"TO STUDY THE ROLE OF DIFFUSION-WEIGHTED MRI IMAGING IN PREDICTING THE RESPONSE TO CONCURRENT CHEMORADIOTHERAPY IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA"

DEPARTMENT OF RADIOTHERAPY
CHRISTIAN MEDICAL COLLEGE
VELLORE 632004

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF
MD BRANCH RADIOTHERAPY
EXAMINATION MAY 2018

TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY
CHENNAI - 600032.
CHRISTIAN MEDICAL COLLEGE, VELLORE
DEPARTMENT OF RADIOTHERAPY

Certificate

This is to certify that the dissertation titled **"TO STUDY THE ROLE OF DIFFUSION-WEIGHTED MRI IMAGING IN PREDICTING THE RESPONSE TO CONCURRENT CHEMORADIOTHERAPY IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA"** is a bonafide work done by Dr Koti Krishna Amulya, Post Graduate Student in the Department of Radiotherapy, Christian Medical College, Vellore during the period from April 2016 to March 2018 and is being submitted to The Tamil Nadu Dr M. G. R Medical University in partial fulfilment of the MD Branch Radiotherapy examination conducted in May 2018.

Guide

Dr. Simon P Pavamani

Professor

Department of Radiotherapy

Christian Medical College

Vellore, India – 632004

Certificate

This is to certify that the dissertation entitled "**TO STUDY THE ROLE OF DIFFUSION-WEIGHTED MRI IMAGING IN PREDICTING THE RESPONSE TO CONCURRENT CHEMORADIOTHERAPY IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA"** is a bonafide work done by Dr. Koti. Krishna Amulya, Post Graduate Student in the Department of Radiotherapy, Christian Medical College, Vellore during the period from April 2016 to March 2018 and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfilment of the MD Branch IX Radiotherapy examination conducted in May 2018

Head of the Department

Dr Selvamani B

Prof and Head of the department

Department of Radiotherapy

Christian Medical College

Vellore, India - 632004

Principal

Christian Medical College

Vellore, India- 632004

Certificate

This is to certify that the dissertation entitled "**TO STUDY THE ROLE OF DIFFUSION-WEