU	1	1	62
Feeding tube	FE	1	1	63
Weight loss	WL	1	1	64
Weight gain	WG	1	1	65

* "Item range" is the difference between the possible maximum and the minimum response to individual items. Most items are scored 1 to 4, giving range = 3.

Principle for scoring

1) **Raw score**

For each multi-item scale, calculate the average of the corresponding items.

$$Raw\ Score = RS = \left\{\frac{(I_1 + I_2 + \dots + I_n)}{n}\right\}$$

For each single-item measure, the score of the concerning item corresponds to the raw score.

There are no reverse scoring items.

2) **Linear Transformation**

To obtain the Score S, standardize the raw score to a 0 – 100 range using the following transformation:

$$\text{Symptom scales: } S = \left\{\frac{(RS-1)}{range}\right\} \times 100$$

Once Raw score and Linear Transformation scores were obtained at the beginning and end of each cycle, the data was compared for any statistically significant change in QoL in each of the 18 domains given in the scoring manual between the following groups:

The comparisons were done between baseline QoL and QoL obtained after 3rd,6th and 9th month of radiotherapy.

The M.D. Anderson Dysphagia Inventory – it is a questionnaire to assess the swallowing ability of patients and consists of one global question and 19 composite questions. (19)

Scoring

Two scores are obtained: a Global Score and a Composite Score.

All questions except for E7 and F2:
- Strongly Agree = 1 point
- Agree = 2 points
- No Opinion = 3 points
- Disagree = 4 points
- Strongly Disagree = 5 point

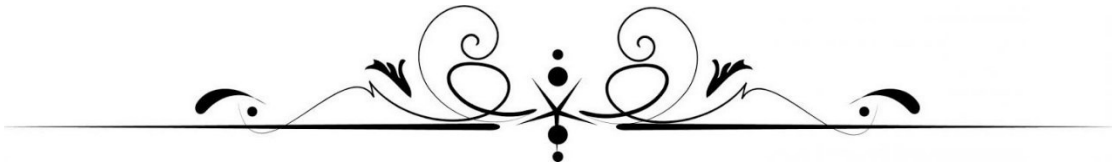
E7 and F2:
- Strongly Agree = 5 points
- Agree = 4 points
- No Opinion = 3 points
- Disagree = 2 points
- Strongly Disagree = 1 point

Global Score: first question (not numbered)
- Global Score ranges from 1 (extremely low functioning) to 5 (high functioning)

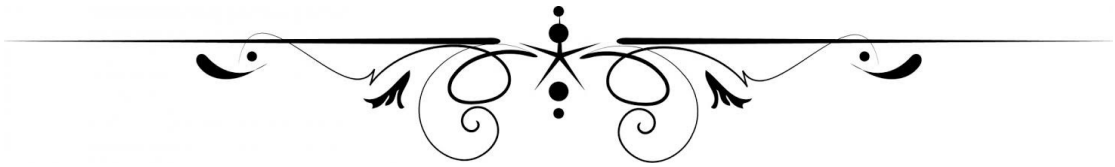
Composite Score: 19 numbered questions
- Calculate total points: add scores for the 19 questions
- Calculate the mean point score: Divide total points by 19
- Calculate final score: Multiply the mean by 20

Composite Score ranges from 20 (extremely low functioning) to 100 (high functioning)

Data Analysis: The Various variables measured were analysed using descriptive and inferential statistics. Distribution of data of categorical variables such as, gender, clinical characteristics, clinical stage, type of prior treatment was expressed as frequency and percentages. The continuous data such as age, QoL, overall survival and progression free survival on Do-IMRT were expressed as mean with standard deviation or median with range. The change in QoL at different follow up time was compared using t test and Mann-Whitney u test. The change in QoL in different subgroups were done using t test and Mann-Whitney u test after proper data arrangement. All statistical analysis was carried out 5% level of significance and $p< 0.05$ is considered statistical significance. The statistical analysis was done using Python and its libraries seaborn, matplotlib, plotly, scipy, scikit learn and python stats module. Survival analysis was done using Kaplan Meier analysis.



RESULTS



RESULTS

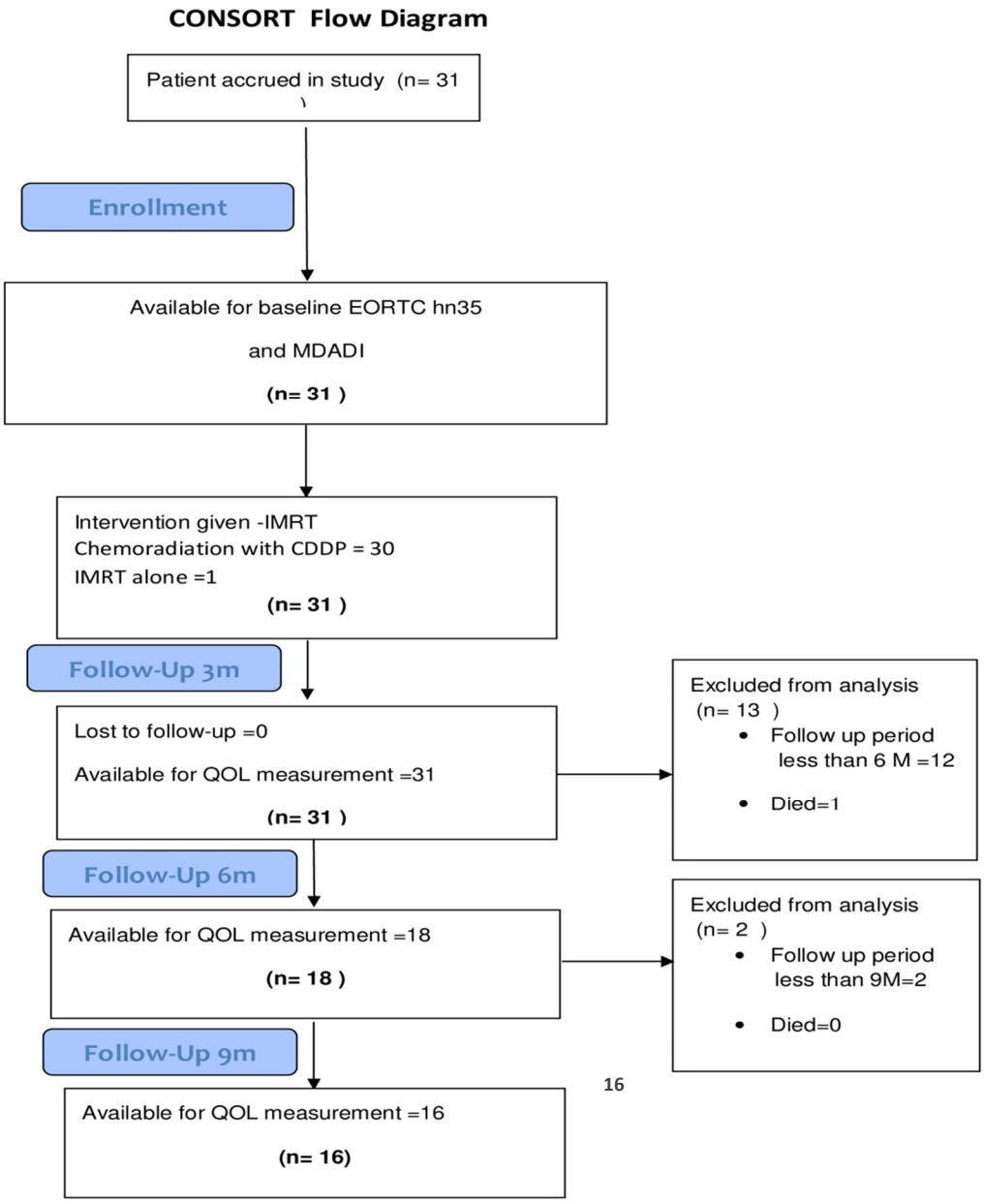


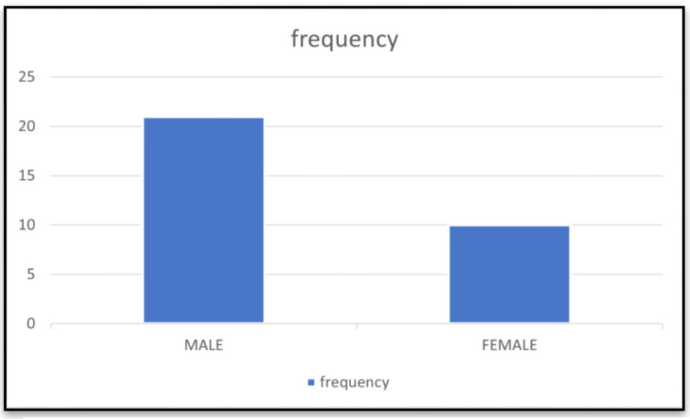
FIGURE 7: CONSORT FLOW DIAGRAM OF STUDY

Total 31 patiesnts were accrued in the study starting from February 2020, and were treated with radical intent using IMRT and mostly with concomitant weekly cisplatin. Besides rotine clinical evaluation for the reponse and toxicity, patients underwent assessment by MD Anderson Dysphagia Inventry (MDADI) and EORTC QOL H & N35 questionnare. All 31 patients were available at the end of 3rd month assessment which fall down to 18 and 16 on 6th and 9th month respectively. By the last follow up done in January, 2022, 6 (19%) patients have died while 25 (81%) are alive.

DEMOGRAPHIC DATA

TOTAL NUMBER OF PATIENTS: 31

GENDER DISTRIBUTION



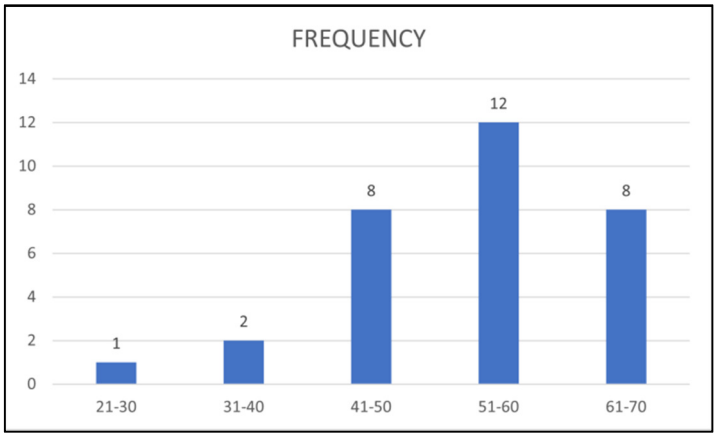
PLOT 1 GENDER DISTRIBUTION

SEX	NUMBER	PERCENTAGE%
M	21	68%
F	10	32%

Table 1- GENDER DISTRIBUTION

Majority of the patients in the study were male (68%).

AGE DISTRIBUTION



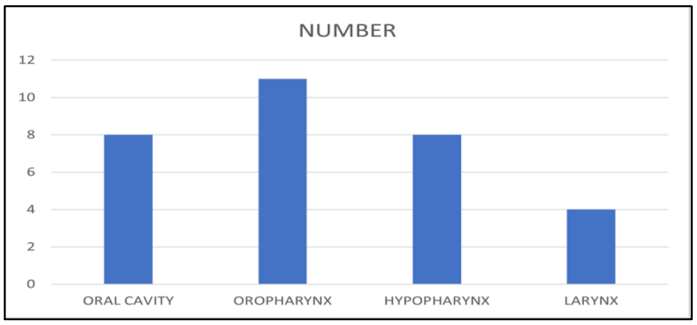
PLOT 2- AGE DISTRIBUTION

AGE GROUP	NUMBER
21-30	1
31-40	2
41-50	8
51-60	12
61-70	8

Table 2-AGE DISTRIBUTION

The majority of the patients in the study were in age group of 51-60 years (38.7%) .

PRIMARY SITE OF DISEASE



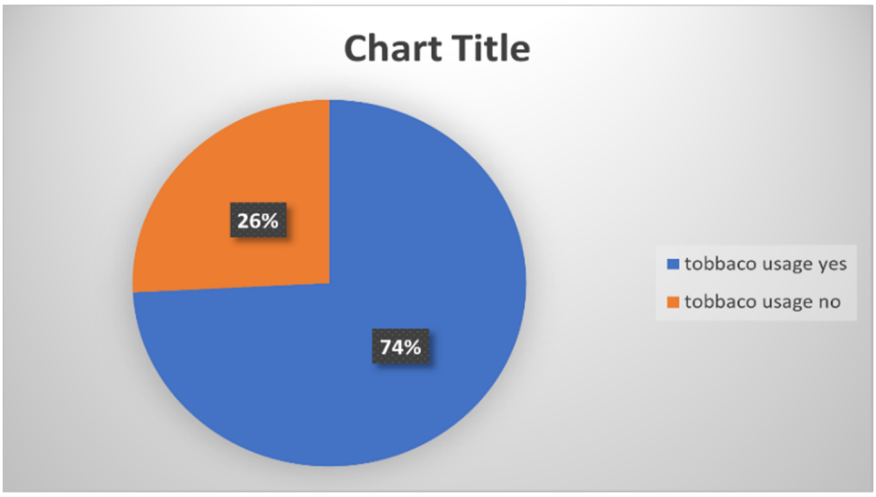
PLOT 3- PRIMARY SITE OF DISEASE

SITE	NUMBER
ORAL CAVITY	8
OROPHARYNX	11
HYPOPHARYNX	8
LARYNX	4

Table 3-PRIMARY SITE OF DISEASE

Majority of patient had oropharynx as there primary site (35.5%) .

TOBACCO USAGE



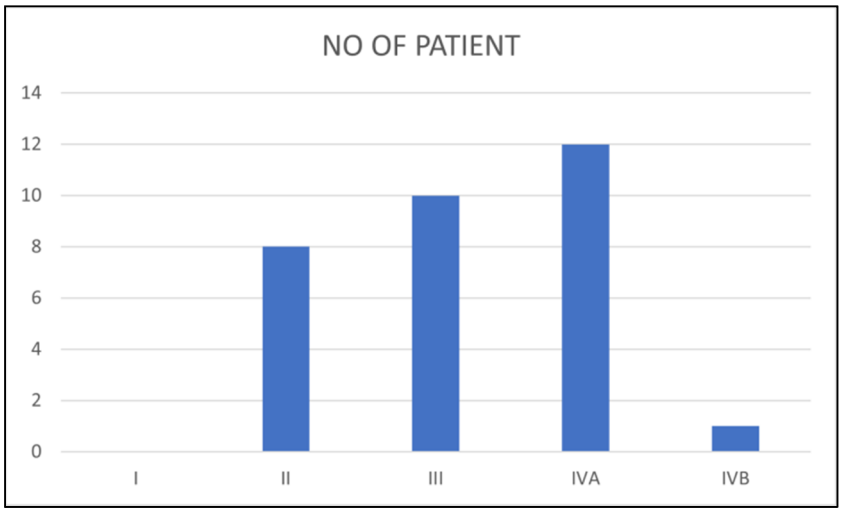
PLOT 4- TOBACCO USAGE

TOBACCO USAGE	YES	NO
	23	8

Table 4- TOBACCO USAGE

Majority of patients were tobacco users (74%).

STAGE AT INITIAL PRESENTATION



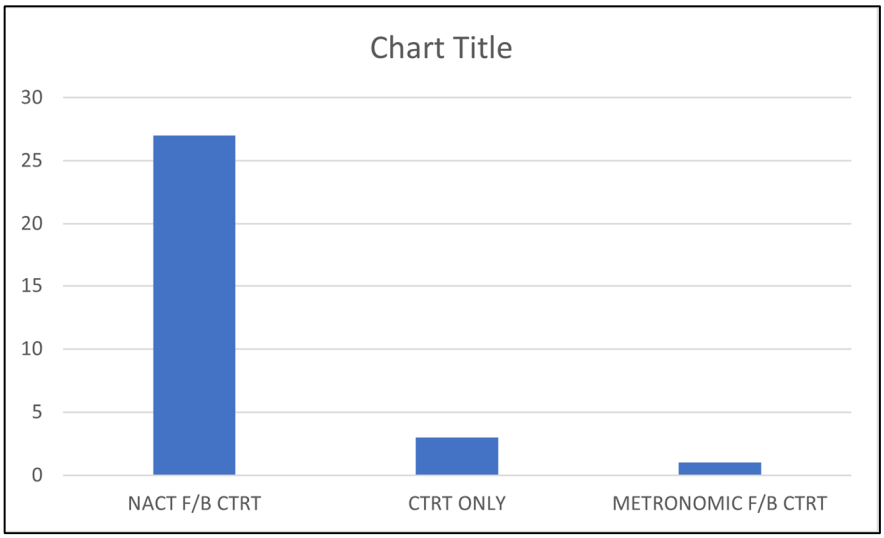
PLOT 5- STAGE AT INITIAL PRESENTATION

INITIAL STAGE	NUMBER OF PATIENTS
I	0
II	8
III	10
IV A	12
IV B	1

Table 5- STAGE AT INITIAL PRESENTATION

Majority of patients had stage IV A disease at presentation (38.7%).

TREATMENT GIVEN



PLOT 6- TREATMENT GIVEN

NACT F/B CTRT	27
CTRT ALONE	3
METRONOMIC F/B RT	1

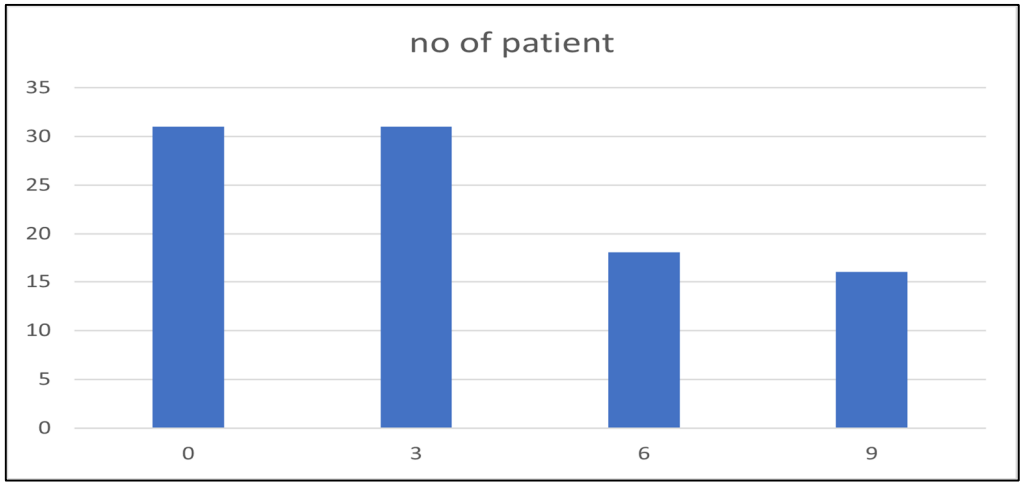
Table 6-TREATMENT

Majority of the patients were treated by Neo-adjuvant chemotherapy followed by chemoradiation (87%).

RESULTS OF QUALITY OF LIFE (QOL)

- Linear transformed scores from 18 QOL scales of EORTC head and neck -35.
  - Total 18 scales with transformed score (range-0 to 100)
  - Reduction in score is an indicator of improved QOL except for the 18th(weight gain -WG scale)
- Md Anderson dysphagia inventory (MDADI)
  - Summarizes to MDADI composite score (20-100), with more the score better the functionality of swallowing
  - Provides a global score from a single question regarding dysphagia (1-5) with more the score better the functionality of swallowing

NO. OF PATIENT AT EACH FOLLOW UP

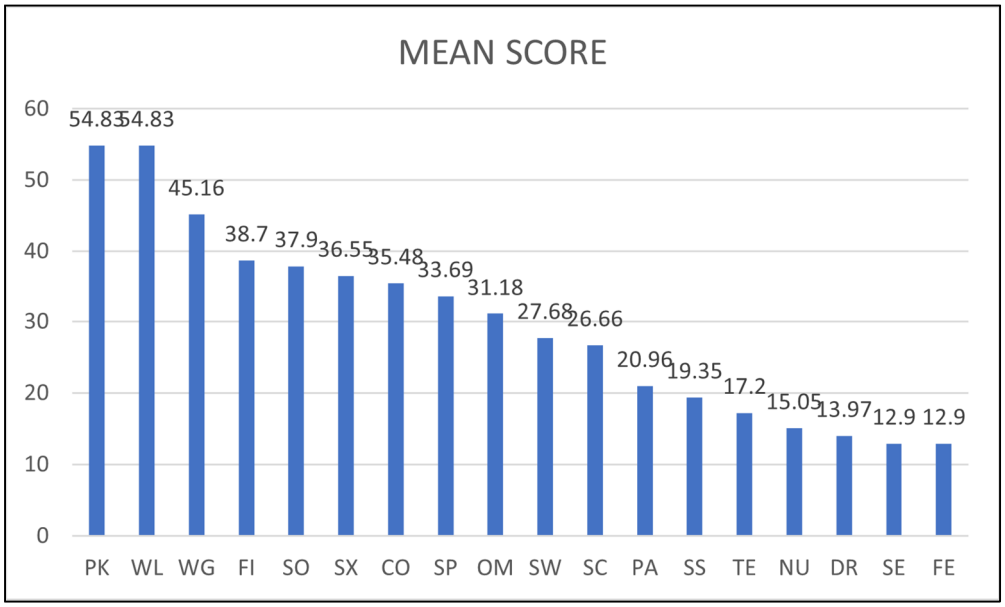


PLOT 7- NO. OF PATIENT AT EACH FOLLOW UP

FOLLOW UP MONTH	NO. OF PATIENTS
BASELINE	31
3	31
6	18
9	16

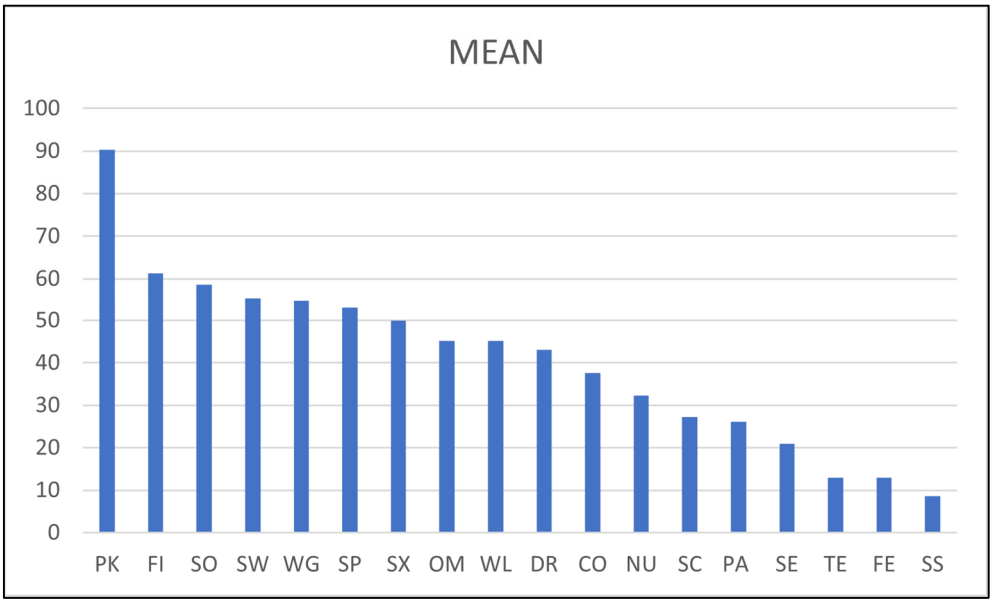
Table 7- PATIENTS AT EACH FOLLOW UP

MEAN EORTC H & N 35 QOL SCORES AT STARTING RADIOTHERAPY (N=31)



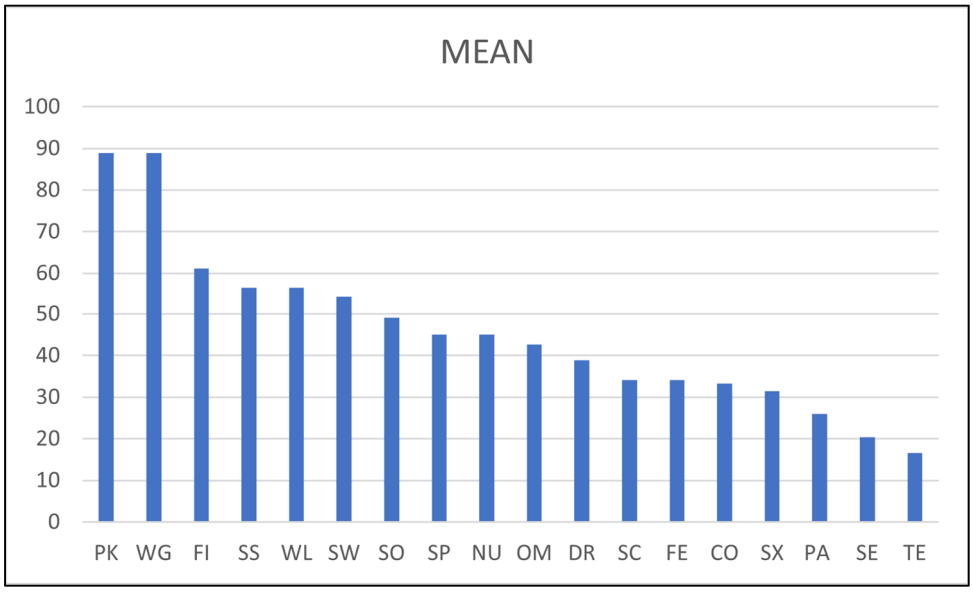
PLOT 8-MEAN EORTC H & N 35 QOL SCORES AT STARTING RADIOTHERAPY (N=31)

MEAN EORTC H & N 35 QOL SCORES AFTER 3 MONTHS FROM STARTING RADIOTHERAPY(N=31)



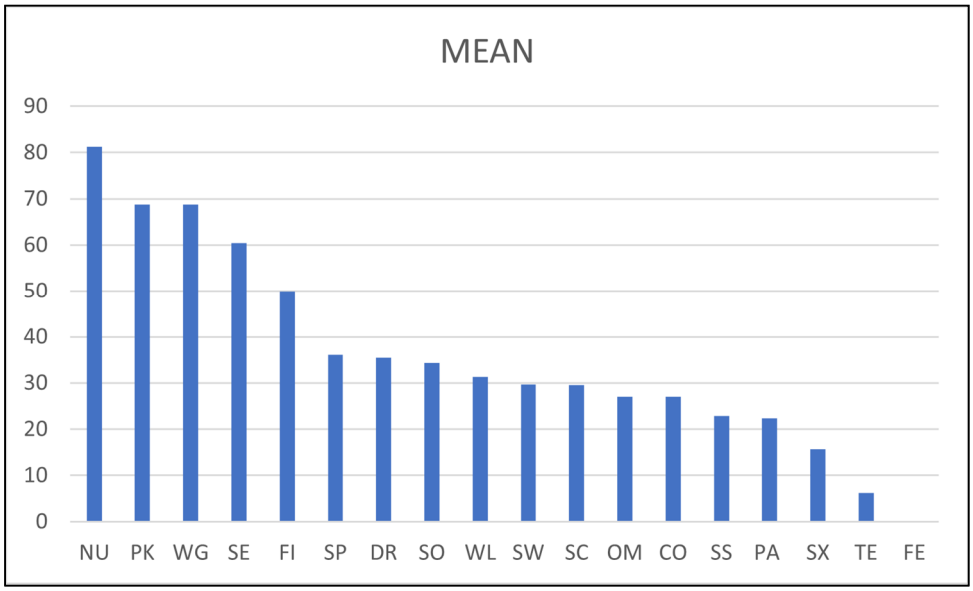
PLOT 9-MEAN EORTC H & N 35 QOL SCORES AFTER 3 MONTHS FROM STARTING RADIOTHERAPY(N=31)

MEAN EORTC H & N 35 QOL SCORES AFTER 6 MONTHS FROM STARTING RADIOTHERAPY(N=18)



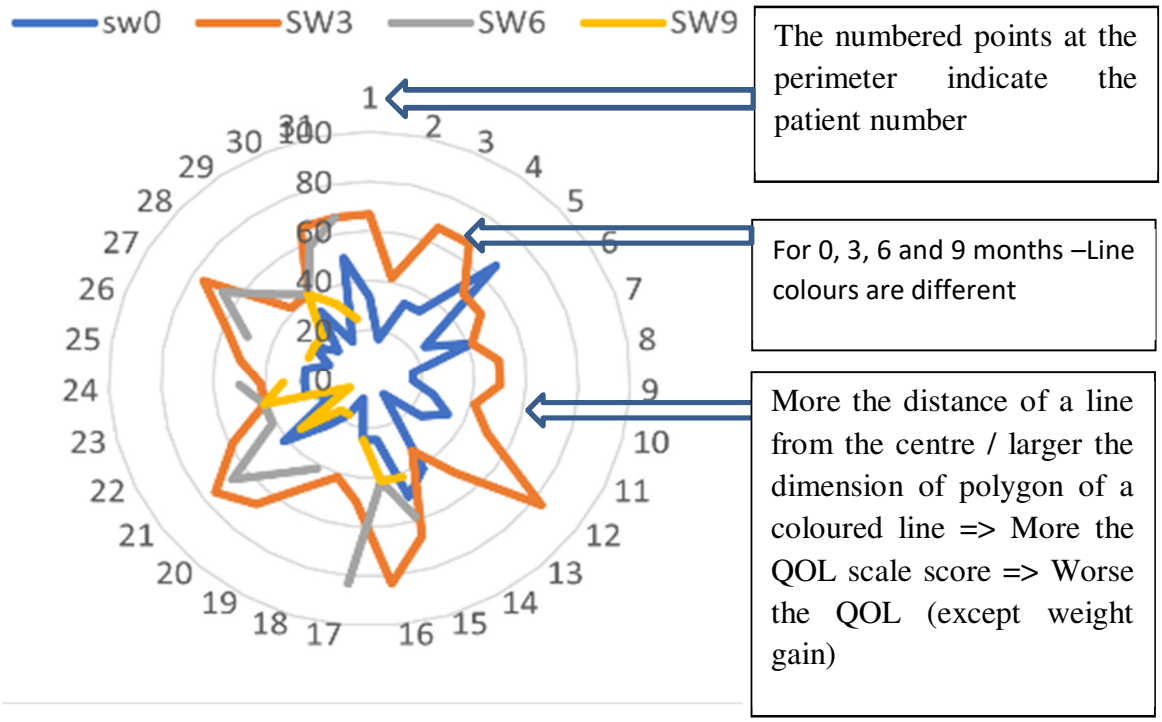
PLOT 10-MEAN EORTC H & N 35 QOL SCORES AFTER 6 MONTHS FROM STARTING RADIOTHERAPY(N=18)

MEAN EORTC H & N 35 QOL SCORES AFTER 9 MONTHS FROM STARTING RADIOTHERAPY(N=16)



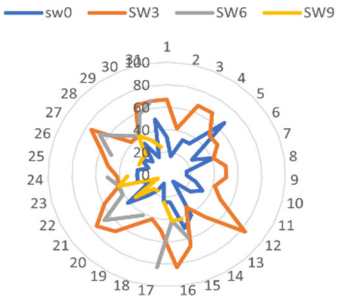
PLOT 11-MEAN EORTC H & N 35 QOL SCORES AFTER 9 MONTHS

The Radar Plots for Plotting EORTC H & N35 Scale for Analyzed Patients (At 0, 3, 6 and 9 Months)



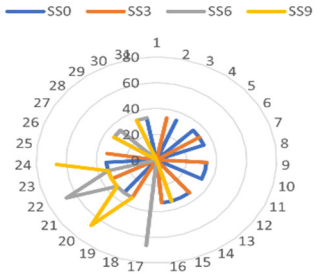
PLOT 12- RADAR PLOT ANALYSIS

To visually analyze the month post treatment, a particular EORTC H & N35 scale was maximum in value, indicating worse QOL (except weight gain (WG)) Radar Plots generated. In the above plot of Swallowing Scale, the ORANGE LINE POLYGON is the largest, thus showing that Swallowing Scores for most of the 31 patients were maximum at month 3. Radar plots were generated for each of the EORTC H & N35 scales with different colored lines for 0, 3, 6 and 9 months.



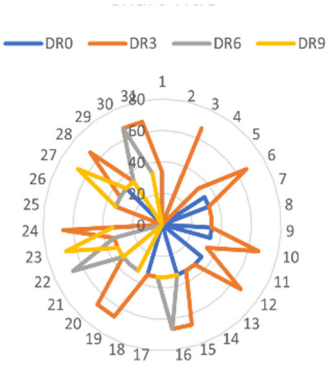
RADAR PLOT FOR SWALLOWING SCORES AT MONTH 0,3,6, AND 9. IT SHOWS THAT PATIENTS HAVE MAXIMUM SWALLOWING DIFFICULTY AT 3RD MONTH AND IT DECREASES FURTHER WITH TIME

PLOT 13- SW RADAR PLOT



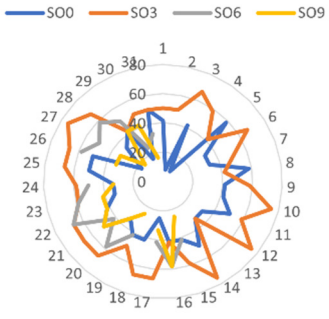
RADAR PLOT FOR STICKY SALIVA SCORES AT MONTH 0, 3, 6, AND 9. IT SHOWS THAT MAXIMUM PATIENTS HAVE COMPLAINT OF STICKY SALIVA AT STARTING OF RADIOTHERAPY

PLOT 14-SS RADAR PLOT



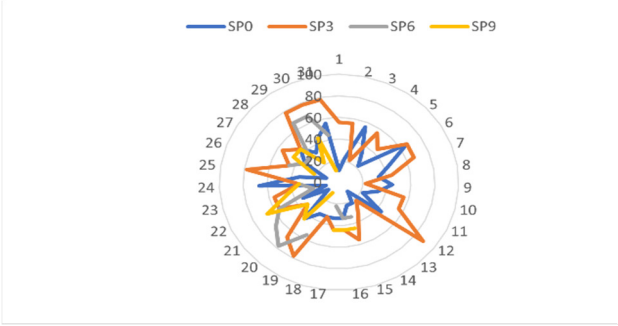
RADAR PLOT FOR DRY MOUTH SCRES AT MONTH 0,3,6,9-IT SHOWS THAT IN MAXIMUM NUMBER OF PATIENTS COMPLAINT OF DRY MOUTH WAS MAXIMUM AT 3 MONTH WHICH FURTHER IMPROVES WITH TIME.

PLOT 15- DR RADAR PLOT



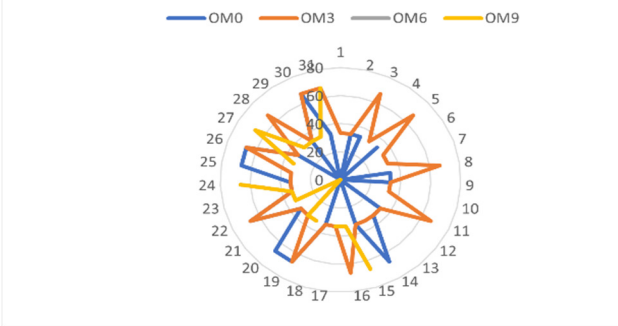
RADAR PLOT FOR SOCIAL EATING AT MONTH 0,3,6,9 – SHOWS THAT IN MAXIMUM NUMBER OF PATIENTS SOCIAL EATING SCORES WERE WORSE AT 3 MONTHS. DURING FURTHER FOLLOW UP IT STARTS DECREASING.

PLOT 16- SO RADAR PLOT



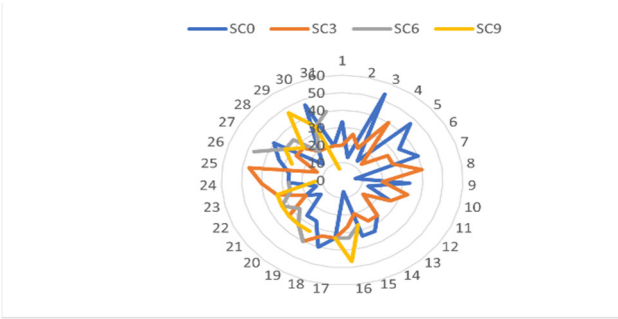
RADAR PLOT FOR SPEECH SCORES AT MONTH 0,3,6,9 – IT SHOWS THAT MAXIMUM PATIENTS HAVE DIFFIICULTY IN SPEAKING AT 3 MONTHS

PLOT 17- SP RADAR PLOT



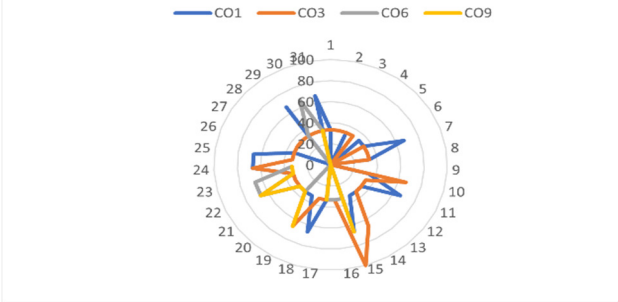
RADAR PLOT FOR MOUTH OPENING SCORES AT MONTH 0, 3, 6, AND 9. IT SHOWS THAT MAXIMUM PATIENTS HAVE DIFFICULT IN MOUTH OPENING AT 0 AND 3 MONTHS

PLOT 18- OM RADAR PLOT



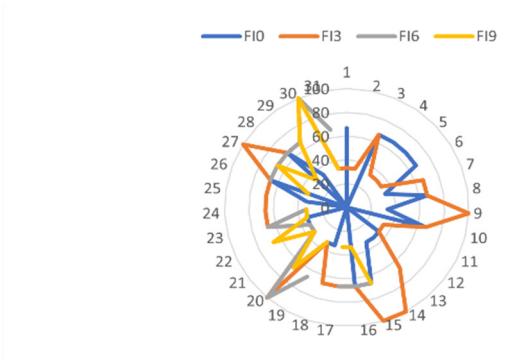
RADAR PLOT FOR SOCIAL CONTACT SCORES AT MONTH 0,3,6, AND 9. IT SHOWS THAT MAXIMUM PATIENTS HAVE DIFFICULTY IN SOCIAL INTERACTION AT STARTING OF RADIATION AND AT 3 MONTHS

PLOT 19- SC RADAR PLOT



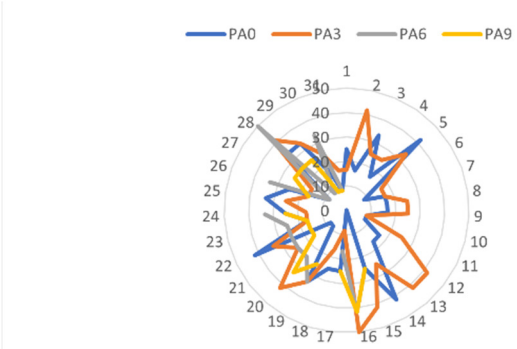
RADAR PLOT FOR COUGH SCORES AT MONTH 0, 3, 6, AND 9. IT SHOWS THAT MAXIMUM PATIENTS HAVE COMPLAINT OF COUGH AT START OF RADIOTHERAPY

PLOT 20- CO RADAR PLOT



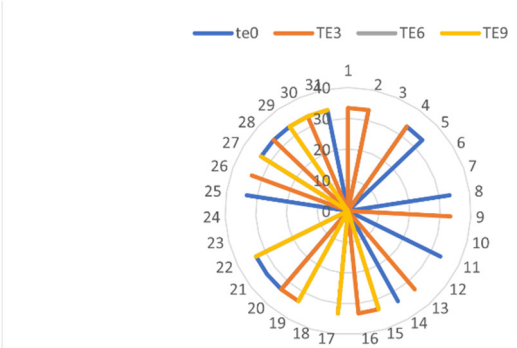
RADAR PLOT FOR FELT ILLSCORES AT MONTH 0,3,6, AND 9 – IT SHOWS THAT MAXIMUM PATIENTS HAVE FEELING OF ILLNESS AT STARTING OF RT AND AT 3 MONTHS

PLOT 21- FI RADAR PLOT



RADAR PLOT FOR PAIN SCORES AT MONTH 0,3,6, AND 9- IT SHOWS THAT MAXIMUM PATIENT COMPLAINS OF PAIN AT 3 MONTHS AFTER RT

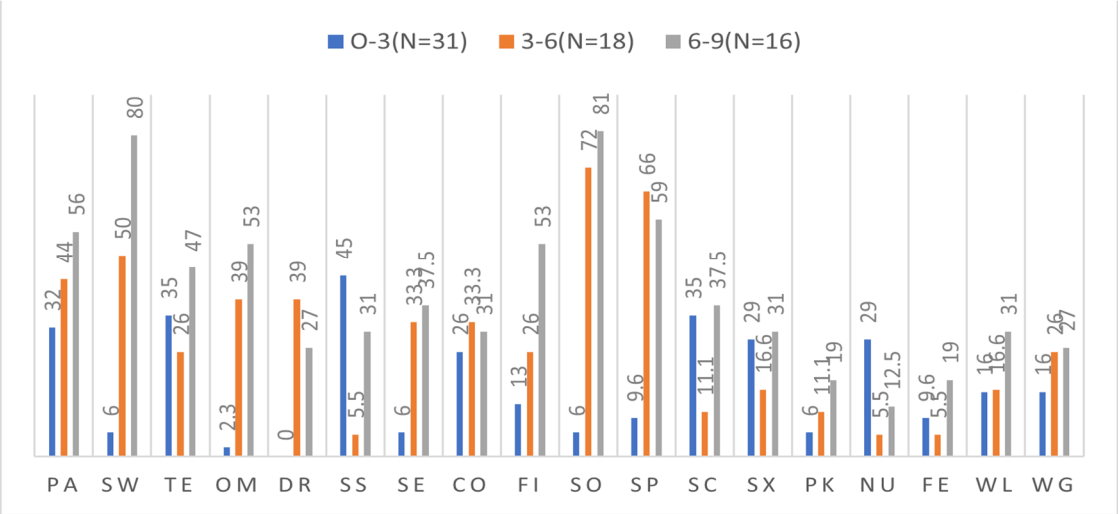
PLOT 22-PA RADAR PLOT



RADAR PLOT FOR TEETH SCORES AT MONTH 0,3,6, AND 9-IT SHOWS THAT MAXIMUM PATIENTS WERE HAVING TOOTH RELATED PROBLEMS AT STARTING OF RADIOTHERAPY.

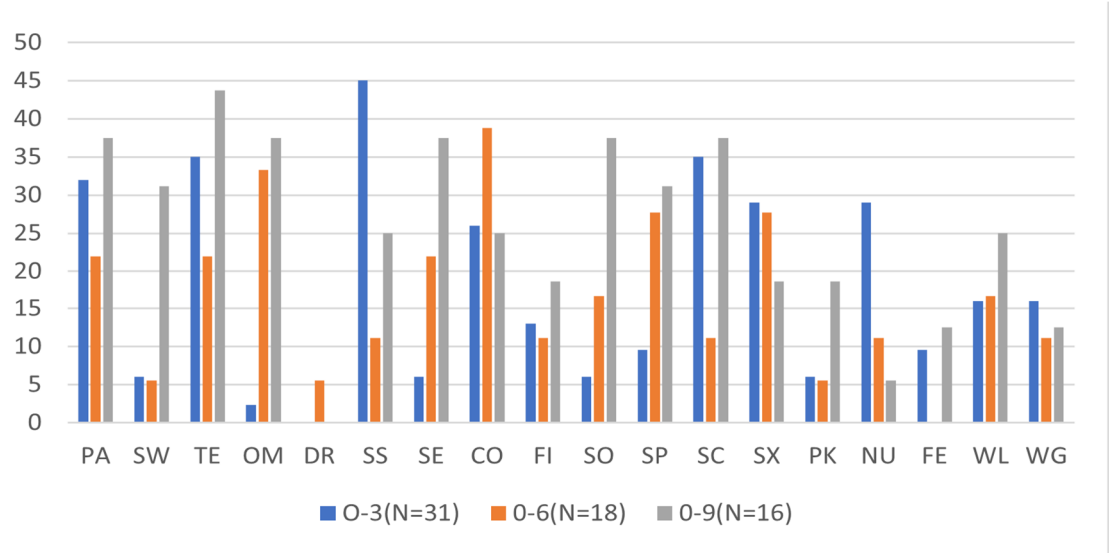
PLOT 23- TE RADAR PLOT

PERCENTAGE OF PATIENTS WITH INDICATIONS OF IMPROVED QOL USING EORTC H & N 35 QOL SCORE AT 3, 6 & 9 MONTHS –



PLOT 24(a)-PERCENTAGE OF PATIENTS WITH INDICATIONS OF IMPROVED QOL USING EORTC H & N 35 QOL SCORE AT 3, 6 & 9 MONTHS –

The linear transformed score of each of the 18 scales of EORTC H & N 35 Questionnaire of each of the patient was compared between baseline and 3 month, 3 month and 6 month and 6 month and 9 month. A patient with score lesser than previous one was counted as having improvement in that particular QOL scale except for the 18th scale for weight gain(WG) where reverse (more the WG score better the QOL). Percentage of patients with improvement in QOL was calculated using denominator equals to patient available for analysis at that time point.

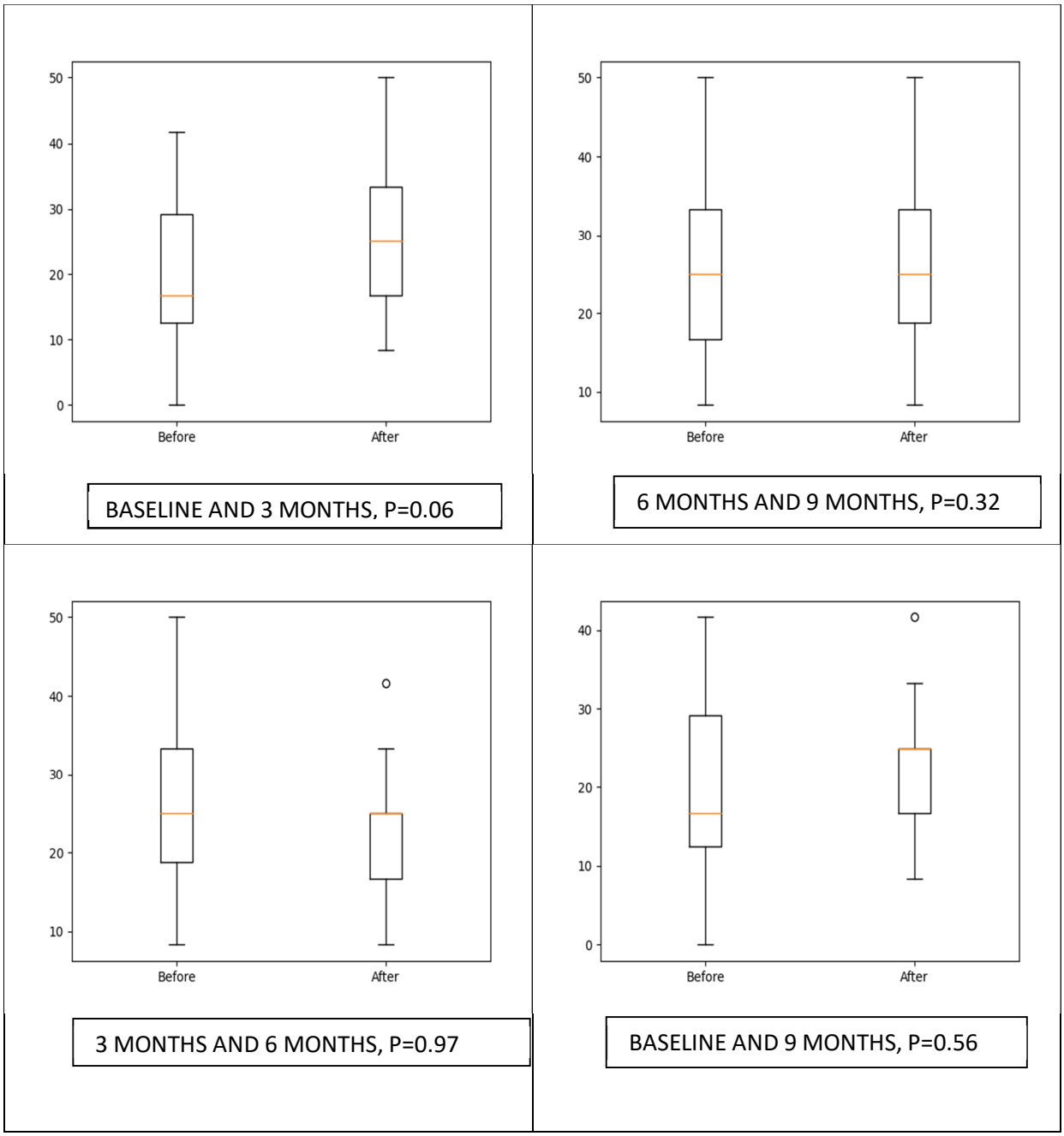


PLOT 24(b)- QOL SCALE SHOWING IMPROVEMENT FROM BASELINE

QOL MEASUREMENT TIME FROM BASELINE	QOL SCALE SHOWING IMPROVEMENT FROM BASELINE IN =/> 25 % OF PATIENTS IN DESCENDING ORDER
3 MONTH	SS,TE,SC,PA,CO,NU
6 MONTH	CO,OM,SP,SX
9 MONTH	TE,SE,SC,SO,OM, SP,WL,SW

The linear transformed score of each of the 18 scales of EORTC H & N 35 Questionnaire of each of the patient was compared between baseline and 3, 6 and 9 month. A patient with score lesser than previous one was counted as having improvement in that particular QOL scale except for the 18th scale for weight gain(WG) where reverse (more the WG score better the QOL) . percentage of patients with improvement in QOL was calculated using denominator equals to patient available for analysis at that time point.

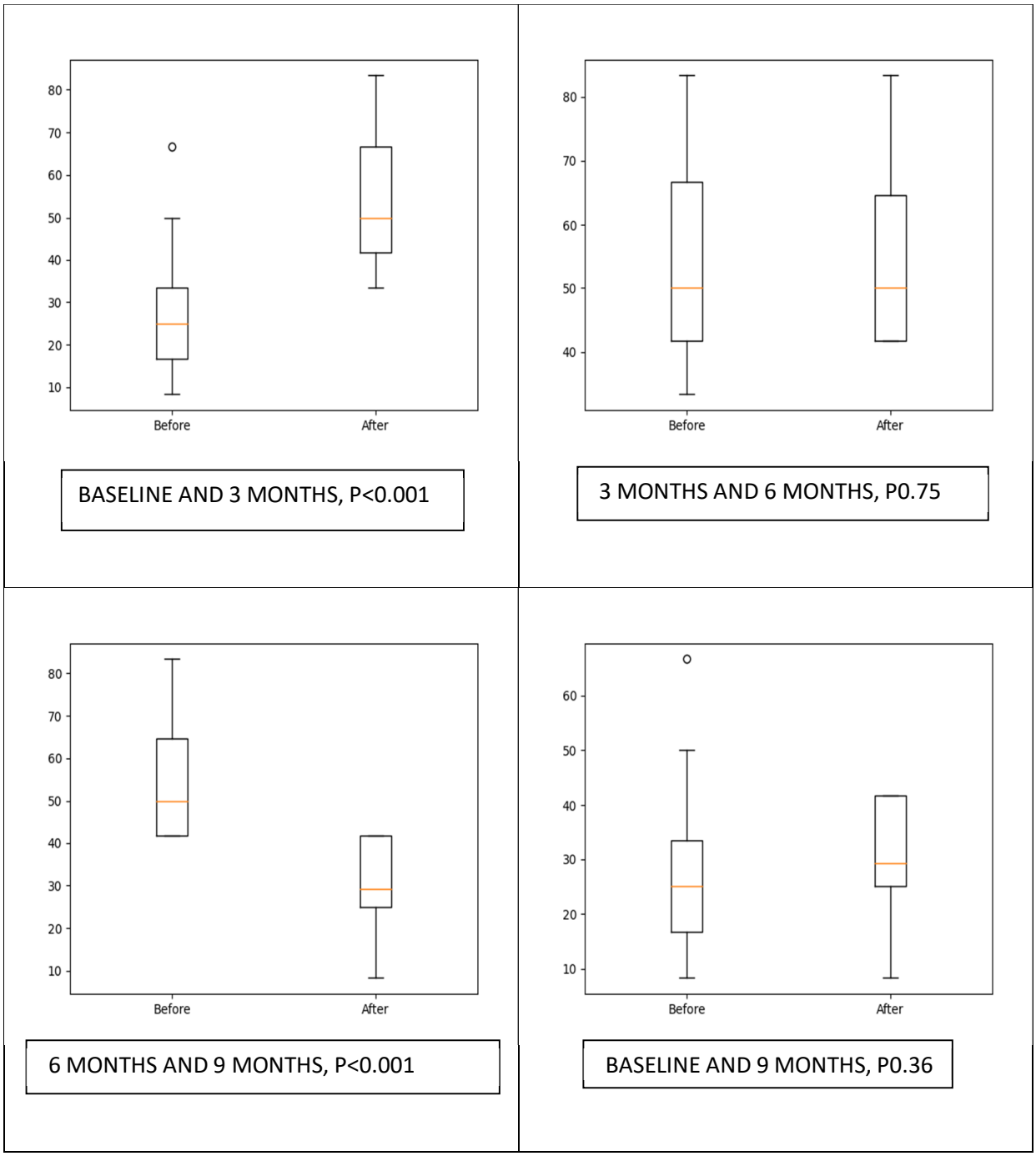
COMPARISON OF EORTC H & N35 PAIN SCORES(PA) -



PLOT 25-COMPARISON OF EORTC H & N35 PAIN SCORES(PA)

Above Box and Whisker plots were plotted to compare pain scores at different follow up times. No statistically significant change was seen in pain scores related QoL for follow up time and age groups.

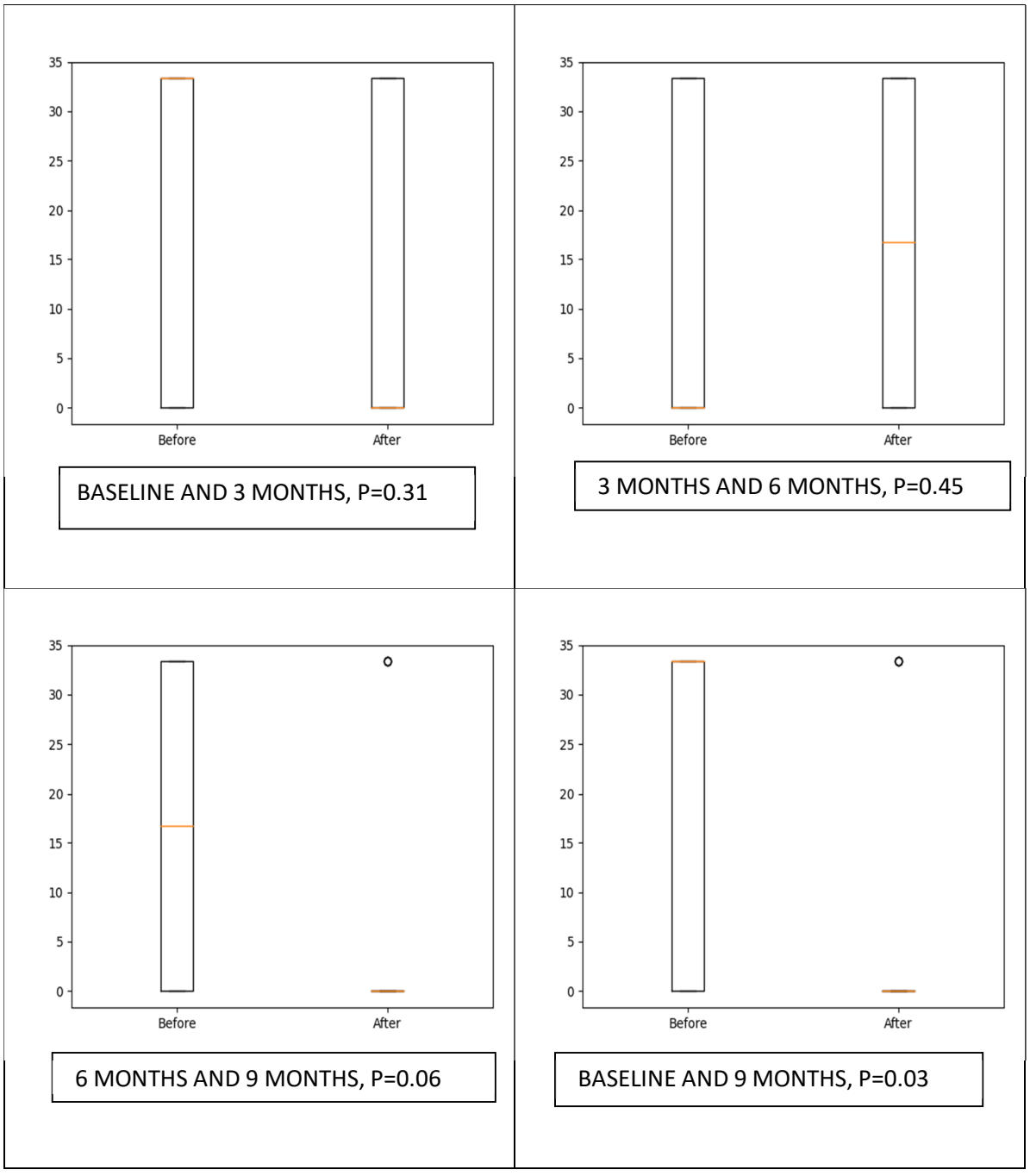
COMPARISON OF EORTC H & N35 SWALLOWING SCORES(SW) AT



PLOT 26-COMPARISON OF EORTC H & N35 SWALLOWING SCORES(SW)

Above Box and Whisker plots were plotted to compare Swallowing scores at different follow up times. Statistically significant change was seen in swallowing scores related QoL between baseline and 3rd month($p<0.001$) and between 6th and 9th month. Thus, there was significant worsening in swallowing scores at 3rd month post RT.

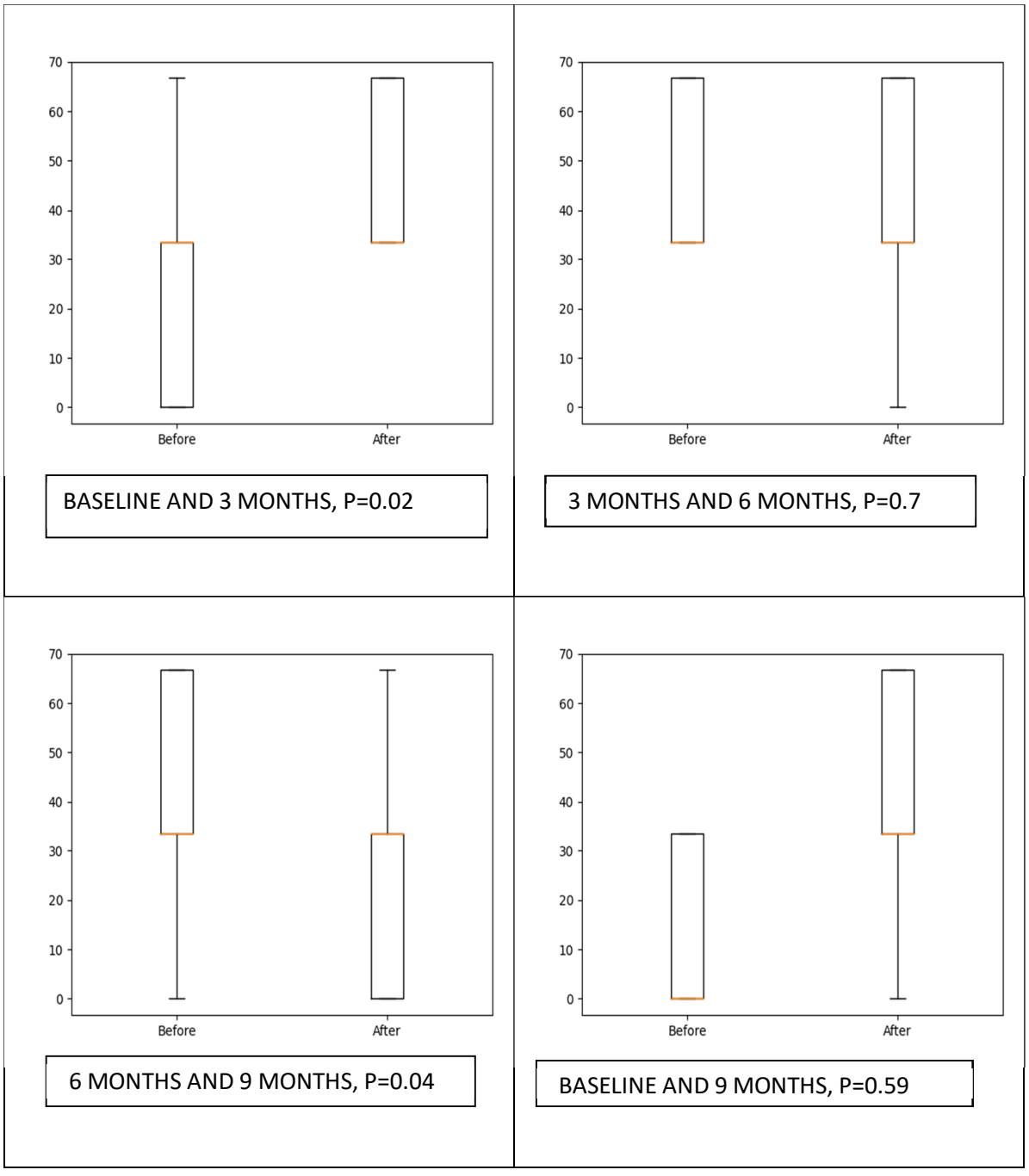
COMPARISON OF EORTC H & N35 TEETH SCORES(TE) AT



PLOT 27-COMPARISON OF EORTC H & N35 TEETH SCORES(TE)

Above Box and Whisker plots were plotted to compare teeth scores at different follow up times. statistically significant change was seen in swallowing scores related QoL between baseline and 9th month(p=0.03). Thus there was significant worsening in swallowing scores at 9th month post RT when compared with baseline scores.

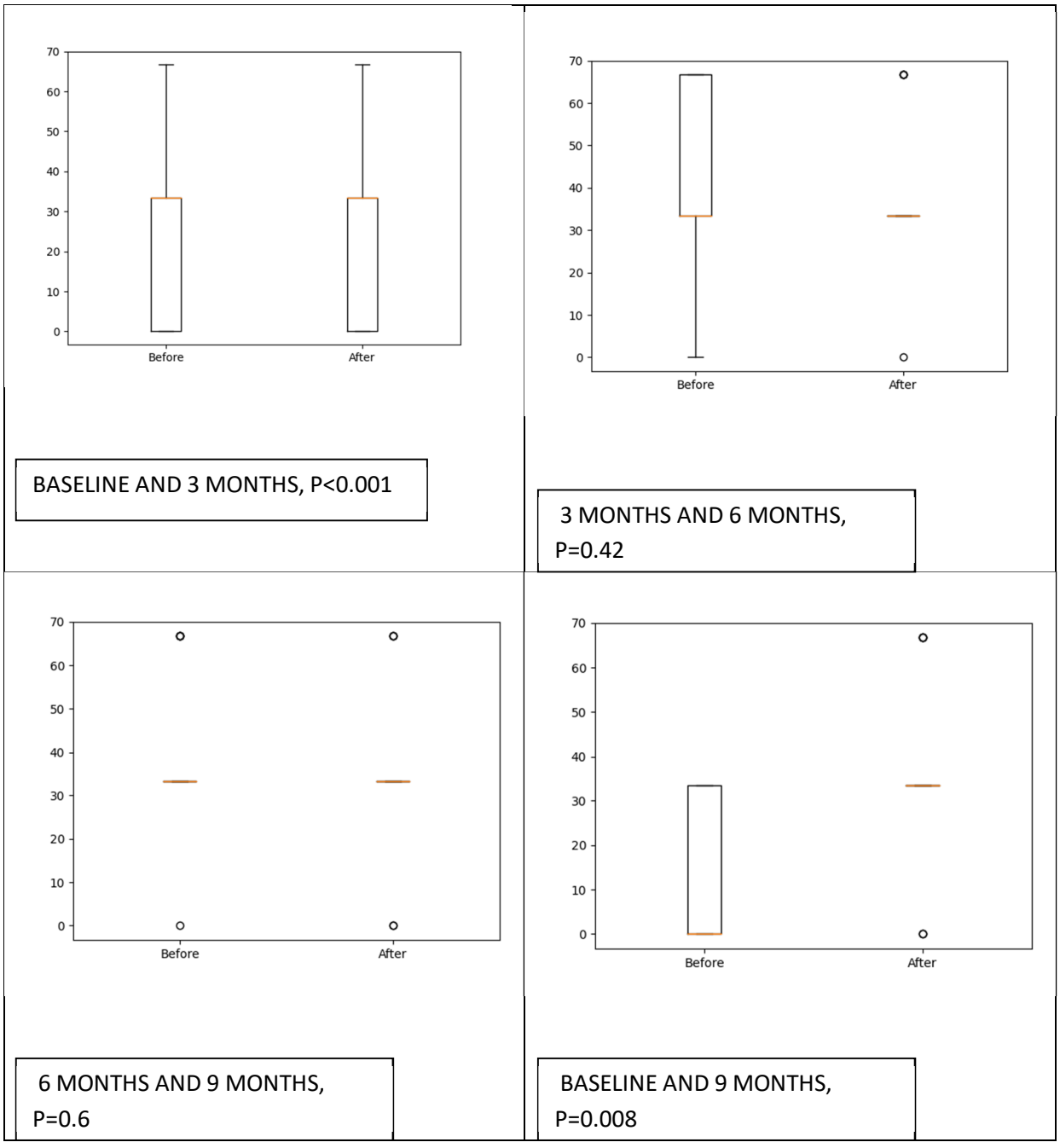
COMPARISON OF EORTC H & N35 MOUTH OPENING SCORES(OM) AT



PLOT 28-COMPARISON OF EORTC H & N35 MOUTH OPENING SCORES(OM)

Above Box and Whisker plots were plotted to compare mouth opening scores at different follow up times. statistically significant change was seen in mouth opening scores related QoL between baseline and 3rd month(p=0.02) and between 6th and 9th month(p=0.04). Thus there was significant worsening in ability to open mouth at 3rd month and at 6th month post RT

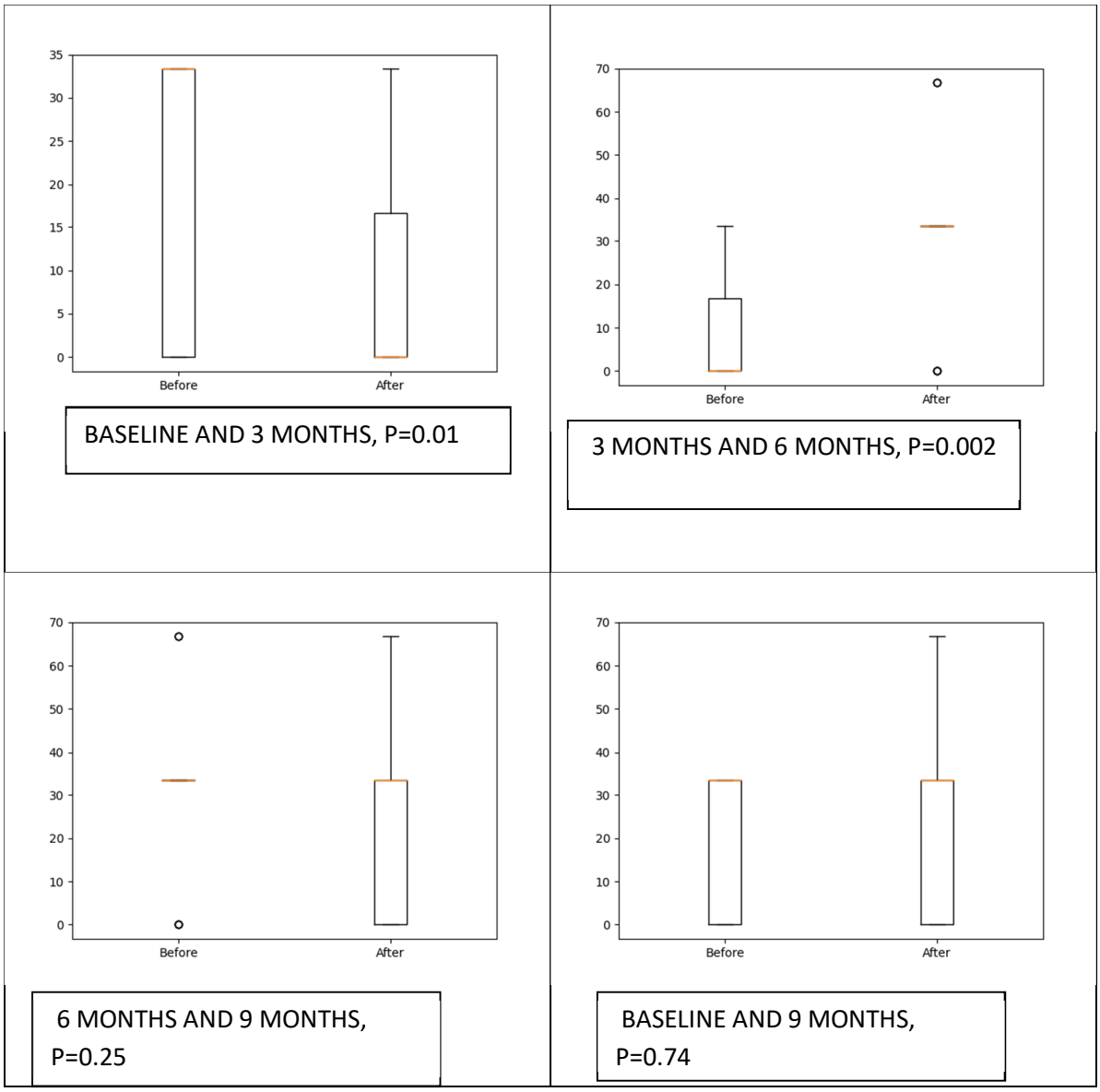
COMPARISON OF EORTC H & N35 DRY MOUTH SCORES(DR) AT-



PLOT 29-COMPARISON OF EORTC H & N35 DRY MOUTH SCORES(DR)

Above Box and Whisker plots were plotted to compare dry mouth scores at different follow up times. statistically significant change was seen in mouth opening scores related QoL between baseline and 3rd month($p<0.001$) and between baseline and 9th month($p=0.008$). Thus, there was significant increase in dryness of mouth at 3rd and 9th month as compared to baseline.

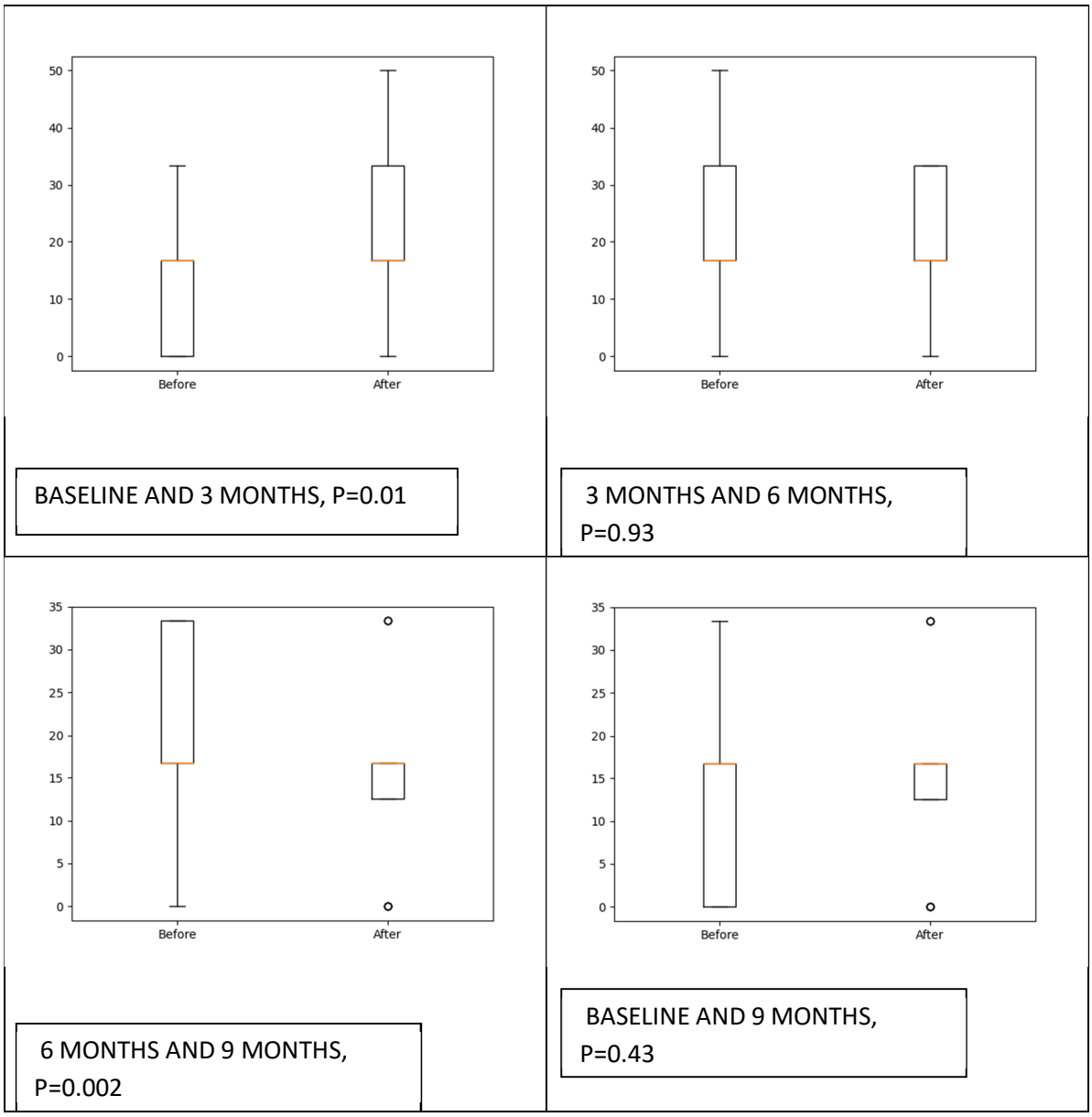
COMPARISON OF EORTC H & N35 STICKY SALIVA SCORES(SS) AT-



PLOT 30-COMPARISON OF EORTC H & N35 STICKY SALIVA SCORES(SS)

Above Box and Whisker plots were plotted to compare sticky saliva scores at different follow up times. statistically significant change was seen in sticky saliva scores related QoL between baseline and 3rd month($p<0.001$)

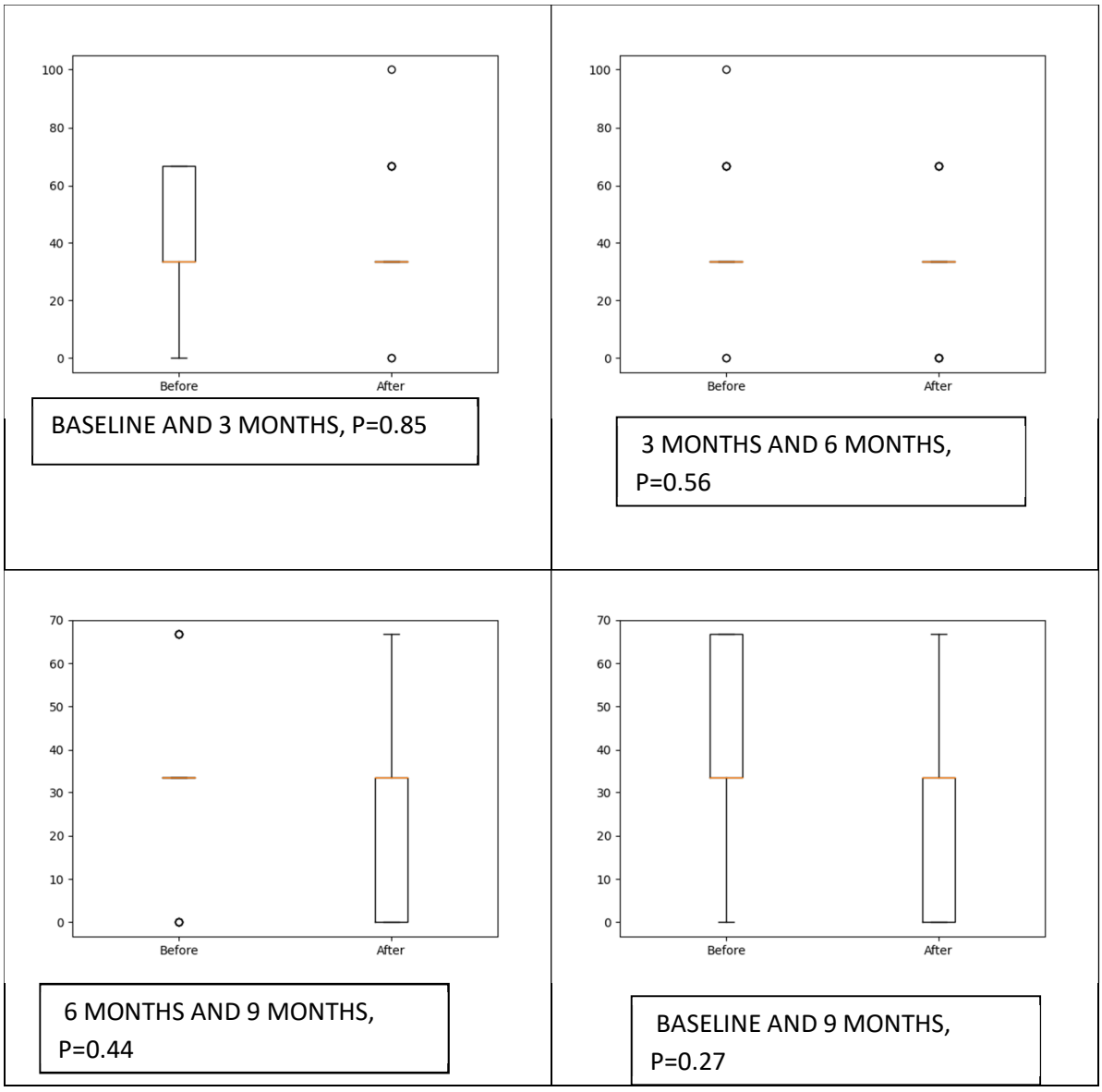
COMPARISON OF EORTC H & N35 SENSES SCORES(SE) AT-



PLOT 31-COMPARISON OF EORTC H & N35 SENSES SCORES(SE)

Above Box and Whisker plots were plotted to compare senses scores at different follow up times. statistically significant change was seen in senses scores related QoL between baseline and 3rd month(p=0.01) and between 6th and 9th month(p=0.002). Thus, there was significant increase in deterioration of sense of taste and smell observed at 3rd and 9th month as compared to baseline

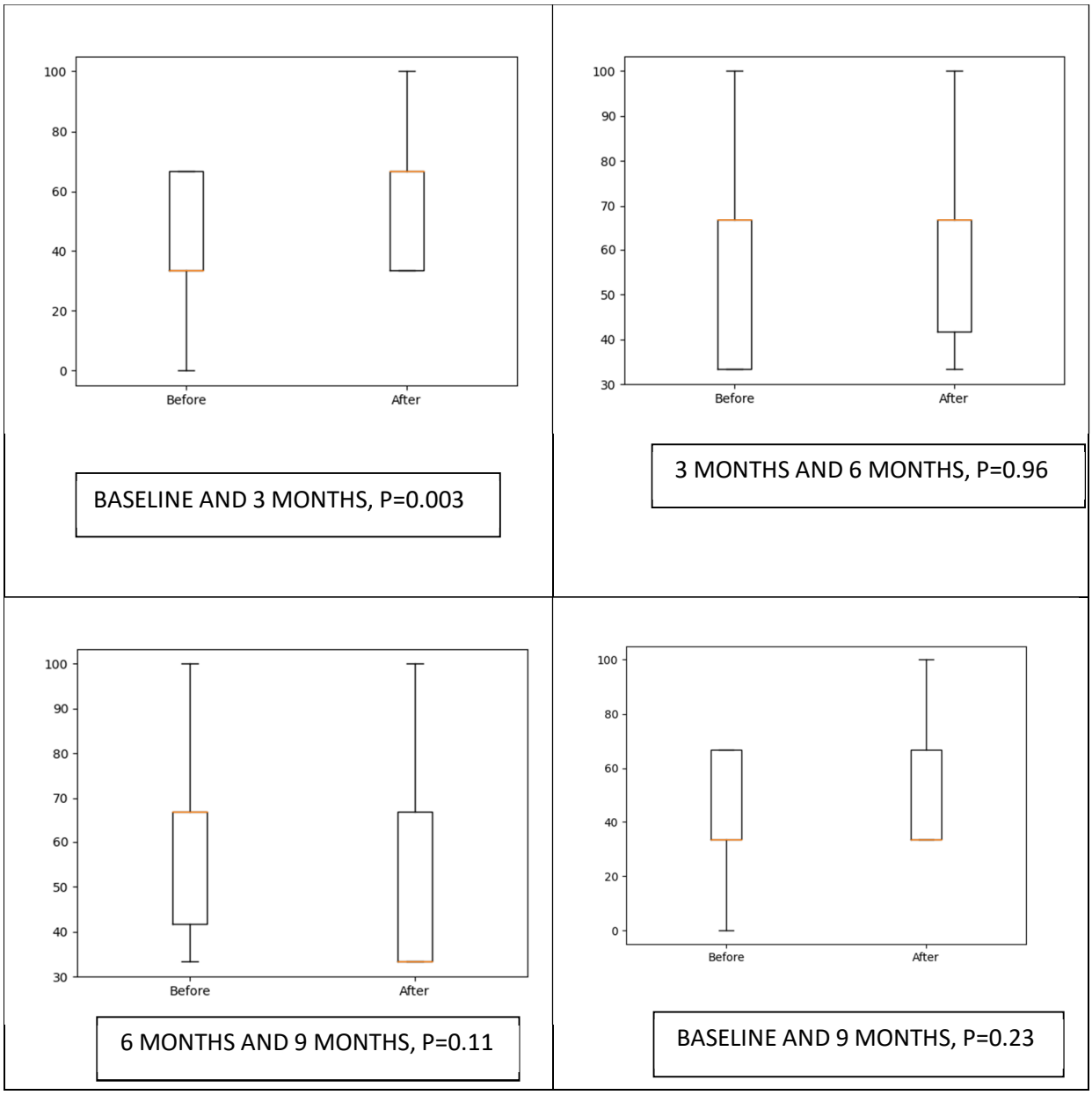
COMPARISON OF EORTC H & N35 COUGHING SCORES(CO) AT



PLOT 32-COMPARISON OF EORTC H & N35 COUGHING SCORES(CO)

Above Box and Whisker plots were plotted to compare coughing scores at different follow up times. No statistically significant change was seen in cough scores related QoL at any duration of follow up.

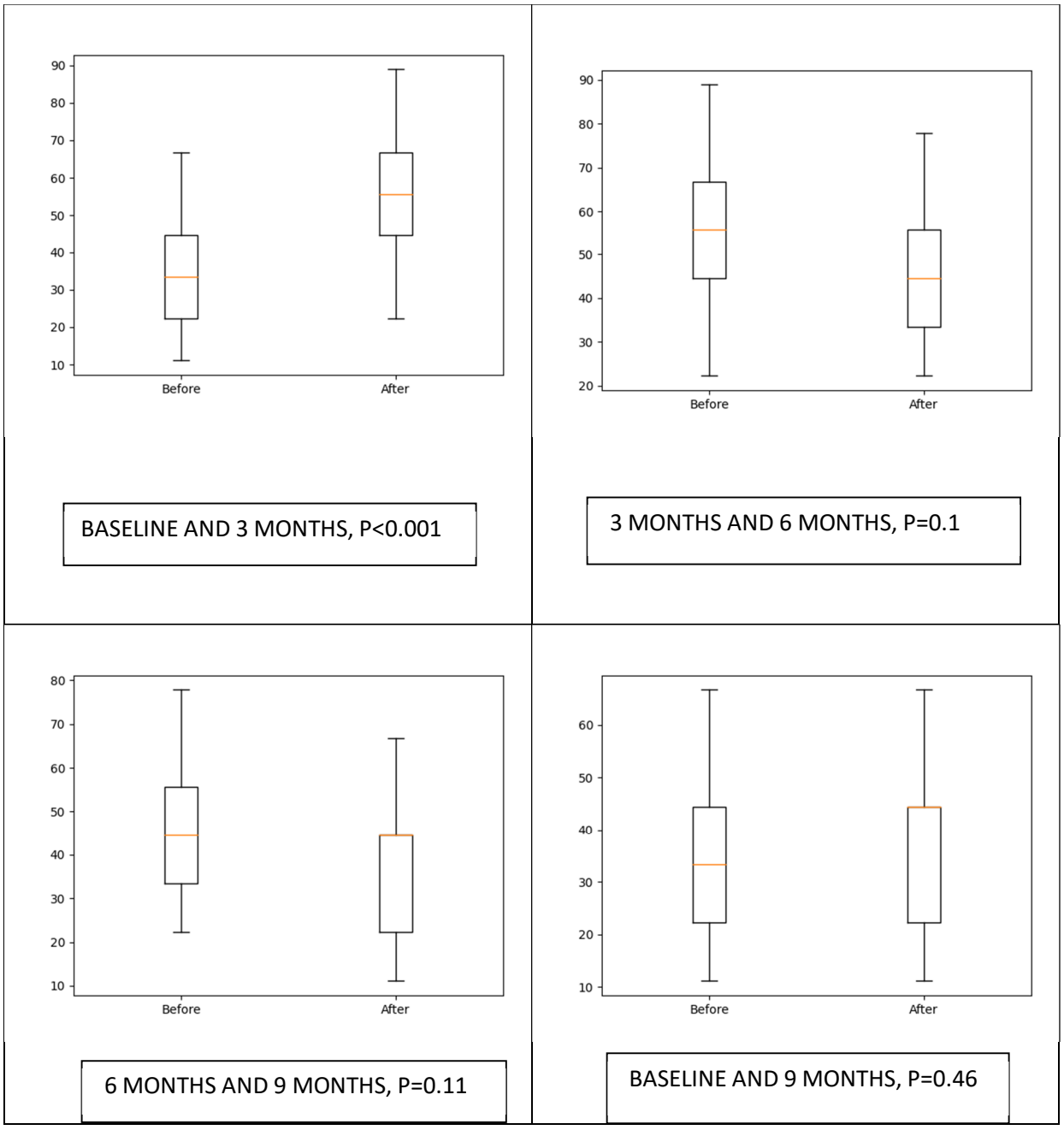
COMPARISON OF EORTC H & N35 FELT ILL SCORES(FI) AT



PLOT 33-COMPARISON OF EORTC H & N35 FELT ILL SCORES(FI)

Above Box and Whisker plots were plotted to compare felt ill scores at different follow up times. statistically significant change was seen in felt ill scores related QoL between baseline and 3rd month(p=0.003). Thus, there was significant increase in feeling of illness among patients observed at 3rd month as compared to baseline

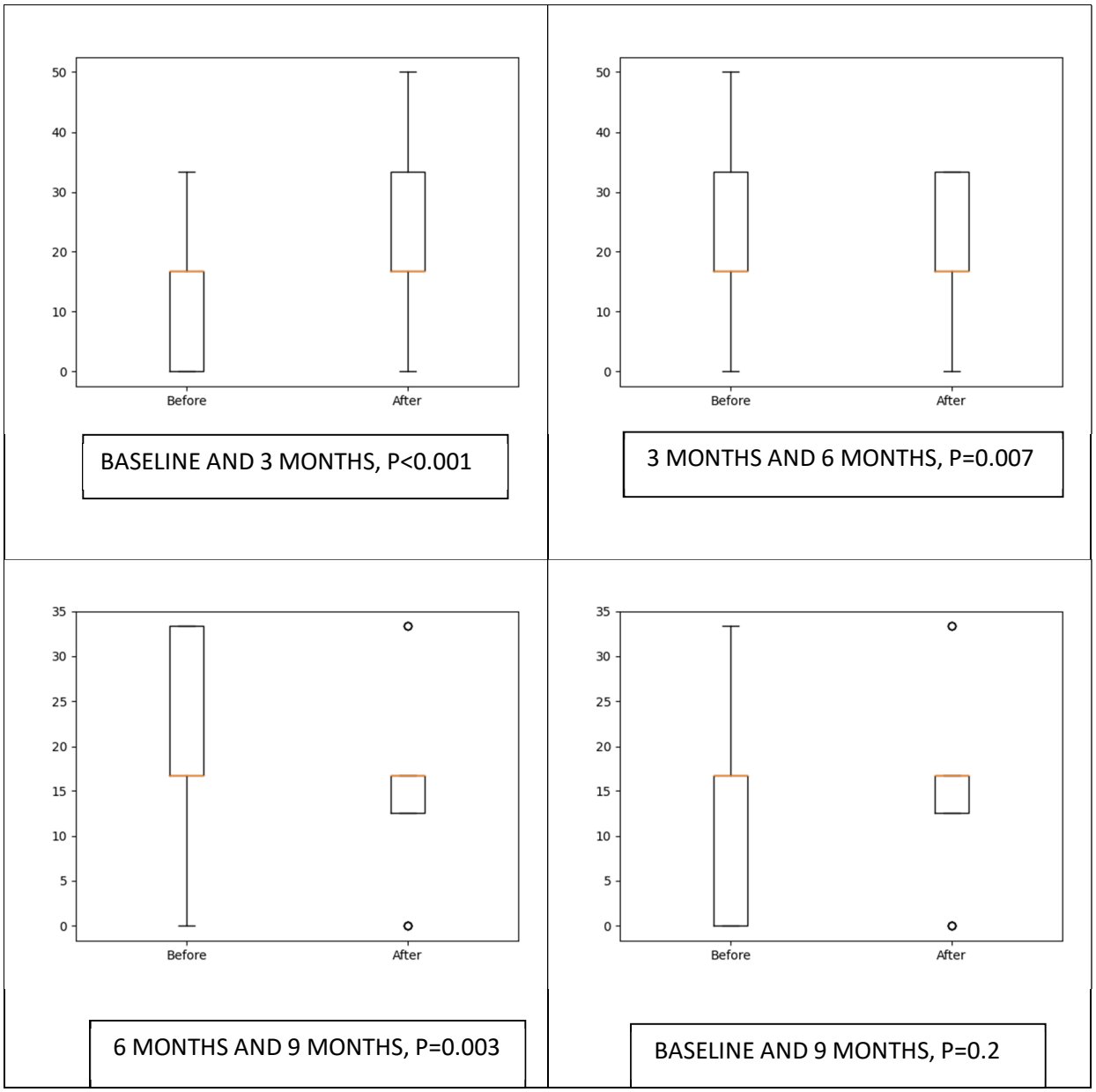
COMPARISON OF EORTC H & N35 SPEECH SCORES (SS)AT



PLOT 34-COMPARISON OF EORTC H & N35 SPEECH SCORES (SS)

Above Box and Whisker plots were plotted to compare speech scores at different follow up times. statistically significant change was seen in speech scores related QoL between baseline and 3rd month($p<0.001$). Thus there was significant worsening in ability to speak among patients observed at 3rd month as compared to baseline

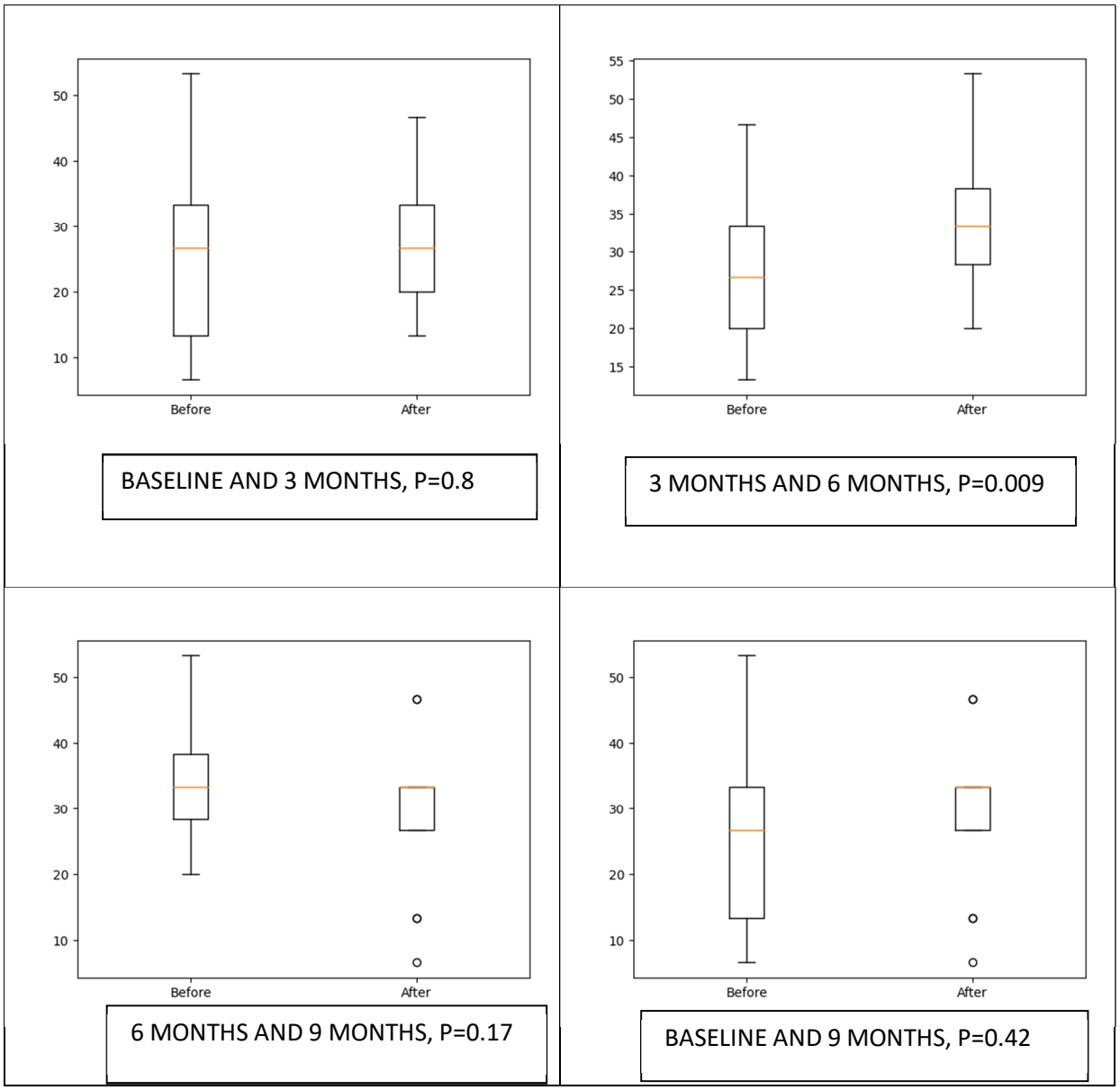
COMPARISON OF EORTC H & N35 SOCIAL EATING SCORES(SO) AT



PLOT 35-COMPARISON OF EORTC H & N35 SOCIAL EATING SCORES(SO)

Above Box and Whisker plots were plotted to compare social eating scores at different follow up times. statistically significant change was seen in social eating scores related QoL between baseline and 3rd month($p<0.001$), between 3rd and 6th month($p=0.007$), between 6th and 9th month ($p=0.003$). Thus there was significant worsening in ability to eat with other peoples and it remains for a longer duration.

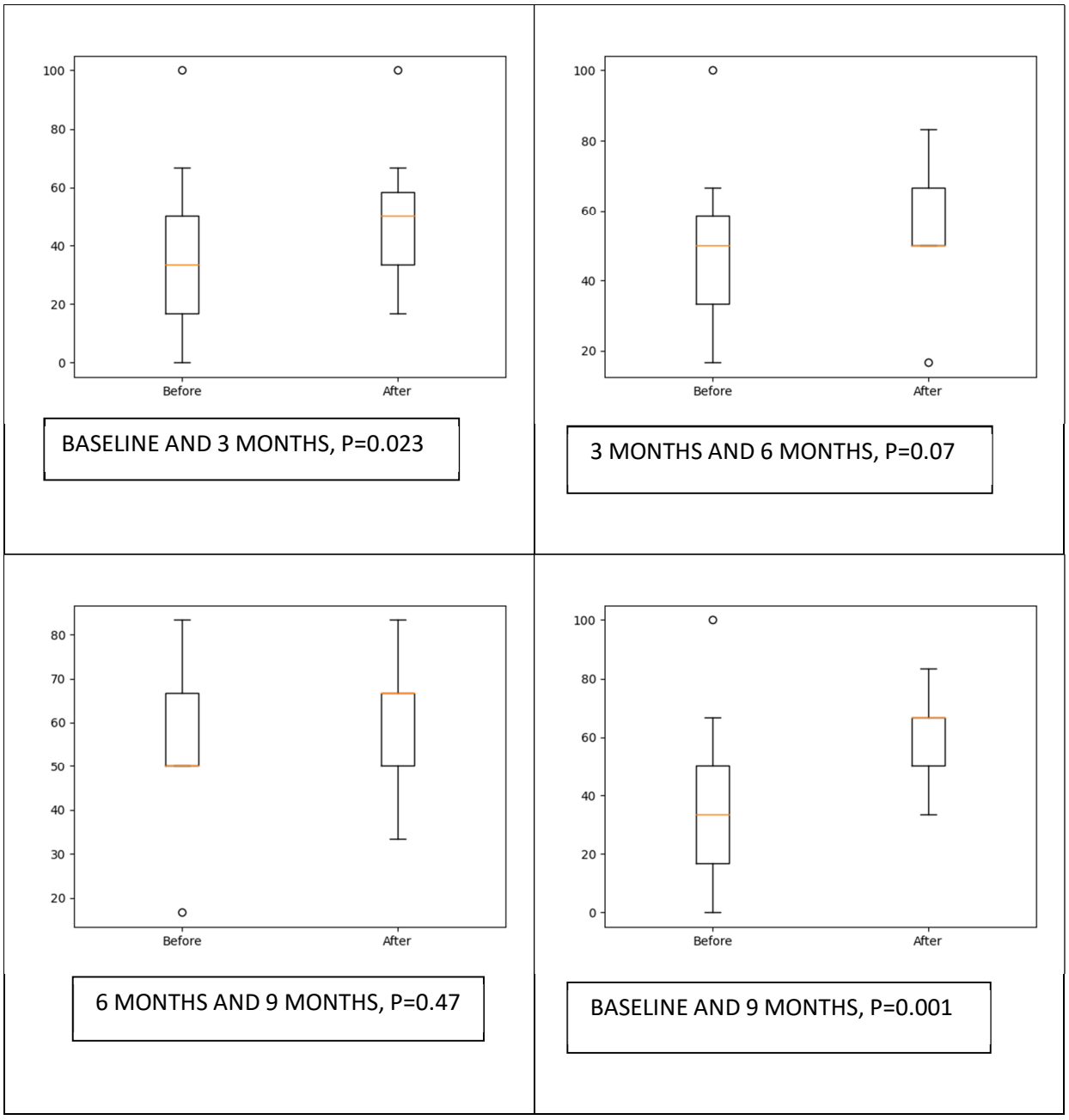
COMPARISON OF EORTC H & N35 SOCIAL CONTACT SCORES(SC) AT



PLOT 36-COMPARISON OF EORTC H & N35 SOCIAL CONTACT SCORES(SC)

Above Box and Whisker plots were plotted to compare social contact scores at different follow up times. statistically significant change was seen in social contact scores related QoL between 3rd month and 6th month(p=0.009). Thus there was significant increase in inability to maintain social contacts with other peoples after 3rd month.

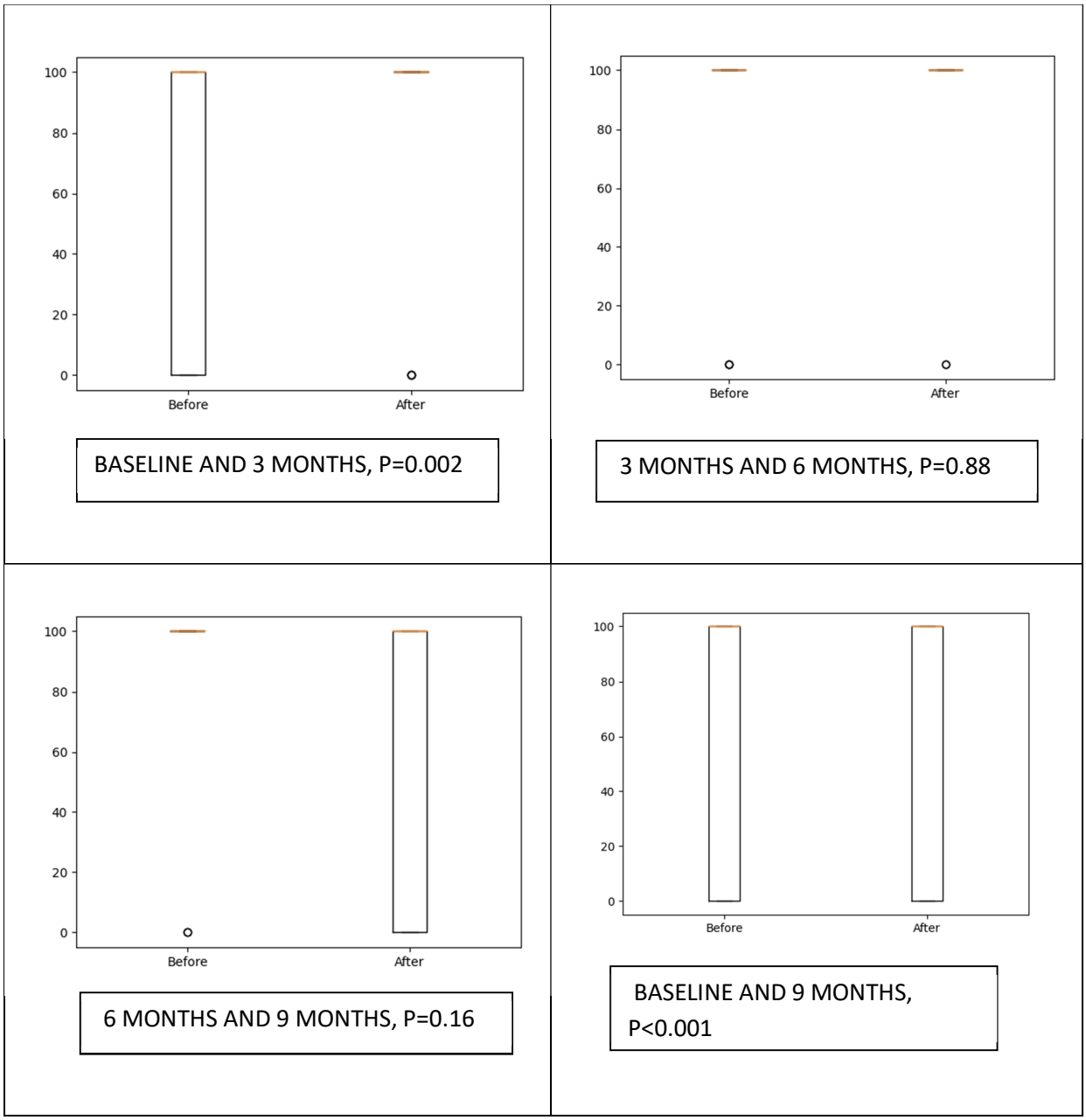
COMPARISON OF EORTC H & N35 SEXUALITY SCORES(SX) AT



PLOT 37-COMPARISON OF EORTC H & N35 SEXUALITY SCORES(SX)

Above Box and Whisker plots were plotted to compare sexuality scores at different follow up times. statistically significant change was seen in sexuality scores related QoL between baseline and 3rd month(p=0.02)3rd month and baseline and 9th month (p=0.001).

COMPARISON OF EORTC H & N35 PAIN KILLERS SCORES(PK) AT

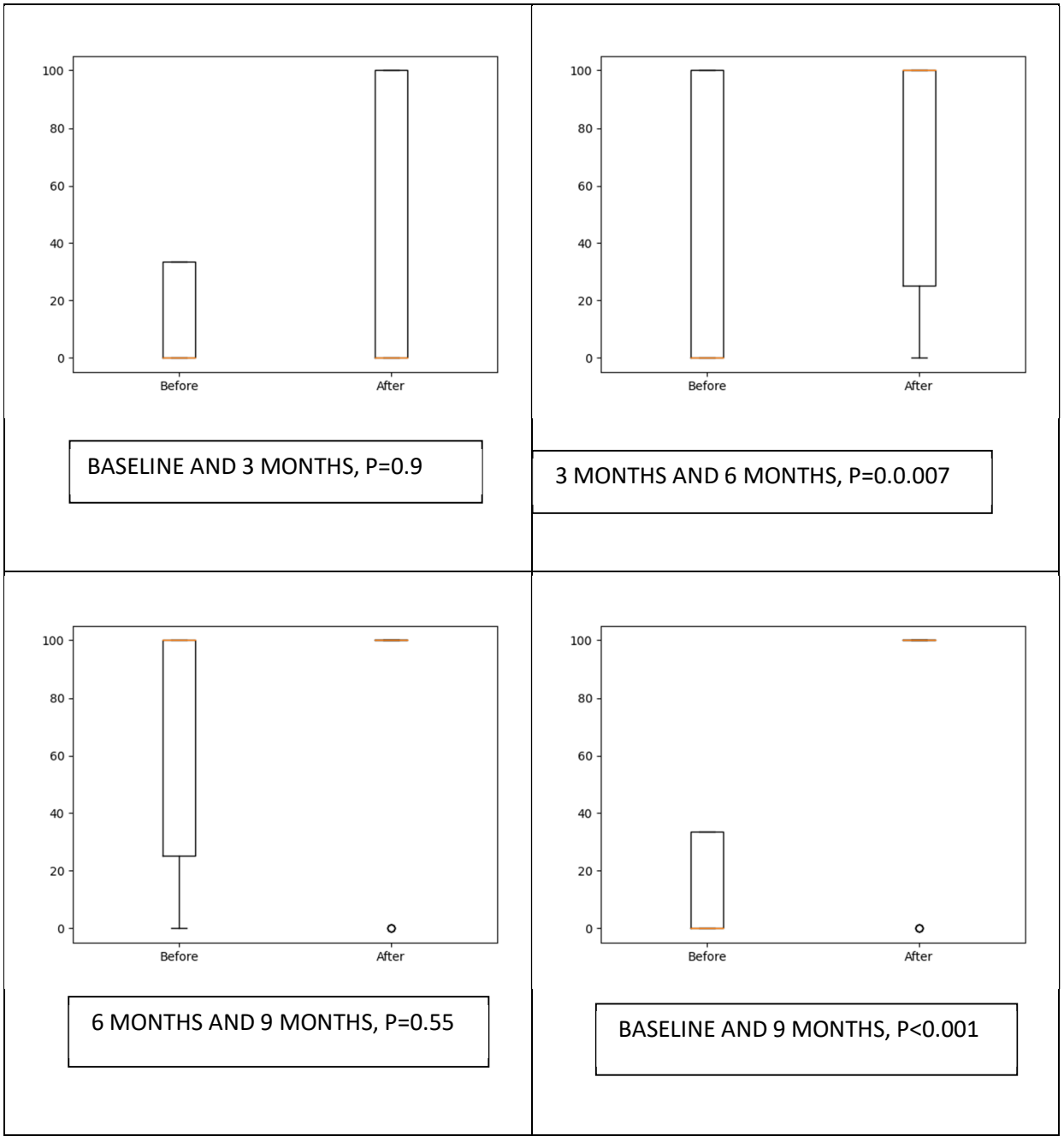


PLOT 38-COMPARISON OF EORTC H & N35 PAIN KILLERS SCORES(PK)

Above Box and Whisker plots were plotted to compare pain killer scores at different follow up time. statistically significant change was seen in pain killer scores related QoL between baseline and 3rd month(p=0.002) and baseline and 9th month(p<0.001). Thus, there was significant increase in use of pain killers at 3 month and at 9 months as compared to baseline.

-

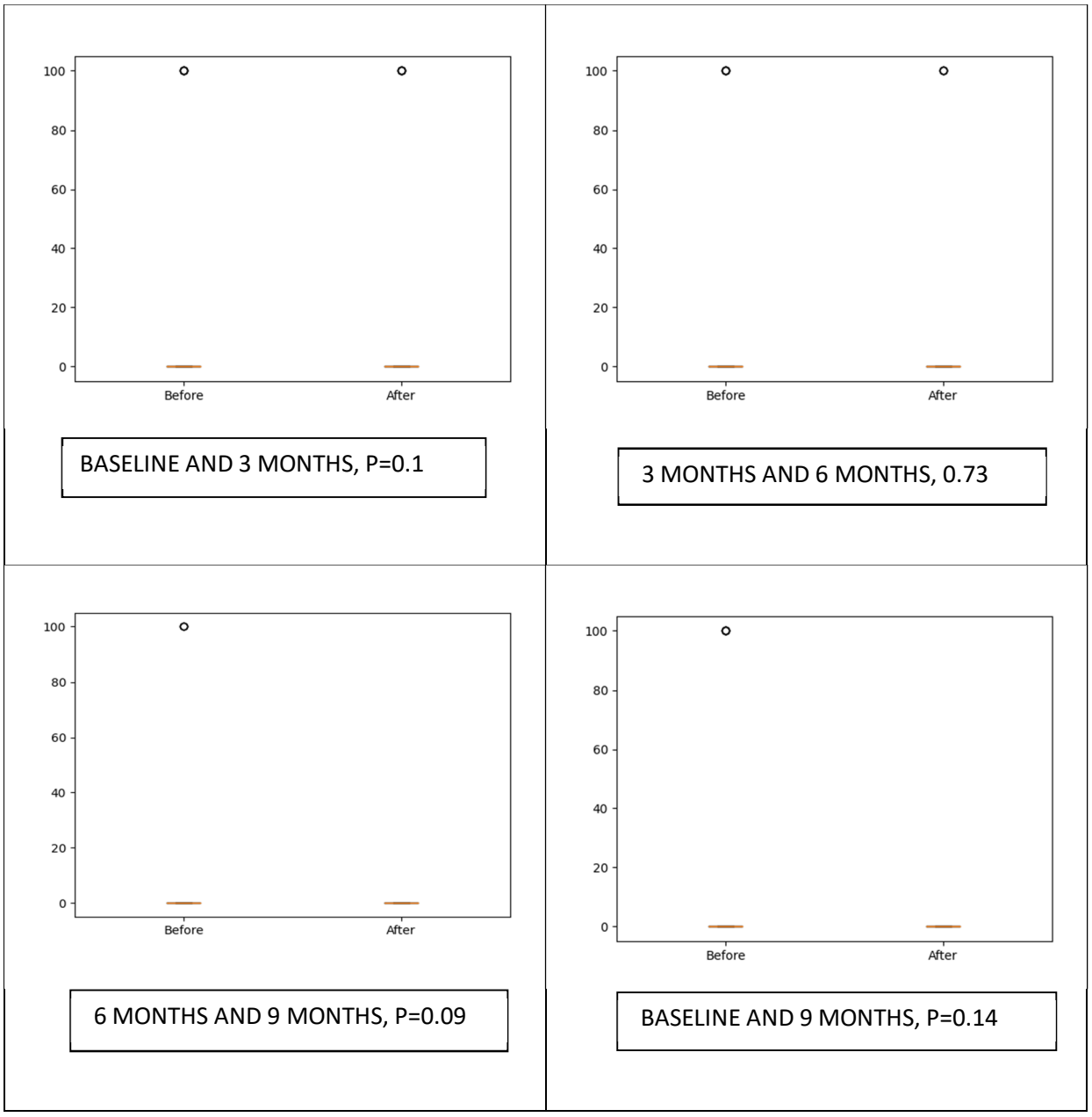
COMPARISON OF EORTC H & N35 NUTRITIONAL SUPPLEMENTS SCORES(NU) AT



PLOT 39-COMPARISON OF EORTC H & N35 NUTRITIONAL SUPPLEMENTS SCORES(NU)

Above Box and Whisker plots were plotted to compare nutritional supplement scores at different follow up time. statistically significant change was seen in nutritional supplement scores related QoL between 3rd and 6th month(p=0.007) and baseline and 9th month(p<0.001). Thus, there was significant increase in use of nutritional supplements at 6th month and at 9th month.

COMPARISON OF EORTC H & N35 FEEDING TUBE SCORES(FE) AT

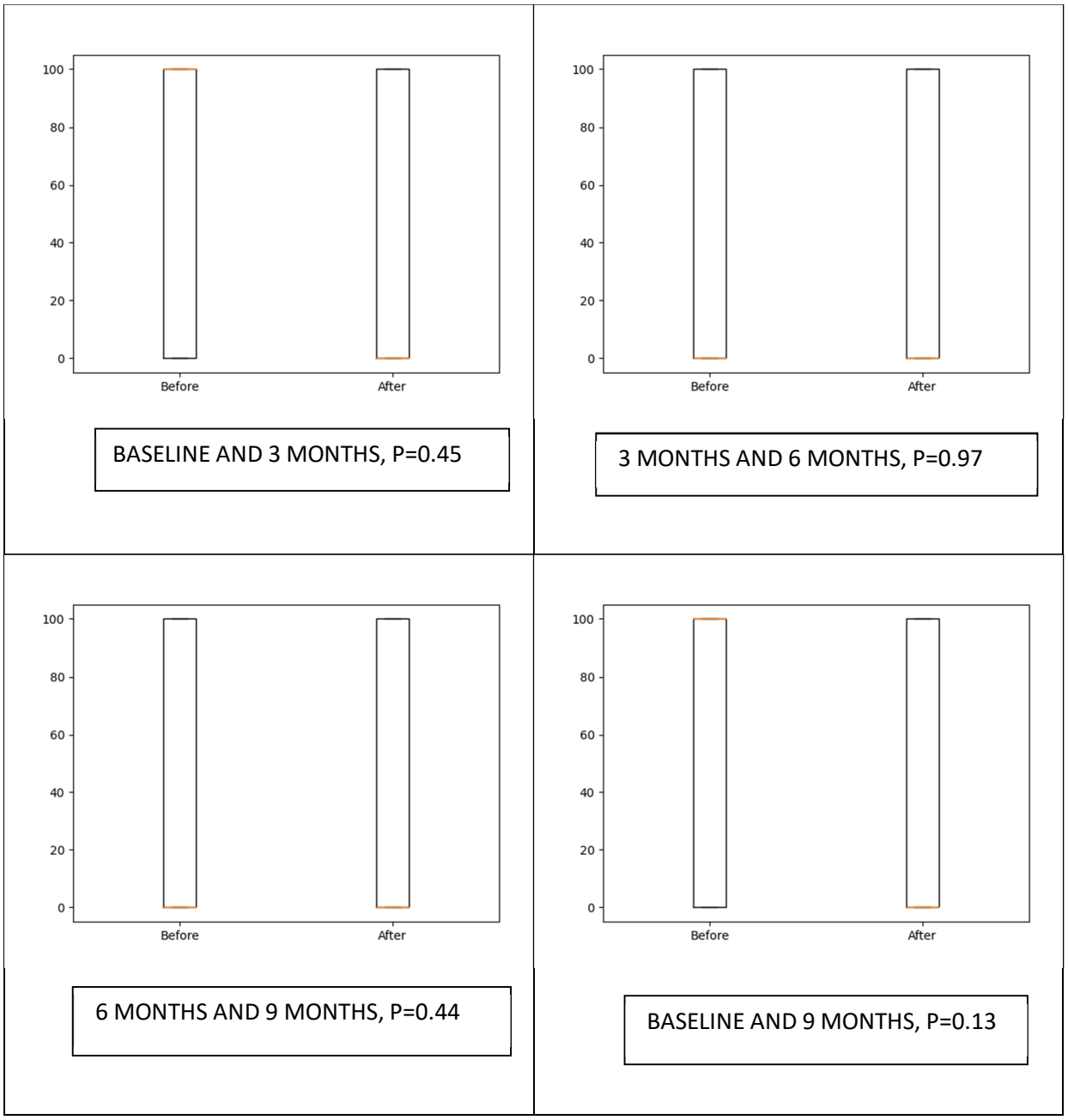


PLOT 40-COMPARISON OF EORTC H & N35 FEEDING TUBE SCORES(FE)

Above Box and Whisker plots were plotted to compare feeding tube scores at different follow up time. statistically significant change was seen in feeding tube scores related QoL between 6^{th} and 9^{th} month(p=0.09)

.

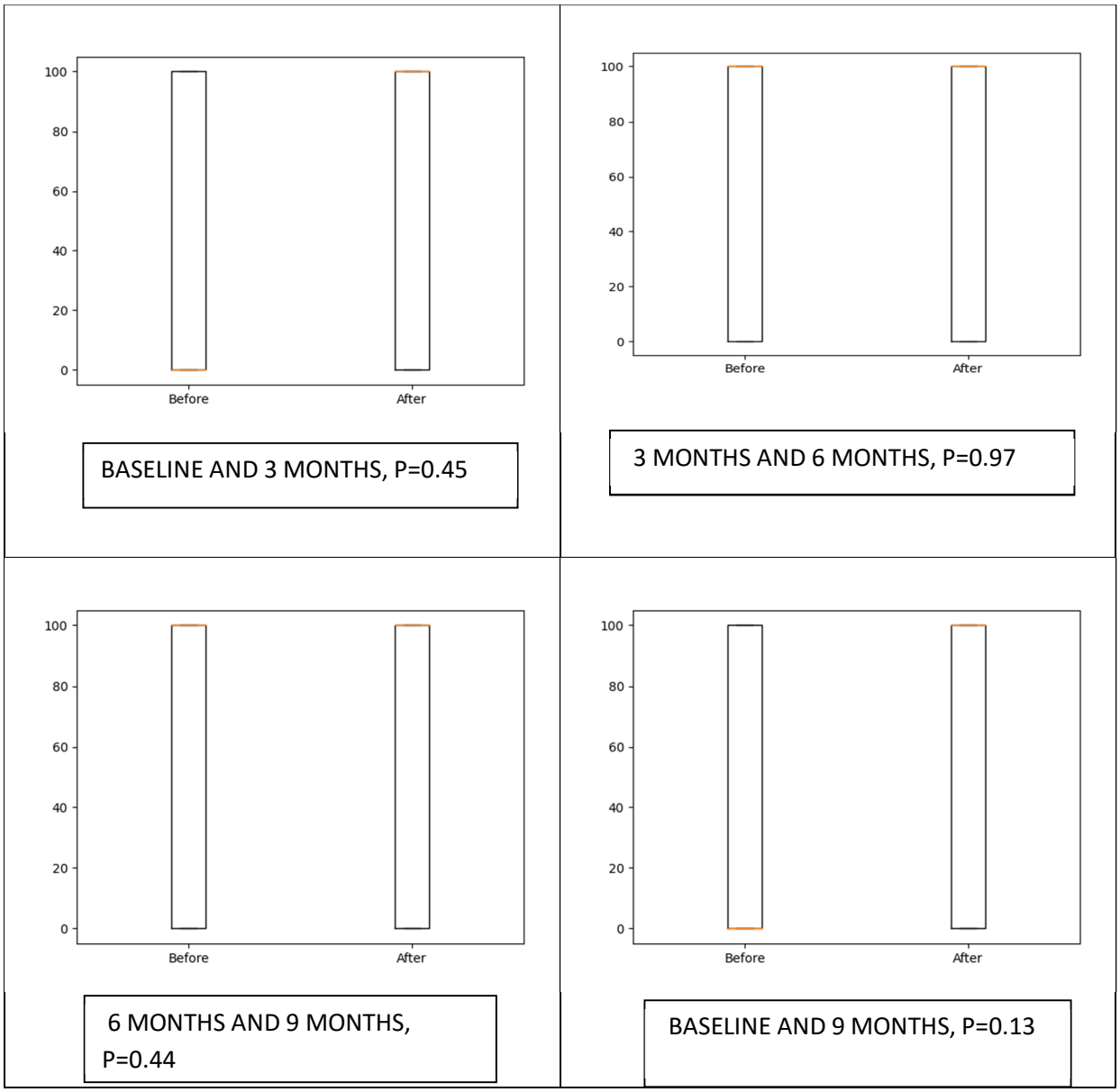
COMPARISON OF EORTC H & N35 WEIGHT LOSS SCORES(WL) AT



PLOT 41-COMPARISON OF EORTC H & N35 WEIGHT LOSS SCORES(WL)

Above Box and Whisker plots were plotted to compare weight loss scores at different follow up time . no statistically significant change was seen in weight loss scores related QOL at any time. thus, there is no significant change in weight during follow up.

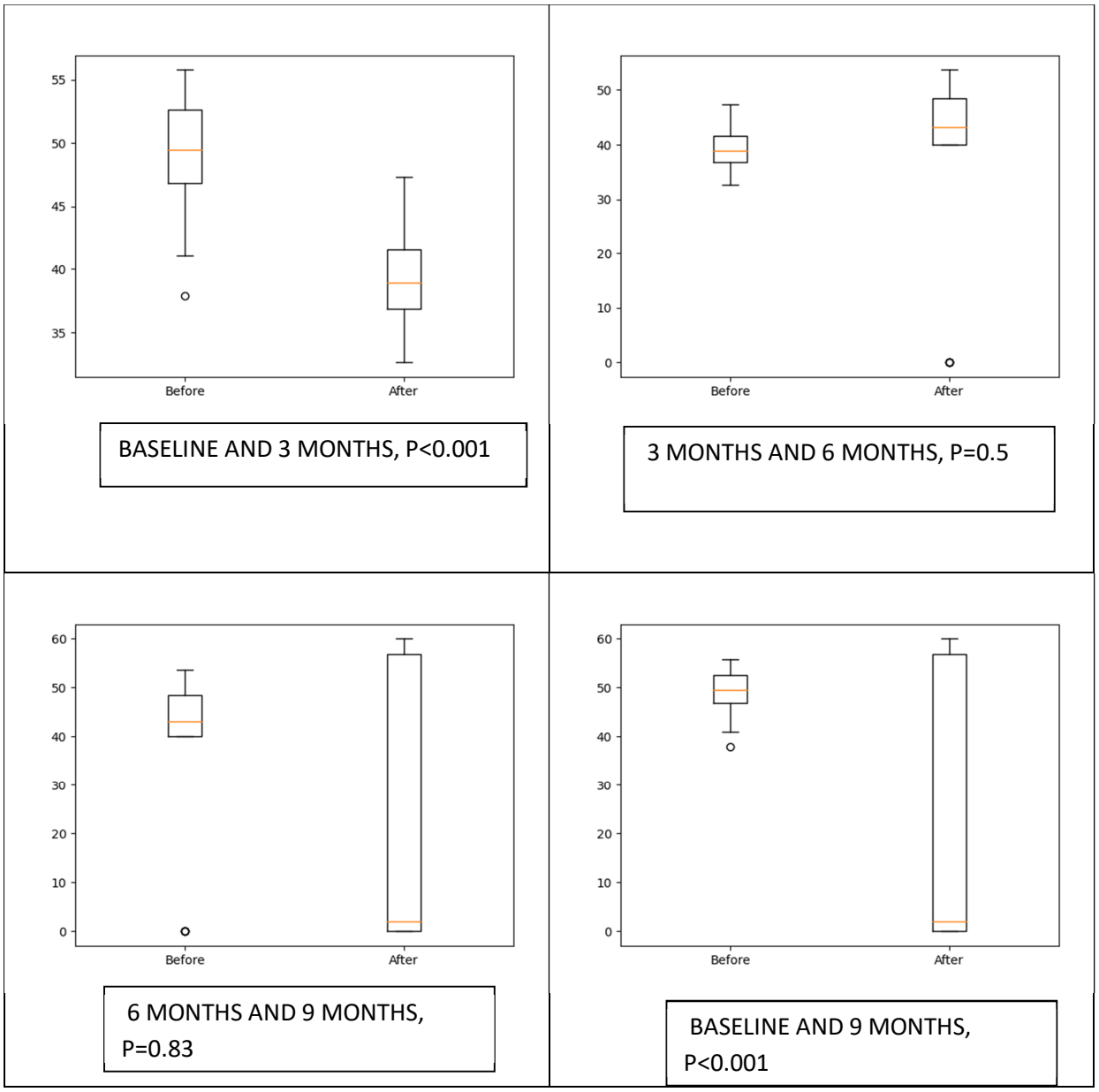
COMPARISON OF EORTC H & N35 WEIGHT GAIN SCORES(WG) AT



PLOT 42-COMPARISON OF EORTC H & N35 WEIGHT GAIN SCORES(WG)

Above Box and Whisker plots were plotted to compare weight gain scores at different follow up time . no statistically significant change was seen in weight gain scores related QOL at any time . thus there is no significant change in weight during follow up.

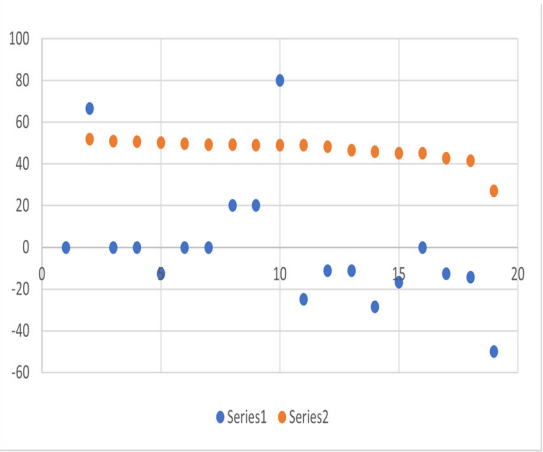
COMPARISON OF MEAN COMPOSITE MDADI SCORE AT-



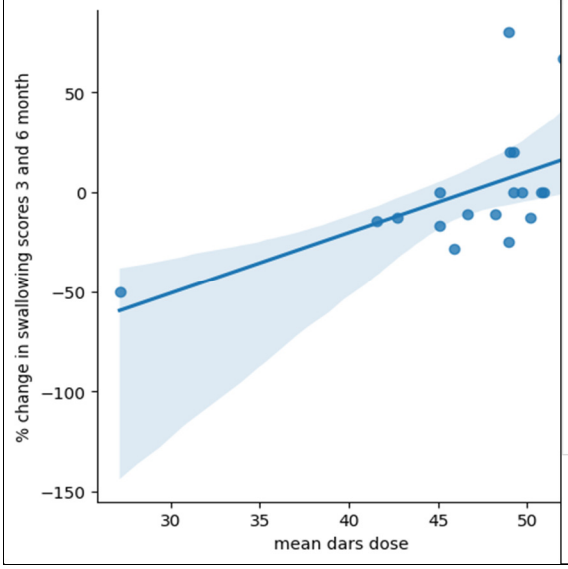
PLOT 43-COMPARISON OF MEAN COMPOSITE MDADI SCORE

Above Box and Whisker plots were plotted to compare mean composite MDADI score at different follow up time. statistically significant change was seen in mean composite MDADI scores between baseline and 3rd month ($p<0.001$) and between baseline and 9th month($p<0.001$) . Thus, there was significant increase in dysphagia at 3 month when compared to baseline

PERCENTAGE CHANGE IN SWALLOWING SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE -



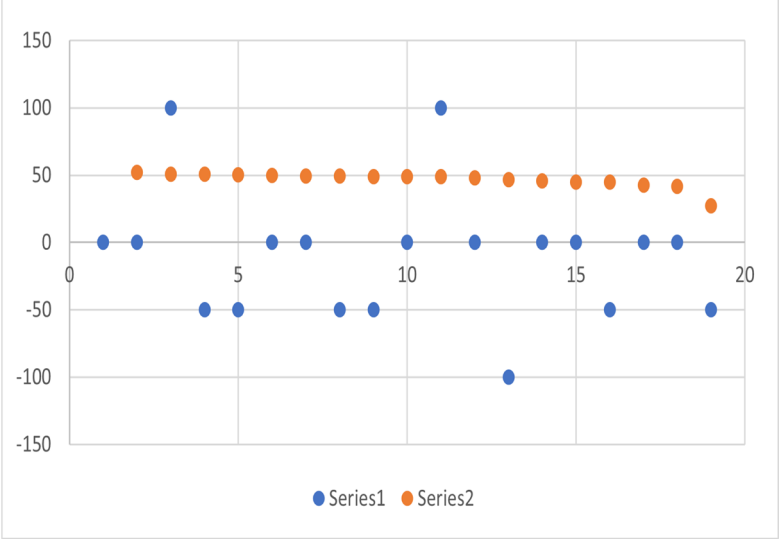
Given scatter plot show relationship between percentage change in SW score between 3rd and 6th month and mean DARS dose Pearson correlation score for this was 0.56 which shows strong positive correlation between the two parameters. Comparison of mean DARS dose with percentage change in global MDADI score between 3 month and 6 months Thus we can conclude that with increase in mean DARS dose percentage negative change in swallowing score also increases implying improvement in swallowing ability



PLOT 44-PERCENTAGE CHANGE IN SWALLOWING SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE

Mann Whitney u test significant at $p<0.01$

PERCENTAGE CHANGE IN DRY MOUTH SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE –

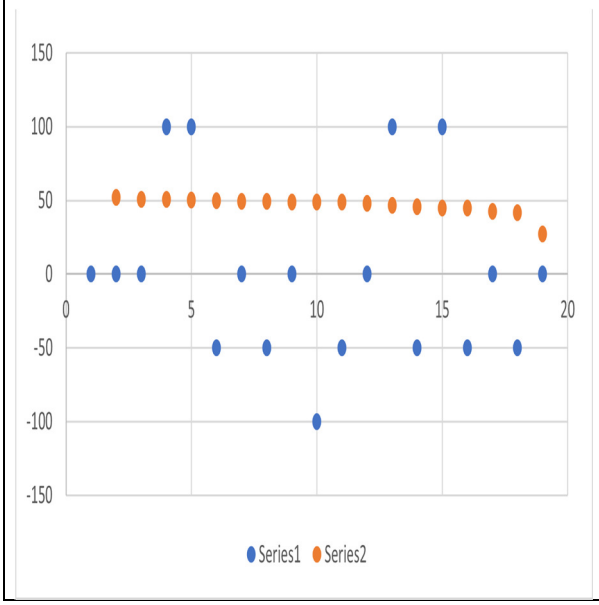


Given scatter plot show relationship between percentage change in DR score between 3rd and 6th month and mean DARS dose.

Pearson correlation score for this was 0.22 which shows mild positive correlation between the two parameters. Thus we can conclude that with increase in mean DARS dose percentage negative change in dry mouth score also increases implying improvement in dryness of mouth at 6 months.

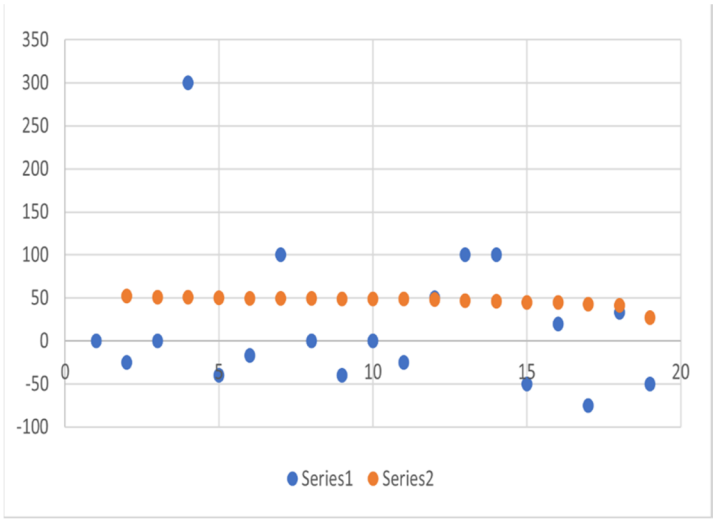
PLOT 45-PERCENTAGE CHANGE IN DRY MOUTH SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE

PERCENTAGE CHANGE IN MOUTH OPENING SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE –

	Given scatter plot show relationship between percentage change in OM score between 3rd and 6th month and mean DARS dose Pearson correlation score for this was 0.06 which shows no correlation between the two parameters. Thus, we can conclude that with increase in mean DARS dose there is no change in percentage change in mouth opening score implying no significant relationship between mean DARS dose and mouth opening

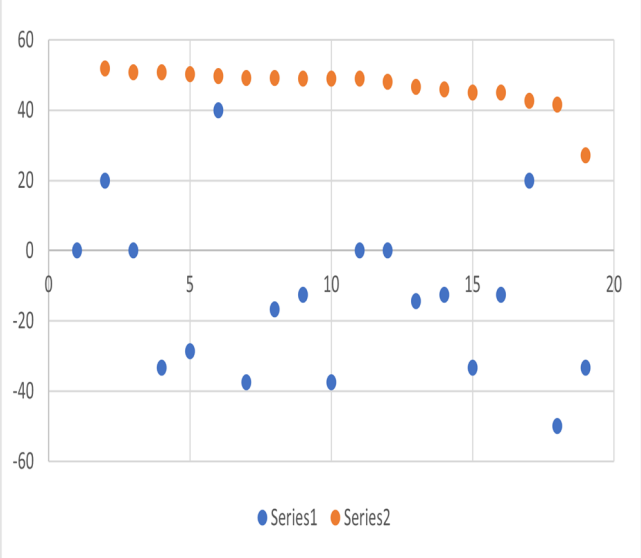
PLOT 46-PERCENTAGE CHANGE IN MOUTH OPENING SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE

PERCENTAGE CHANGE IN PAIN SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE -

	Given scatter plot show relationship between percentage change in PA score between 3rd and 6th month and mean DARS dose Pearson correlation score for this was 0.25 which shows mild positive correlation between the two parameters. Thus, we can conclude that with increase in mean DARS dose percentage negative change in pain score also increases implying decrease in pain at 6 months

PLOT 47-PERCENTAGE CHANGE IN PAIN SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE

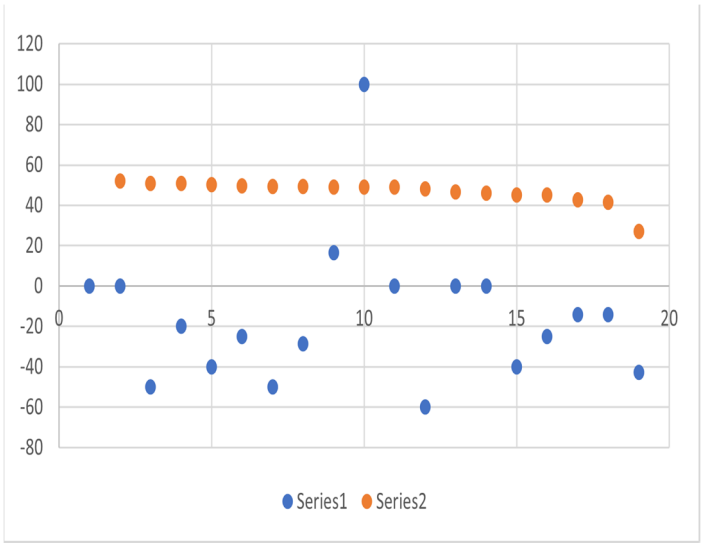
PERCENTAGE CHANGE IN SOCIAL EATING SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE -



Given scatter plot show relationship between percentage change in SO score between 3rd and 6th month and mean DARS dose Pearson correlation score for this was 0.28 which shows mild positive correlation between the two parameters. thus, we can conclude that with increase in mean DARS dose percentage negative change in social eating score also increases implying that patients feel more comfortable in eating in front of others at 6 months post Rt as compared to 3 months

PLOT 48-PERCENTAGE CHANGE IN SOCIAL EATING SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE

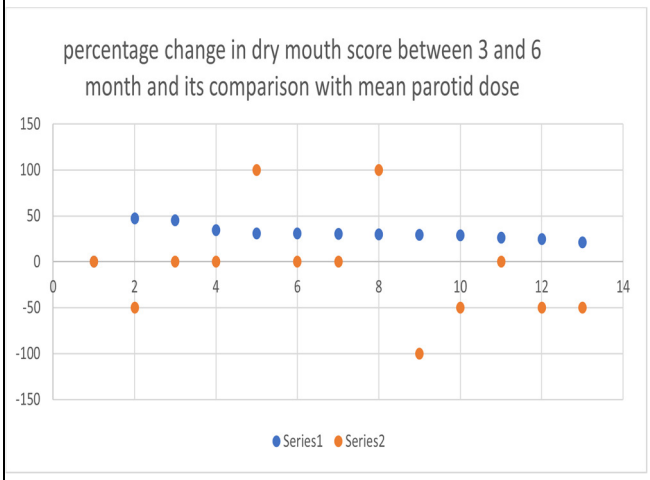
PERCENTAGE CHANGE IN TEETH SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE -

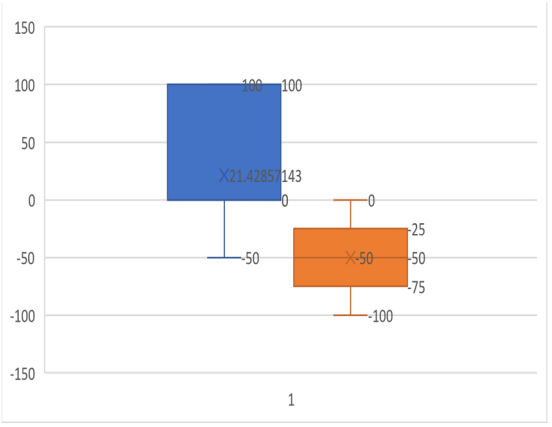


Given scatter plot show relationship between percentage change in TE score between 3rd and 6th month and mean DARS dose pearson correlation score for this was 0.16 which shows mild positive correlation between the two parameters. Thus, we can conclude that with increase in mean DARS dose percentage negative change in speech score also increases implying improvement in ability to communicate at 6 months as compared to 3rd month.

PLOT 49-PERCENTAGE CHANGE IN TEETH SCORE BETWEEN 3RD AND 6TH MONTH AND ITS COMPARISON WITH MEAN DARS DOSE

PERCENTAGE CHANGE IN DRY MOUTH SCORE BETWEEN 3 AND 6 MONTH AND ITS COMPARISON WITH MEAN PAROTID DOSE





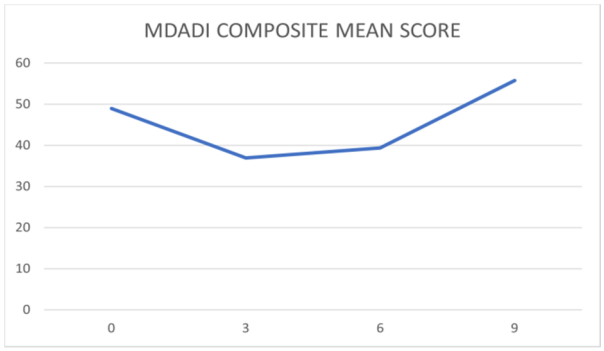
Mann Whitney u test significant at $p<0.05$

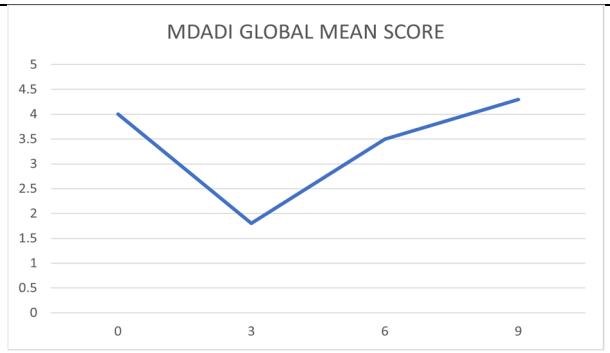
PLOT 50-Percentage change in dry mouth score between 3 and 6 month and its comparison with mean parotid dose

MDADI

MONTH	COMPOSITE MEAN MDADI DOSE	GLOBAL MEAN MDADI DOSE
0	**48.96**	**4**
3	**36.94**	**1.8**
6	**39.38**	**3.5**
9	**55.78**	**4.3**

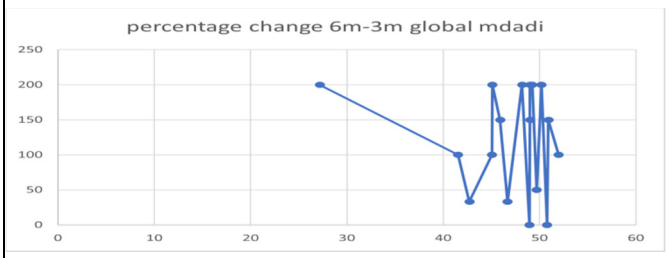
Table 8- COMPARISON OF MEAN COMPOSITE AND GLOBAL MDADI SCORE WITH TIME





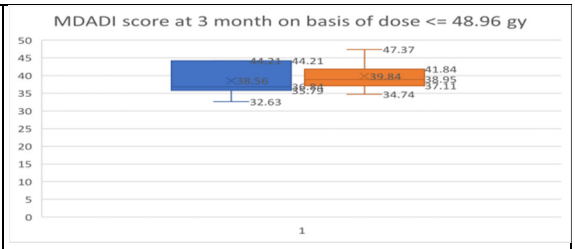
PLOT 51- COMPARISON OF MEAN COMPOSITE AND GLOBAL MDADI SCORE WITH TIME

COMPARISON OF MEAN DARS DOSE WITH PERCENTAGE CHANGE IN GLOBAL MDADI SCORE BETWEEN 3 MONTH AND 6 MONTH –



Pearson correlation score- -0.15

Mann Whitney u test Not significant at p>0.05

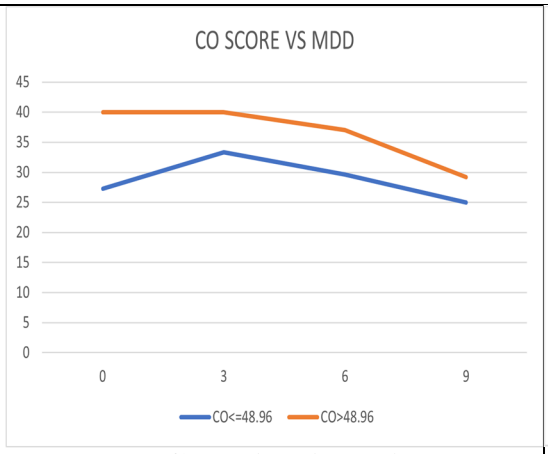


the median was almost similar with no statistical significance between the groups. Mann Whitney u test not significant at p<0.05

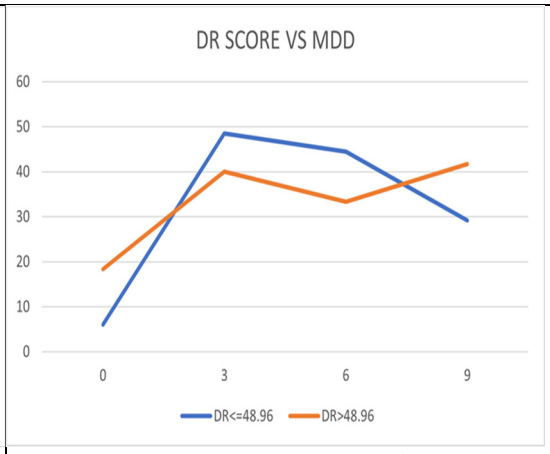
PLOT 52-MDADI SCORE AT 3 MONTH ON BASIS OF DOSE

PLOT 53-COMPARISON OF MEAN DARS DOSE WITH PERCENTAGE CHANGE IN GLOBAL MDADI SCORE BETWEEN 3 MONTH AND 6 MONTHS

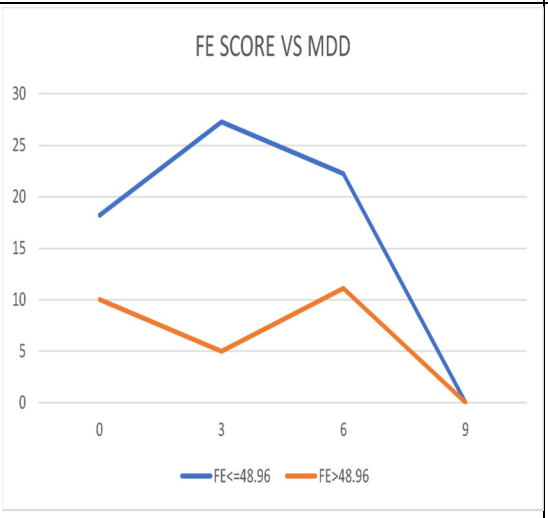
COMPARISON OF ABSOLUTE SCORES OF EORTC H & N 35 DOMAINS AT EACH FOLLOW UP WITH MEAN DARS DOSE((µDD)



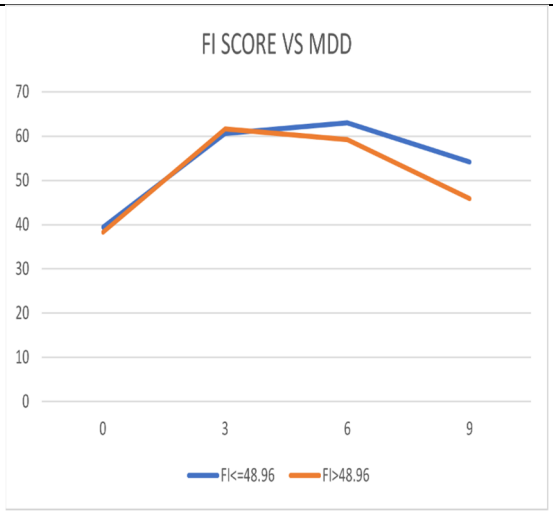
Coughing (Mean)



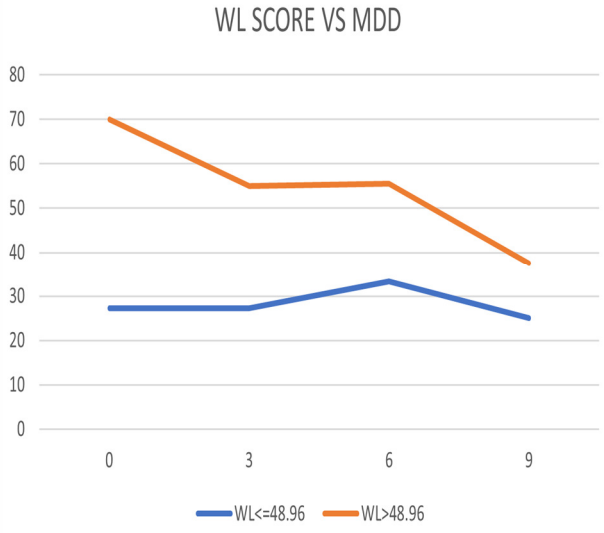
Dry Mouth (Mean)



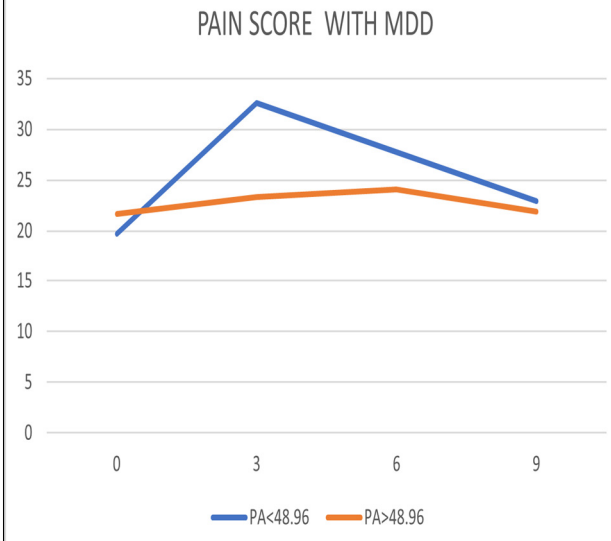
Feeding Tube (Mean)



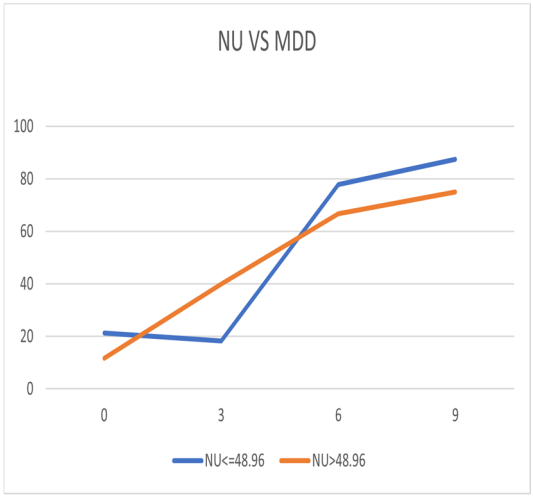
Felt Ill (Mean)



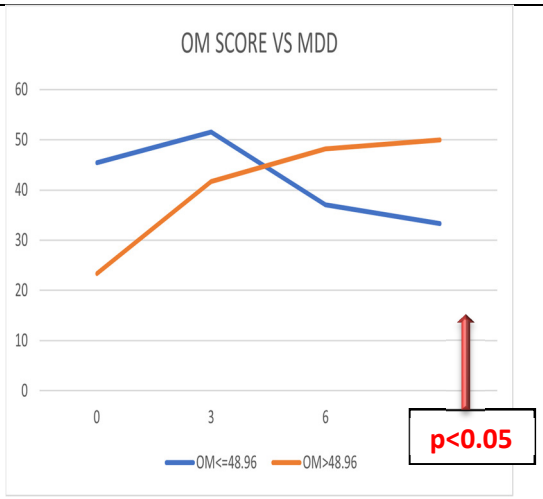
Weight Loss (Mean)



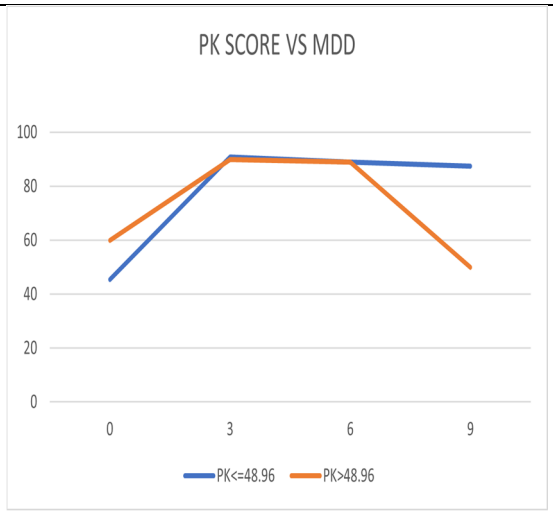
Pain (Mean)



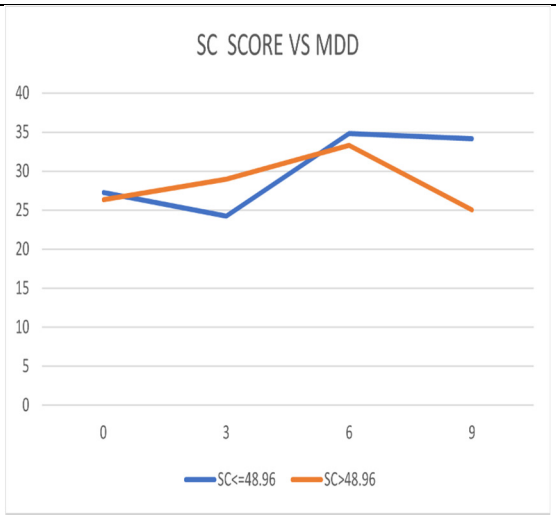
Nutrition Supplement (Mean)



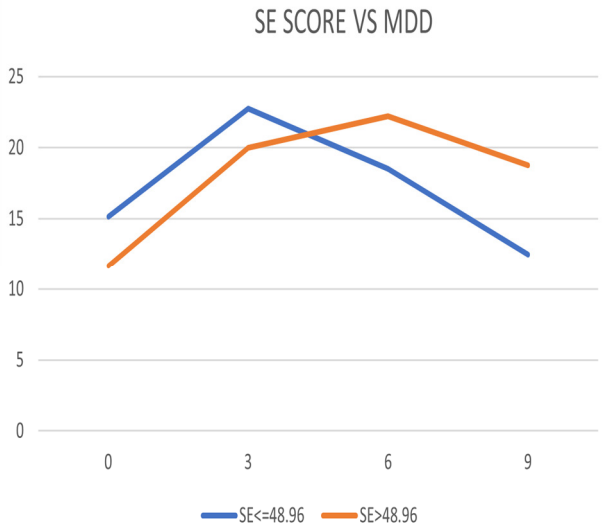
Mouth Opening (Mean): Significant diff at 9 months



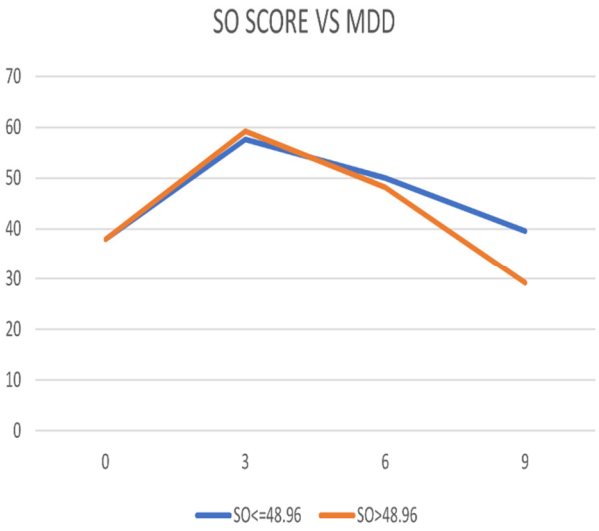
Pain Killer Use (Mean)



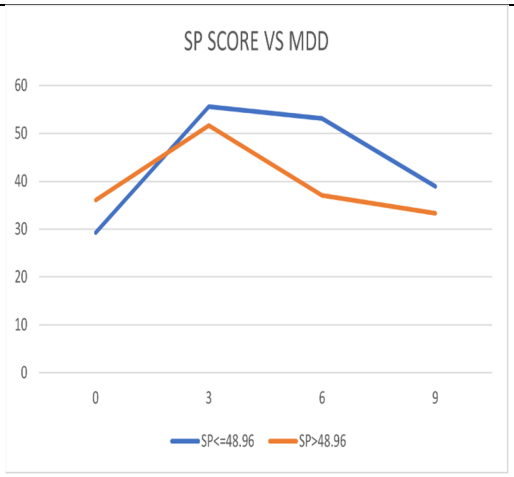
Social Contact (Mean)



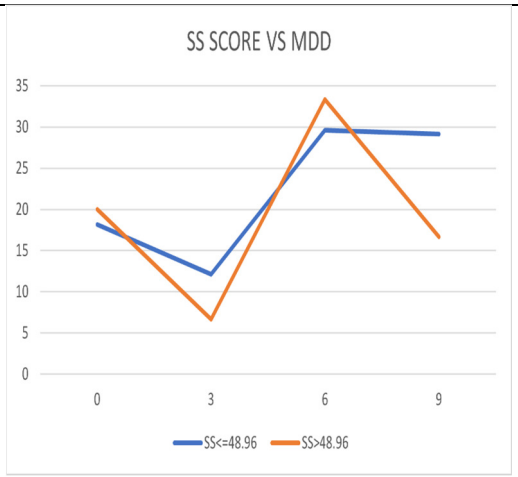
Senses (Mean)



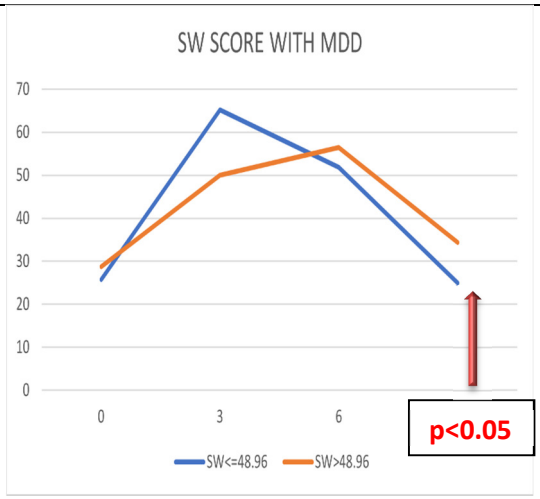
Social Eating (Mean)



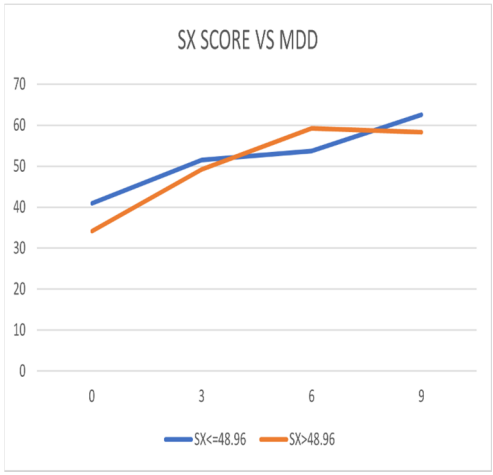
Speech (Mean)



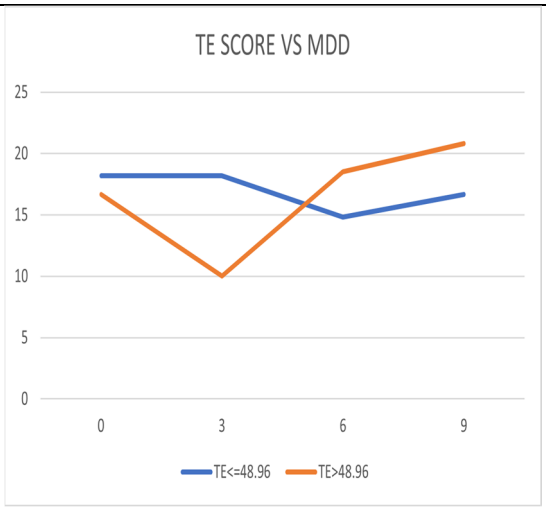
Sticky Saliva (Mean)



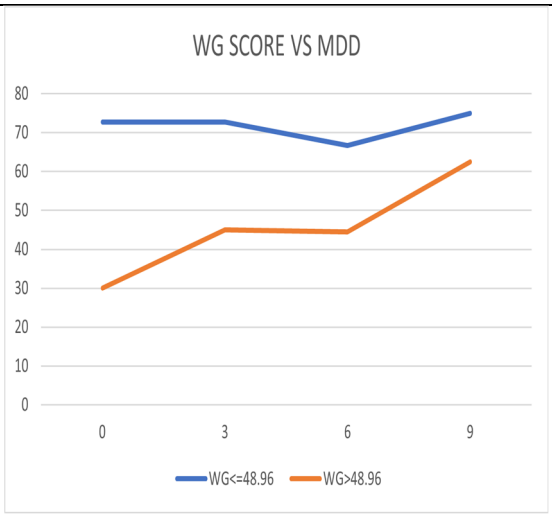
Swallowing (Mean) : Difference significant at 9 m



Sexuality (Mean)



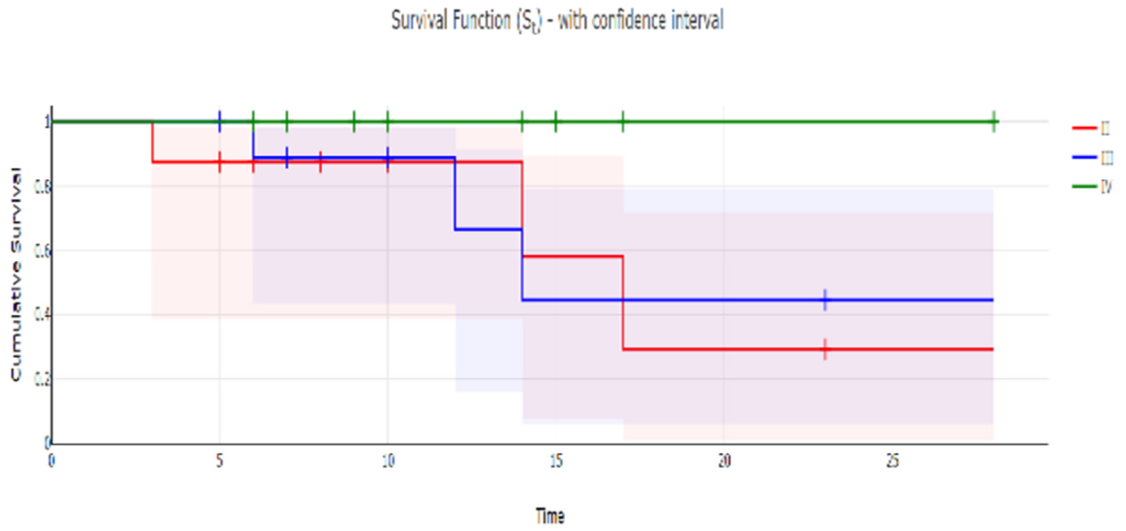
Teeth (Mean)



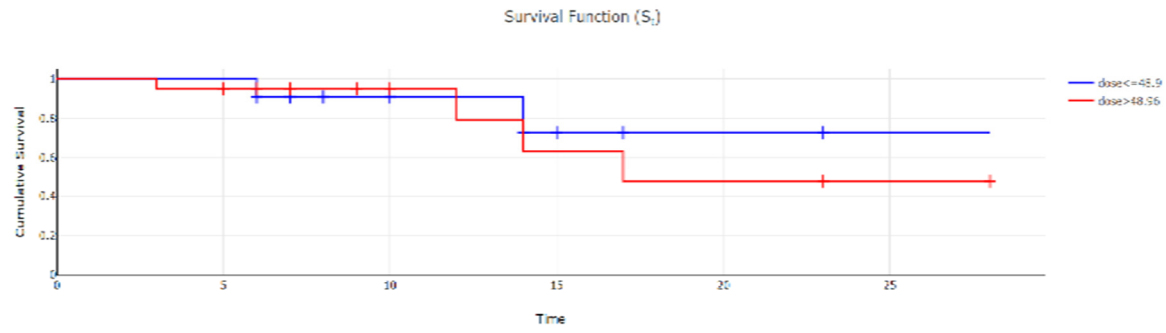
Weight Gain (Mean)

PLOT 54- COMPARISON OF ABSOLUTE SCORES OF EORTC H & N 35 DOMAINS AT EACH FOLLOW UP WITH MEAN DARS DOSE (µDD)

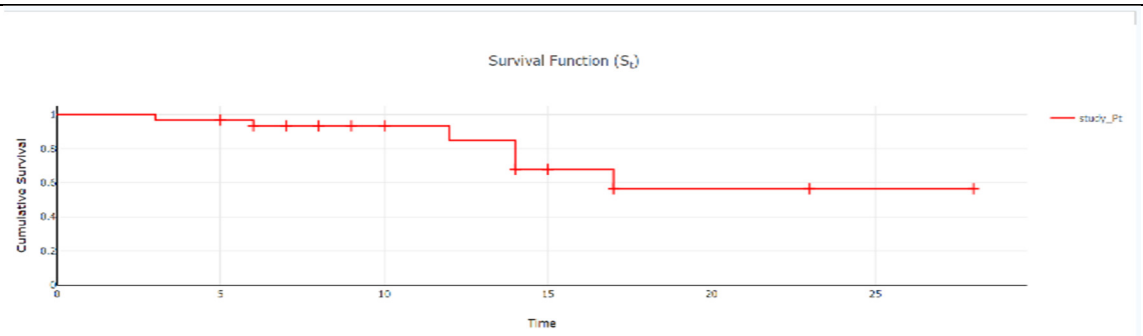
SURVIVAL ANALYSIS



Kaplan Meier Survival Analysis with groups according to the site of primary (p=0.135)



Kaplan Meier Survival Analysis with group according to DOSE(p=0.656)

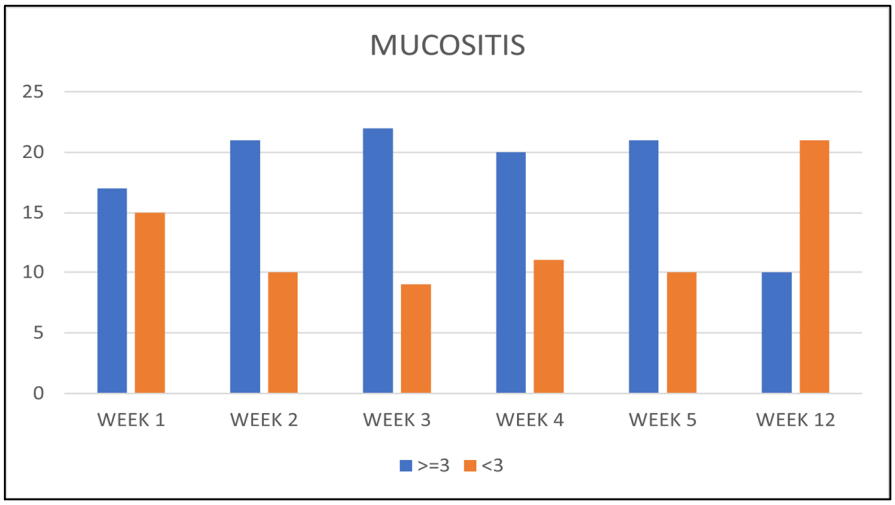


Overall Kaplan Meier Survival Analysis

PLOT 55- SURVIVAL ANALYSIS

RESULTS OF TOXICITY (CTCAE v 5.0)

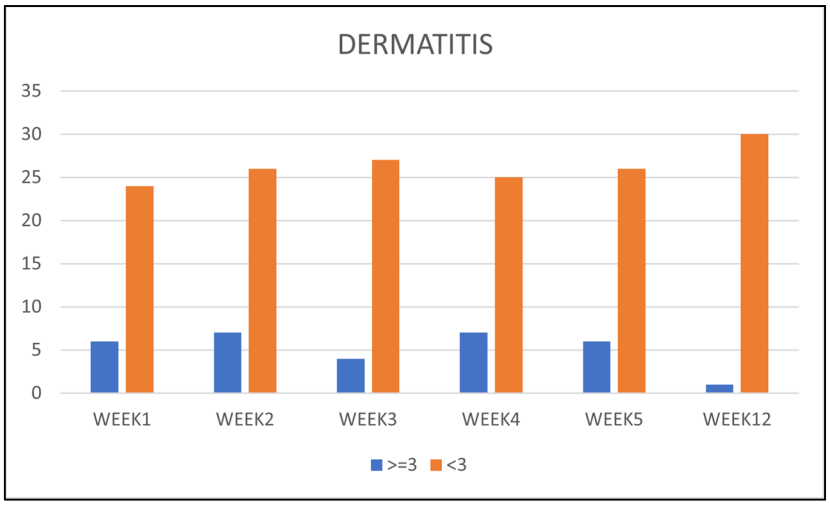
MUCOSITIS



PLOT 556- MUCOSITIS

Maximum > 3/4 grade Mucositis was seen at third week of chemoradiotherapy (70%)

DERMATITIS



PLOT 567- DERMATITIS

Maximum > 3/4 grade Dermatitis was seen at second week of chemoradiotherapy (20%)

DISCUSSION

DISCUSSION

Head and Neck Squamous Cell Cancer (H & NSCC) is the leading cause of cancer related morbidity and mortality in India(35). While surgery or radiation therapy alone are the only main pillars of treatment for very early disease, majority of patients present in locally advanced stage and need multimodal treatment(36). Radiation therapy plays a crucial role in adjuvant treatment for the patients who have been operated and attains primary role in sites or stage which are inoperable. Oral cavity is the most frequent site amenable by surgery while most other sites like oropharynx, hypopharynx, larynx and paranasal sinuses are treated with concomitant radiation therapy and cisplatin-based chemotherapy. Concomitant Chemoradiation offers organ preservation approach in larynx where salvage surgery can be done for those who progress or recur despite chemoradiation therapy. Radical radiation therapy given in doses of 66-70 Gy over 6 to 7 weeks period in H & NSCC is the most common standard treatment of H & NSCC treated with curative intent. It has its own toll in form of early toxicities like mucositis and dermatitis within 90 days of treatment, and many more adverse effects lasting for the life of patient like dryness of mouth, difficulty in swallowing, teeth problems and fibrosis. The present study focused on evaluating adverse effects on patients swallowing functions when treated with modern Intensity Modulated Radiation Therapy (IMRT) in H & NSCC. With IMRT, it is possible to identify and limit doses to structures which have been shown the role in dysphagia associated with radiation therapy. The structures of Superior, Middle and Inferior Constrictors, Base of Tongue, Superior Glottis, Glottic Larynx, Cricopharyngial Muscles, Cervical Oesophagus and Oesophageal Inlet Muscles have been found to play maximum roles in dysphagia produced by radiation therapy and are collectively called as Dysphagia Aspiration Related Structures (DARS)(16). Most of the time it is difficult to spare these structures in patients with large primaries located in the vicinity such as in oropharynx and that too in a busy Radiation Oncology Department, when the treatment of primary becomes the priority. The study attempted to cautiously minimize the dose to DARS < 50Gy in patients of H & NSCC treated with IMRT and concomitant cisplatin chemotherapy.

Patient Characteristics and the Treatment

In demographics the majority of the patients were male (78%), aged 51-60 years (39%) and tobacco users (74%). The results are redundant to all studies from India as it is clearly linked

to tobacco being the main causative agent for H & NSCC and more frequently used by males in the region(35,37).

Majority of these patients in the study had primary in Oropharynx (36%) followed by Hypopharynx (26%). Chemoradiation is the main modality for the H & NSCC of Oro-Hypopharynx and the study included only patients treated with radical doses of radiation therapy. Stage wise most patients were AJCC stage IV (39%) and had received Platinum based Neoadjuvant Chemotherapy (NACT) (87%). NACT was included in the treatment decisions for most patients of hypopharynx for down staging of disease and many with oropharyngeal as a bridge treatment before they could get slots for Chemo-IMRT due to logistic reasons(38,39). Almost all 100% patients could complete their treatment with IMRT 66-70 Gy in 33-35 fractions along with concomitant weekly cisplatin-based chemotherapy. In all patients 95% of PTV was covered by 95% or more of prescribed dose. DARS structures were attempted with constraint of D50 < 50Gy during planning with IMRT, but without compromising dose coverage of the PTV. In the present study the mean DARS dose achieved for all 31 patients was 51.4 Gy. Most patients could receive 5 cycles of concomitant cisplatin (40mg/m^2) based chemotherapy.

The Quality-of-Life Tools (Functional Tool – MDADI and Symptom Scale – EORTC H & N35)

Two validated tools to assess swallowing functions were used for the study. MD Anderson Dysphagia Inventory (MDADI) and European Organization for Research and Treatment of Cancer (EORTC) Head and Neck 35 (H & N35) questionnaire. While there are 20 questions in MDADI which yield a global score and a composite score, there are 35 questions in EORTC H & N35 which get transformed to 18 scales of QOL(15,19). While more the MDADI score indicates betterment, it's reverse for 17 scales of EORTC H & N35 where lesser the score indicates better QOL. The 18th scale of EORTC H & N35 is weight gain (WG) which is directly proportional to the improvement of QOL.

The QOL Measurements and Time Trends

At the time of accrual in the study most of the patients had highest EORTC H & N35 scores (worse QOL) of pain killer usage (mean 54.8), weight loss (mean 54.83), felt ill (mean 38.7), social eating (mean 37.9) and sexuality (mean 36.5). The least score was in feeding tube (mean 13). For preliminary visual examination to identify the main period out of months 3, 6

or 9, at which a particular QOL scale was highest (indicating worst QOL, except for weight gain), radar plots were used for each of the 18 scales of EORTC H & N35(40). Almost all QOL scales were having highest value at the month 3 from the treatment. This was expected, as acute adverse effects of radiation continue impact on QOL for first 3 months post radiation and then gradually resolve with time. As was also observed in the IMRT vs. 3DCRT trial in H & NSCC conducted in Tata Memorial Hospital, Mumbai, adverse effects post 3 months are mostly late effects which start and exhibit themselves later, as compared to acute toxicities in the initial 90 days(14). The EORTC H & N35 QOL scores peaked at 3 months post IMRT in PARSPORT trial of parotid sparing(41). The desired benefits of IMRT to spare parotids, in the study were visible as better resolution of these scores gradually post 3rd month onwards. In yet another large study from Taiwan with 675 nasopharyngeal cancers treated with IMRT, maximum post treatment EORT H & N35 scores were reported at 3 months from the treatment(42). The changes in each of the QOL scores were explored at timelines of 3rd, 6th and again at 9th months of the treatment.

The MDADI global as well as composite scores also had nadir at month 3 (global [gl] =1.8 out of 5 and composite [cp] = 36.94 out of 100) and then gradually improved on 6th (gl=3.5 and cp=39.38) and 9th months (gl=4.3 and cp=55.78). The differences of scores between baseline, month 3rd, 6th and 9th were significant.

The Mean DARS Dose (µDD) and Changes in the QOL

The mean linear transformed score for each of the 18 scales of EORTC H & N35 showed worst QOL in the 3rd month from the treatment. Thereafter started resolving. For analysing the association of QOL parameters with the dose to DARS, mean of dose to all DARS structures was calculated for each patient and termed as Mean DARS Dose (µDD). From the scatter plots of µDD and changes in QOL, it was found that most changes showed difference with cut off µDD of 48.96 Gy. Thus, additional analysis were done for group of patients with µDD </= 48.96 and µDD > 48.96.

Although statistically insignificant, the EORTC H & N35 scores for patients with µDD </= 48.96 were lesser at 3rd month for Coughing, Weight Loss, Nutritional Supplement, Social Contact. At month 6th scores reduced (QOL improved) additionally for Mouth Opening, Senses, Swallowing, Sexuality and Teeth. Finally at the maximum follow up assessment time of 9 months, in our study, all 18 QOL parameters improved in group with µDD </= 48.96 for Coughing, Dry Mouth, Feeding Tube, Weight Loss, Mouth Opening, Senses, Swallowing and

Teeth Score. Interestingly, Swallowing (SW) and Mouth (OM) Opening scores were *significantly lesser* for the μDD </= 48.96 Gy at 9th month ($p<0.05$).

The score for a QOL for a patient is not only dependent on the treatment factors but may as well on host differences and perception of a patient for that particular domain of the QOL. As a common perception in the society and also as a result of counselling before the treatment, most patients expect a deterioration in the QOL during the treatment and lasting for some time after the anti-cancer therapy. Their main concern is survival and resolution of adverse effects, so that they can dispose duties of their life with reasonable QOL. To analyse that, percentage change in the QOL score was examined. As the peak of worst QOL was experienced by patients in their follow up at 3rd month, its resolution at next follows up at 6th months was analysed by calculating percentage change of score at 6th month as compared from 3rd month. The DARS dose value of μDD is supposed to affect the Swallowing QOL maximum and indeed, the study found a novel finding of almost linear relationship between μDD and Percentage Change in EORTC H & N35 Swallowing Score between 6th and 3rd month (Pearson correlation coefficient = 0.55, strong correlation). As QOL is inversely related with scores of EORTC H & N35 scores, this implied more the μDD, worse the QOL of swallowing. The μDD cut off at which the percentage changes transformed from positive to negative was at μDD=48.96 Gy. The difference in percentage change of swallowing analysis was significant below and above the cut off dose of μDD=48.96 Gy, with $p < 0.01$. Such a linear model of relationship between mean DARS dose and swallowing is a novel finding of the study and can be further confirmed and validated for modelling prospectively and also from retrospective data from the previous studies.

Eisburch et. al in their article describing DARS, proposed dose constraints for DARS equal to 50 Gy or lower, as this was the lowest dose at which they could observe stricture in the pharynx(16). On the basis of these studies a randomized controlled trial evaluating standard IMRT without DARS constraints and Do-IMRT (Dysphagia optimised IMRT) with constraint of DARS < 50 Gy prescribed during IMRT planning was conducted. As per preliminary results of 'DARS' (CRUK/14/014) trial published by Nutting et. al. in 2020, they could achieve mean dose to Superior and Middle Pharyngeal Constrictor Muscles around 49.7 Gy in the Do-IMRT arm. This mean dose was as high as 57 Gy in standard IMRT arm in which there was significantly inferior outcomes in swallowing(17). In the present study the mean DARS dose for all 31 patients combined was 51.4 Gy. There was significant difference

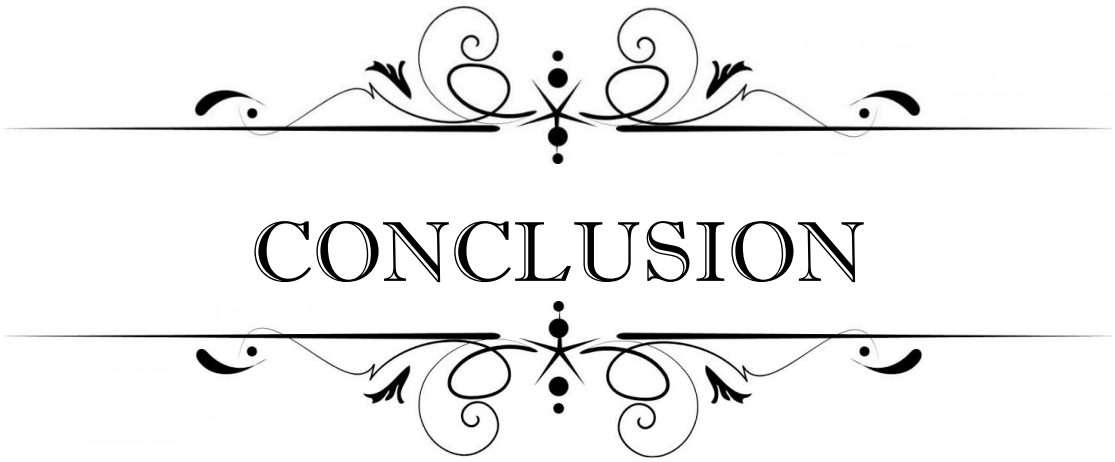
at cut off of μDD=48.96Gy and a novel linear relationship between μDD and percentage change in the swallowing scale of patients.

Neither the Composite nor the Global MDADI functional score could detect any significant difference between μDD of less than or equal, and more than 48.96Gy.
The median mean parotid dose of the study patients was 30.5Gy (14.8Gy to 55Gy). The high dose of 55Gy was in an oral cancer patient. The literature recommends keeping the mean dose to the parotid < 26Gy to prevent xerostomia. As less than 5 patients were available at the month 6, with the mean parotid dose < 26Gy, the statistical analysis could be done with Mann Whitney U test only when mean parotid dose groups were separated at 29.51 Gy. The EORTC H & N35 Dry Mouth scale was significantly different between patients with mean parotid dose of less than or equal, and more than 29.51Gy. There was difference of 71 points in Dry Mouth scale between the patients grouped by dose less than or equal to *verses* more than, 29.51 Gy ($p < 0.05$).

The Survival Analysis

Till the time of last date of follow up and data analysis, only 6/31 (19%) patients have died. With only 19% of events, the study has not reached sufficient follow up and median overall survival not yet reached. Similarly, disease free survival has not yet reached. Survival was also analysed for different groups using Kaplan Meir Plots and χ^2 test. Overall survival did not significantly differ when grouped according to the primary site or the stage of H & NSCC ($p>0.10$). In a study between 3DCRT and IMRT in H & NSCC, 78% patients belonged to stage III and IV H & NSCC in the IMRT arm with 3 year survival of70.6%(14). The survival may thus gradually reveal with time. After the sufficient follow up, survival analysis can be repeated for the study patients.

As there was significant difference in percentage improvement in the swallowing QOL at 6 months as compared to 3rd month between patients with Mean DARS Dose (μDD) of </= 48.98 Gy or > 48.96 Gy and also in the mean swallowing scores at 9 months, overall survival between these groups was also analysed. The overall survival between these dose groups was not found to have any significant difference. Thus, with reduction of μDD below 48.96 Gy, there was benefit in late QOL of swallowing, without any compromise in the survival of the patients.



CONCLUSION

CONCLUSION

Head and Neck Squamous Cell Cancers (H & NSCC) are the leading cause of cancer related mortality and suffering in world, more so in India. With radiation therapy alone or chemoradiation as the main curative modality for most of the patients, and adjuvant therapy for remaining others, the continuous evolution of radiation therapy techniques and doses plays an important role in this large population of H & NSCC patients. Optimum dose to targets which can increase tumour control and minimum dose to organs at risk to limit the adverse effects of radiation therapy is the Holy Grail, towards which the Radiation Oncology gradually strives to reach. With increased accessibility to Linear Accelerators and Computerised Treatment Planning, the first major stride in optimization of radiation was Intensity Modulated Radiation Therapy (IMRT) and in the treatment of HNSCC, foremost goal was to spare the parotid glands. IMRT can sculpt complex dose distribution and confirm to 3-dimensional curved tissues and organs. The parotid and other salivary glands, uninvolved by the tumour, take the brunt of curative dose of conventional radiation, while radiation traverses towards the deeper targets. This results in dryness of mouth which is often the main cause of cured patients pleading for some medicines or substitutes of saliva, where none has been found to be effective. A major concern of IMRT was, that in an overenthusiasm for restricting doses to organs, like parotids in head and neck, geographical miss of target volumes or any compromise in the overall survival should not happen. The cautious community of radiation oncologists conducted large number of randomized studies and created evidence that without catastrophe of compromising tumour control, IMRT could restrict doses to parotids, reducing xerostomia. However, the results were lesser and conflicting when patient reported quality of life measures were measured. After fruitful attempts to identify reasonable constraints to reduce xerostomia, recently additional structure as superior, middle and inferior pharyngeal constrictors, cricopharyngeal muscle, base of tongue, supra-glottic larynx, glottis, cervical esophagus and esophageal inlet muscles, were identified as Dysphagia and Aspiration Related Structure (DARS). Recently reported phase III randomized clinical trial ‘DARS’ again reassured that without compromising the survival, dose constraints of these structures could translate into better quality of life in almost all the multiple domains ranging from swallowing, social eating, sticky saliva, mouth opening, weight gain etc. Interestingly, Nutting et. al., the investigators with credit for completing the first of its kind of randomized study and coining the term – Dysphagia Optimized Intensity Modulated Radiation Therapy (Do-IMRT) , have themselves wondered if the radiation

oncology community is ready to *'swallow'* the practise of sparing the DARS. Contouring of DARS structures take additional time and effort besides inducing anxiety during planning, as the tumour targets are often in their close vicinity.

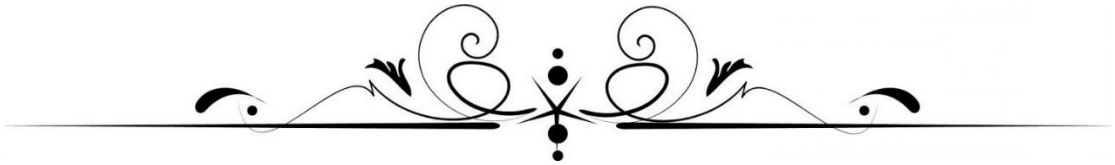
With the evidence from the randomized study of Nettings et.al, establishing safety of Do-IMRT, the present study attempted to constraint the dose to DARS in HNSCC presenting in a busy environment in a tertiary care centre in India, a country caring for maximum number of H NSCC patients. The prospective study objectively measured the treatment parameters, adverse effects and Quality of Life (QOL) using two rationale and validated tools – MDADI and EORTC H & N35. MD Anderson Dysphagia Inventory (MDADI), a functional measurement where more the score, more is the functionality of the patient while EORTC H & N35 extensively captures 18 domains of QOL through its 18 symptom scales. More the score of a scale, more is the symptom and worse the concerned QOL.

Do-IMRT was indeed feasible in a busy Radiation Oncology Department, even without dedicated resources and stringency of a randomized clinical trial. Almost all the QOL were worst at 3^{rd} month post treatment and improved gradually with time. The study introduced one novel term, method and finding each. A simplified summary stats was calculated from each patient's IMRT plan – Mean DARS Dose (μDD) which was arithmetic mean of D50 (Dose received by 50% volume) of each of the 9 DARS structures segmented. In order to capture the change in swallowing QOL from its worst nadir at 3^{rd} months post treatment, percentage change in EORTC H & N35 swallowing score at 6^{th} month from the 3^{rd} month was calculated. Most previous studies have either examined the raw scores or their change from the baseline with time. Interestingly, this yielded a novel linear relationship between the μDD and Percentage Change in Swallowing at the 6^{th} month from 3^{rd} month. The correlation was quite strong with Pearson Correlation r = 0.56. Also, the QOL equation switched from positive percentage changes in swallowing scores (deterioration in QOL) to negative percentage changes in swallowing (improvement in QOL) at the μDD=48.96Gy. The mean EORTC H & N35 scores for patients grouped in two groups using μDD cut off of 48.96 Gy showed that patients with lower μDD had better resolution of QOL in almost all the parameters with differences reaching statistical significance for swallowing and mouth opening at 9^{th} month. The strong linear correlation discovered, thus created an internal control within the study reinforcing that the reduced doses to DARS indeed translated to better QOL of swallowing. Such a linear model of DARS dose and QOL scores can be explored further with larger number of patients.

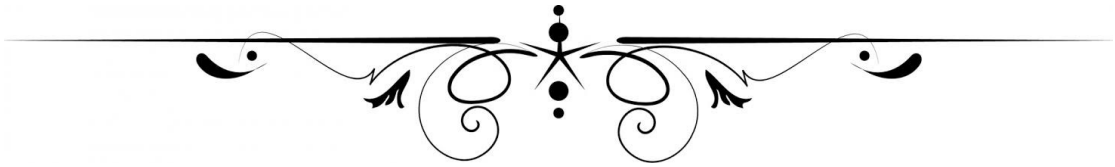
At the time of analysis, most of the study patients are disease free and alive and thus neither median survival nor median disease-free survival has been reached. With longer follow up time, widening of QOL differences, more significant results and survival results will emerge.

The current study also draws attention to three points pertaining to Head and Neck Cancers:

1. Despite maximal efforts of Parotid Sparing and Do-IMRT, surviving patients have significant amount of compromised quality of life issues, as can be seen in even randomized clinical trials as PARSPORT and DARS trial (CRUK/14/014). Thus, there is need to further improve the treatment of HNSCC with better tumour control and lesser toxicity.
2. More honest efforts for the primary prevention of H NSCC by tobacco control.
3. Increased secondary prevention by increasing awareness and screening of at-risk population by support of Non-Communicable Disease Control (NCDC) program.



LIMITATIONS OF THE STUDY



LIMITATIONS OF STUDY

The study was a single arm prospective study. The follow up period was less and very few events of either relapse or death have happened till the date of analysis, thereby neither the median progression free survival nor the median overall survival was reached. The sample size of 31 was further grouped for analysis of relationship between the dose to DARS and QOL scores. The groups were thus not having normal distribution and also prohibited the use of parametric tests. Such small number of patients in each group were possibly not even powered to detect the difference sought. A linear relationship was found between mean DARS dose and percentage change in swallowing scores, however same needs to be corroborated with a larger sample size. Most of the changes in QOL were attributed to Do-IMRT without the use of matched controls. A randomized clinical trial with sufficient sample size and power to detect the differences and corroborate the linear model between the DARS dose and QOL scores can mitigate the limitations of the present study.

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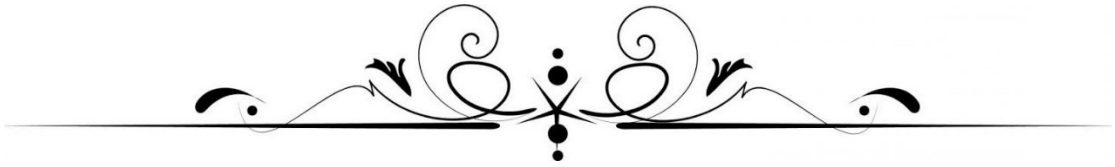

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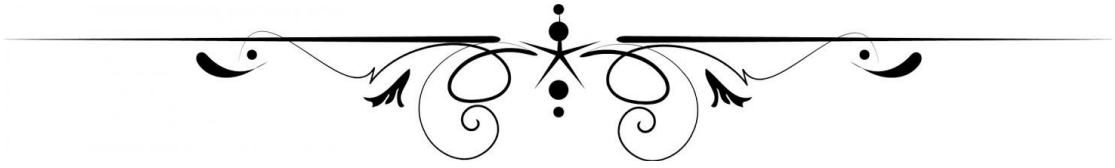

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ANNEXURES

ANNEXURE I

Ethics Clearance

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/2030 Date: 01/01/2020

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2019-20/990**

Project title: **"Quality of life in patients receiving dysphagia optimized intensity modulated radiotherapy (Do-IMRT) in head and neck cancers"**

Nature of Project: **Research Project**

Submitted as: **M.D. Dissertation**

Student Name: **Dr.Mukul Choubisa**

Guide: **Dr.Puneet Pareek**

Co-Guide: **Dr.Jeewan Ram, Dr. Amit Goyal & Dr. Darwin**

This is to inform that members of Institutional Ethics Committee (Annexure attached) met on **23-12-2019** and after through consideration accorded its approval on above project. Further, should any other methodology be used, would require separate authorization.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

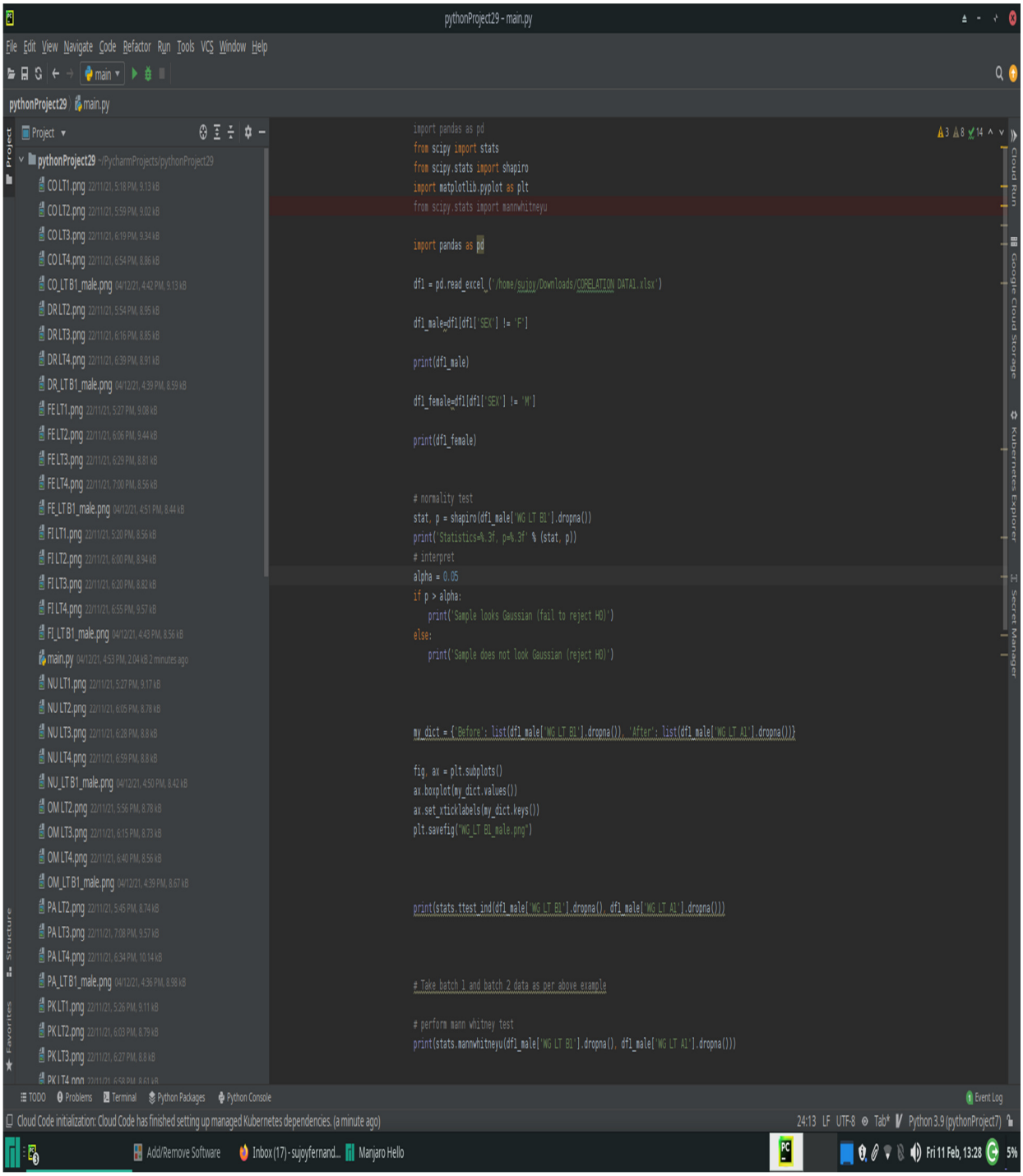
On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Enclose:
1. Annexure 1

ANNEXURE II

PYTHON CODE



ANNEXURE III

ALL INDIA INSTITUTE OF MEDICAL SCIENCES

Jodhpur, Rajasthan

Informed Consent Form

Title of Thesis/Dissertation : "**Quality of Life in Patients Receiving Dysphagia Optimized Intensity Modulated Radiotherapy (Do-IMRT) in Head and Neck Cancers**"

Name of PG Student : Dr. MUKUL CHOUBISA Tel. No.9661517771

Patient/Volunteer Identification No. : _____

I, _____ S/o or D/o _____

R/o_____

___

give my full, free, voluntary consent to be a part of the study titled "**Quality of Life in Patients Receiving Dysphagia Optimized Intensity Modulated Radiotherapy (Do-IMRT) in Head and Neck Cancers**" the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from **AIIMS Jodhpur** or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of PG Student

1. Witness 1
   _____
   Signature
   Name: _____
   Address: _____
   _____

2.Witness
_____
Signature
Name: _____
Address: _____
_____

ANNEXURE IV

अखिल भारतीय आयुर्विज्ञान संस्थान

जोधपुर, राजस्थान

सूचित सहमति प्रपत्र

थीसिस / शोध प्रबंध का शीर्षक: डिस्पैगिया अनुकूलित तीव्रता वाले रेडियोथेरेपी (Do-IMRT) **प्राप्त करने वाले रोगियों में जीवन की गुणवत्ता का मूल्यांकन करने के लिए एक एकल हाथ भावी अध्ययन सिर और गर्दन के कैंसर में**

पीजी छात्र का नाम: डॉ। मुकुल चौबीसा No.9661517771

रोगी / स्वयंसेवक पहचान संख्या: _____

मैं, _____ S / o **या** D / o _____

आर / **ओ** _____

अध्ययन का एक हिस्सा बनने के लिए मेरी पूर्ण, स्वतंत्र, स्वैच्छिक सहमति दें "सिर और गर्दन के कैंसर में डिस्फेगिया अनुकूलित तीव्रता वाले रेडियोथेरेपी (Do-IMRT) **प्राप्त करने वाले रोगियों में जीवन की गुणवत्ता का मूल्यांकन करने के लिए एक एकल हाथ का भावी अध्ययन, प्रक्रिया और प्रकृति" जिसमें से मुझे अपनी पूरी संतुष्टि के लिए अपनी भाषा में समझाया गया है। मैं पुष्टि करता हूं कि मुझे सवाल पूछने का अवसर मिला है। मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और बिना किसी कारण के किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार से अवगत हूं। मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्रित जानकारी को एम्स के जोधपुर के जिम्मेदार व्यक्ति द्वारा नियामक अधिकारियों से देखा जा सकता है। मैं इन व्यक्तियों को अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।**

दिनांक : _____

_____

स्थान: _____ **हस्ताक्षर / बाएं अंगूठे का निशान**

यह प्रमाणित करने के लिए कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त हुई है।

दिनांक : _____

_____

जगह: _____

पीजी छात्र के हस्ताक्षर

1. **साक्षी** 2. **गवाह**_____

हस्ताक्षर **हस्ताक्षर**

नाम **नाम**: _____

पता **पता** : _____

ANNEXURE V

Patient Information Sheet

Part-1

You are invited to take part in this study entitled "**Quality of life in patients receiving dysphagia optimized intensity modulated radiotherapy (Do-IMRT) in head and neck cancers.**".

It is informed that it is entirely voluntary and you may refuse to take part or discontinue at any time without losing your right to adequate clinical care.This research is aimed at studying the effect on quality of life in patients of head and neck cancer on administrating dysphagia optimized radiotherapy . If the outcome comes out to be better, a protocol for adding dysphagia optimization can be added to standard protocol No extra test or Investigations are needed as a part of the study. All the records will be kept confidential.

You have the right to ask for any further information that you require. In case of any doubt regarding the study you are welcome to contact the undersigned personally or telephonically.

Part-2

Investigator's statement

I have explained the purpose, procedures, benefits and harms of the study in detail to the patient/ patient's relative.

All information regarding the study has been disclosed.

Enough Time and Opportunity for asking questions regarding the study was given to the patient/ patient's relative.

Investigator signature:- Witness signature:-

ANNEXURE VI

रोगी सूचना पत्र

भाग ---- पहला

आपको इस अध्ययन में भाग लेने के लिए आमंत्रित किया गया है, जिसका शीर्षक है "सिर और गर्दन के कैंसर में डिस्फेगिया ऑप्टिमाइज़्ड इंटेंसिटी मॉड्यूलेटेड रेडियोथेरेपी (Do-IMRT) प्राप्त करने वाले मरीजों में जीवन की गुणवत्ता का मूल्यांकन करने के लिए एक एकल हाथ का भावी अध्ययन।

"।यह सूचित किया जाता है कि यह पूरी तरह से स्वैच्छिक है और आप पर्याप्त नैदानिक देखभाल के अपने अधिकार को खोए बिना किसी भी समय हिस्सा लेने या बंद करने से इनकार कर सकते हैं।

इस शोध का उद्देश्य डिस्फेगिया अनुकूलित रेडियोथेरेपी के प्रबंधन पर सिर और गर्दन के कैंसर के रोगियों में जीवन की गुणवत्ता पर प्रभाव का अध्ययन करना है। यदि परिणाम बेहतर होगा, तो डिस्पैगिया अनुकूलन को जोड़ने के लिए एक प्रोटोकॉल मानक प्रोटोकॉल में जोड़ा जा सकता है। अध्ययन के एक हिस्से के रूप में कोई अतिरिक्त परीक्षण या जांच की आवश्यकता नहीं है।

सभी रिकॉर्ड गोपनीय रखे जाएंगे।

आपके पास कोई और जानकारी मांगने का अधिकार है, जिसकी आपको आवश्यकता है।अध्ययन के संबंध में किसी भी संदेह के मामले में आप व्यक्तिगत या टेलीफोन पर अधोहस्ताक्षरी से संपर्क करने का स्वागत करते हैं।

भाग 2

अन्वेषक का कथन

मैंने रोगी / रोगी के रिश्तेदार को अध्ययन के उद्देश्य, प्रक्रिया, लाभ और हानि के बारे में विस्तार से बताया है।

अध्ययन के संबंध में सभी जानकारी का खुलासा किया गया है।

रोगी / रोगी के रिश्तेदार को अध्ययन के संबंध में प्रश्न पूछने का पर्याप्त समय और अवसर दिया गया।

अन्वेषक हस्ताक्षर: -

साक्षी हस्ताक्षर: -

फोन नंबर:-

ANNEXURE VII

EORTC HEAD &NECK 35

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

ANNEXURE VIII

EORTC HEAD &NECK 35

HINDI

EORTC QLQ - H&N35

मरीज कभी कभी निम्न रोग लक्षणों या परेशानियों की शिकायत करते हैं | कृपया इंकित करे कि पिछले एक सप्ताह के दौरान आपने किस हद तक इन रोग लक्षणों या परेशानियों का अनुभव किया है | आपको जो उत्तर सबसे अधिक सही लगे, उसके अंक पर कृपया अंकित करे ||

पिछले एक सप्ताह के दौरान	बिलकुल नही	थोडासा	थोडा अधिक	बहुत अधिक
३१.क्या आपके मुँह में दर्द उठा था?	१	२	३	४
३२.क्या आपके जवडों में दर्द उठा था?	१	२	३	४
३३.क्या आपके मुँह में कसौलापन हुआ था?	१	२	३	४
३४.क्या आपके गले में दर्द हुआ था?	१	२	३	४
३५.क्या आपको तरल पदार्थ निगलने में तकलीफ हुई थी?	१	२	३	४
३६.क्या आपको पिसा हुआ पदार्थ निगलने में तकलीफ हुई थी?	१	२	३	४
३७.ठोस खाना निगलने में क्या आपको तकलीफ हुई थी?	१	२	३	४
३८.निगलने के दौरान क्या आपका दम घुटता है?	१	२	३	४
३९.क्या आपके दॉतो को लेकर आपको कोई परेशानी हुई थी?	१	२	३	४
४0.कया आपका मुँह ज्यादा खोलने में तकलीफ हुई थी?	१	२	३	४
४१.क्या आपके मुँह में कभी सूखापन महसूस हुआ था?	१	२	३	४
४२.क्या आपका थूक चिपचिपा हुआ था?	१	२	३	४
४३.क्या आपकी सूंघने की क्षमता के बारे में आपको कोई समस्या हुई थी?	१	२	३	४
४४.क्या आपके स्वाद की क्षमता के बारे में आपको कोई समस्या हुई थी?	१	२	३	४
४५.क्या आपको खॉसी हुई थी?	१	२	३	४
४६.क्या आपको गले में खराश थी?	१	२	३	४
४७.क्या आपको लगताा था कि आप बीमार हैं?	१	२	३	४
४८.क्या आपका स्वरूप आपको परेशान करता था?	१	२	३	४

अगले पन्ने पर

पिछले एक सप्ताह के दौरान	बिलकुल नही	थोडासा	थोडा अधिक	बहुत अधिक
४९. क्या आप खाने में कठिनाई महसूस करते थे?	१	२	३	४
५०. क्या आपको अपनें परिवार के सामने खाना-खाने में कठिनाई हुई थी?	१	२	३	४
५१. क्या आपको दूसरे लोगों के सामने खाना खाने में कठिनाई हुई थी?	१	२	३	४
५२. अपने भोजन का आनंद उठाने में क्या आपको तकलीफ हुई थी?	१	२	३	४
५३. क्या आपको दूसरे लोगों के साथ बात करने में तकलीफ हुई थी?	१	२	३	४
५४. क्या आपको टेलीफोन पर बात करने में तकलीफ हुई थी?	१	२	३	४
५५. क्या आपको अपने परिवार के साथ सामाजिक संपर्क रखने में तकलीफ हुई थी?	१	२	३	४
५६. क्या आपको अपने दोस्तों के साथ सामाजिक संपर्क करने में तकलीफ हुई थी?	१	२	३	४
५७. क्या आपको आम जनता के सामने जाने में तकलीफ हुई थी ?	१	२	३	४
५८. क्या आपको परिवार या दोस्तों के साथ शरीरिक संपर्क करनें में तकलीफ हुई थी?	१	२	३	४
५९. क्या आपको यौन संबंध में रूचि कम लगती थी?	१	२	३	४
६०. क्या आपको यौन संबंधी आनंद में कमी लगती थी?	१	२	३	४

पिछले एक सप्ताह के दौरान	नही	हॉ
६१. क्या आपने दर्द निवारक दवाई ली थी?	१	२
६२. क्या आपने (जीवनसत्व छोडकर)कोई पूरक पोषण पदार्थ का सेवन किया था?	१	२
६३. क्या आपने खाने के लिए नली का प्रयोग किया था?	१	२
६४. क्या आपका वजन कम हुआ था?	१	२
६५. क्या आपका वजन वढ गया था?	१	२

ANNEXURE IX

The M.D. Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week.

My swallowing ability limits my day-to-day activities.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E2. I am embarrassed by my eating habits.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F1. People have difficulty cooking for me.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P2. Swallowing is more difficult at the end of the day.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E7. I do not feel self-conscious when I eat.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E4. I am upset by my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P6. Swallowing takes great effort.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E5. I do not go out because of my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F5. My swallowing difficulty has caused me to lose income.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P7. It takes me longer to eat because of my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P3. People ask me, "Why can't you eat that?"

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E3. Other people are irritated by my eating problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P8. I cough when I try to drink liquids.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F3. My swallowing problems limit my social and personal life.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F2. I feel free to go out to eat with my friends, neighbors, and relatives.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P5. I limit my food intake because of my swallowing difficulty.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P1. I cannot maintain my weight because of my swallowing problems.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E6. I have low self-esteem because of my swallowing problems.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P4. I feel that I am swallowing a huge amount of food.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F4. I feel excluded because of my eating habits.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

Thank you for completing this questionnaire!

Source: Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. Arch Otolaryngol Head Neck Surg. 2001;127:870–876. [PubMed]

Two scores are obtained: a Global Score and a Composite Score.

All questions except for E7 and F2:
- Strongly Agree = 1 point
- Agree = 2 points
- No Opinion = 3 points
- Disagree = 4 points
- Strongly Disagree = 5 point

E7 and F2:
- Strongly Agree = 5 points
- Agree = 4 points
- No Opinion = 3 points
- Disagree = 2 points
- Strongly Disagree = 1 point

Global Score: first question (not numbered)
- Global Score ranges from 1 (extremely low functioning) to 5 (high functioning)

Composite Score: 19 numbered questions
- Calculate total points: add scores for the 19 questions
- Calculate the mean point score: Divide total points by 19
- Calculate final score: Multiply the mean by 20

- Composite Score ranges from 20 (extremely low functioning) to 100 (high functioning)

****

Note about interpretation

"A recent methodological paper suggests that a change of 20 points in an individual's within-subject MDADI scores may be meaningful.[18] We agree with this notion as a 20-point change in an individual's MDADI scores over time equates to consistently moving responses up or down one level on the 5-point Likert ratings of the questionnaire (e.g., from "strongly agree" to "agree", or from "disagree" to "strongly disagree")." (Hutcheson, et al)

18. Lu W, Wayne PM, Davis RB, et al. Acupuncture for dysphagia after chemoradiation in head and neck cancer: rationale and design of a randomized, sham-controlled trial. Contemp Clin Trials. 2012;33:700–711. [PMC free article] [PubMed]

Hutcheson K, Portwood M, Lisec A, et al. What is a Clinically Relevant Difference in MDADI Scores between Groups of Head and Neck Cancer Patients? Laryngoscope. 2015 Nov 6. [10.1002/lary.25778]

ANNEXURE X

AJCC 8TH EDITION TNM CLASSIFICATION OF HEAD AND NECK CANCERS (EXCEPT CARCINOMA NASOPHARYNX)

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for the Oral Cavity (including mucosa of lip) (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage, mucosal melanoma, and cutaneous squamous cell carcinoma of the vermilion lip are not included)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor ≤2 cm with depth of invasion (DOI)* ≤5 mm
T2	Tumor ≤2 cm, with DOI* >5 mm and ≤10 mm *or* tumor >2 cm and ≤4 cm, with DOI* ≤10 mm
T3	Tumor >2 cm and ≤4 cm, with DOI* >10 mm *or* tumor >4 cm, with DOI* ≤10 mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor >4 cm, with DOI* >10 mm *or* tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face) Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

*DOI is depth of invasion and *not* tumor thickness.

Regional Lymph Nodes (N)

Clinical N (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension, and ENE(–)
N2b	Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); *or* metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for the Oral Cavity (including mucosa of lip) (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage, mucosal melanoma, and cutaneous squamous cell carcinoma of the vermilion lip are not included)

Regional Lymph Nodes (N)

Pathological N (pN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension, and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE (+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE (+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)

GX	Cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1,T2	N1	M0
	T3	N0,N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Oropharynx (p16-)

TX		Primary tumor cannot be assessed
Tis		Carcinoma *in situ*
T1		Tumor 2 cm or smaller in greatest dimension
T2		Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3		Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4		Moderately advanced or very advanced local disease
	T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
	T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

**Note:* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Hypopharynx

TX		Primary tumor cannot be assessed
Tis		Carcinoma *in situ*
T1		Tumor limited to one subsite of hypopharynx and/or 2 cm or smaller in greatest dimension
T2		Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures larger than 2 cm but not larger than 4 cm in greatest dimension without fixation of hemilarynx
T3		Tumor larger than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophageal mucosa
T4		Moderately advanced or very advanced local disease
	T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophageal muscle or central compartment soft tissue*
	T4b	Very advanced local disease Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

**Note:* Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N)

Clinical N (cN) - Oropharynx (p16-) and Hypopharynx

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2		Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
	N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
	N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
	N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3		Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in any node(s) and clinically overt ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
	N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N):
Pathological N (pN) - Oropharynx (p16-) and Hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+) *or* a single contralateral node of any size and ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

American Joint Committee on Cancer (AJCC)
TNM Staging System for HPV-Mediated (p16+) Oropharyngeal Cancer (8th ed., 2017)
(Not including: P16-negative (p16-) cancers of the oropharynx)

Primary Tumor (T)
T0 No primary identified
T1 Tumor 2 cm or smaller in greatest dimension
T2 Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3 Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced local disease
Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*
Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Regional Lymph Nodes (N)
Clinical N (cN)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 One or more ipsilateral lymph nodes, none larger than 6 cm
N2 Contralateral or bilateral lymph nodes, none larger than 6 cm
N3 Lymph node(s) larger than 6 cm

Pathological N (pN)
NX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in 4 or fewer lymph nodes
pN2 Metastasis in more than 4 lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
No grading system exists for HPV-mediated oropharyngeal tumors

Prognostic Stage Groups

Clinical

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage III	T0,T1,T2,T3	N3	M0
	T4	N0,N1,N2,N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3,T4	N0,N1	M0
Stage III	T3,T4	N2	M0
Stage IV	Any T	Any N	M1

American Joint Committee on Cancer (AJCC) TNM Staging System for the Larynx (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone and cartilage, and mucosal melanoma of the lip and oral cavity are not included)

Primary Tumor (T)

TX Primary tumor cannot be assessed

Tis Carcinoma *in situ*

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility

T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx

T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage

T4 Moderately advanced or very advanced

T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility

T1a Tumor limited to one vocal cord

T1b Tumor involves both vocal cords

T2 Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility

T3 Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage

T4 Moderately advanced or very advanced

T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis

T1 Tumor limited to the subglottis

T2 Tumor extends to vocal cord(s) with normal or impaired mobility

T3 Tumor limited to larynx with vocal cord fixation and/or inner cortex of the thyroid cartilage

T4 Moderately advanced or very advanced

T4a Moderately advanced local disease
Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Larynx (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Regional Lymph Nodes (N)

Clinical N (cN)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)

N2 Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–);
or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–);
or metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)

N2a Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)

N2b Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)

N2c Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)

N3 Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–);
or metastasis in any lymph node(s) with clinically overt ENE(+)

N3a Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−)

N3b Metastasis in any lymph node(s) with clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

American Joint Committee on Cancer (AJCC)
TNM Staging System for the Larynx (8th ed., 2017)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Pathological N (pN)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)
N2 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a Metastasis in a single ipsilateral node, 3 cm or smaller in greatest dimension and ENE(+); *or* metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3 Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral lymph nodes and any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−)
N3b Metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral lymph nodes any with ENE(+); or a single contralateral node of any size and ENE(+)

**Distant Metastasis (M)*

M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

American Joint Committee on Cancer (AJCC)
TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017)
(Squamous cell carcinoma and salivary gland carcinoma of all head and neck sites *except* HPV-related oropharynx cancer, nasopharynx cancer, melanoma, thyroid carcinoma, and sarcoma. Staging of the patient who presents with an occult primary tumor and EBV-unrelated and HPV-unrelated metastatic cervical lymphadenopathy is also included.)

Regional Lymph Nodes (N)

Clinical N (cN): For patients who are treated with primary nonsurgical treatment without a cervical lymph node dissection.

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2 Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, ENE(-)
N2a Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in any node(s) with clinically overt ENE(+) (ENE_c)[2]
N3a Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b Metastasis in any node(s) with clinically overt ENE(+) (ENE_c)[2]

[1]Midline nodes are considered ipsilateral nodes.
[2]ENE_c is defined as invasion of skin, infiltration of musculature, dense tethering or fixation to adjacent structures, or cranial nerve, brachial plexus, sympathetic trunk, or phrenic nerve invasion with dysfunction.

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

American Joint Committee on Cancer (AJCC)
TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017)
(Squamous cell carcinoma and salivary gland carcinoma of all head and neck sites *except* HPV-related oropharynx cancer, nasopharynx cancer, melanoma, thyroid carcinoma, and sarcoma. Staging of the patient who presents with an occult primary tumor and EBV-unrelated and HPV-unrelated metastatic cervical lymphadenopathy is also included.)

Regional Lymph Nodes (N)

Pathological N (pN): For patients who are treated surgically with a cervical lymph node dissection.

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); *or* metastases in multiple ipsilateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2a	Metastasis in a single ipsilateral node 3 cm or less in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes any size and ENE(+) in any node; *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes any size and ENE(+) in any node; *or* a single contralateral node of any size and ENE(+)

[1]Midline nodes are considered ipsilateral nodes.
[2]ENE detected on histopathologic examination is designated as ENE_{mi} (microscopic ENE ≤ 2 mm) or ENE_{ma} (major ENE > 2 mm). Both ENE_{mi} and ENE_{ma} qualify as ENE(+) for definition of pN.
Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Anatomic Stage/Prognostic Groups

Stage III	T0	N1	M0
Stage IVA	T0	N2	M0
Stage IVB	T0	N3	M0
Stage IVC	T0	Any N	M1

Continued

ANNEXURE XI

CTCAE 5.0 COMMON TOXICITIES AND GRADING

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements. **Navigational Note:** -					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting. **Navigational Note:** -					
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing. **Navigational Note:** -					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal. **Navigational Note:** -					
Generalized muscle weakness	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites. **Navigational Note:** -					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels. **Navigational Note:** -					

ANNEXURE XII

MASTER CHART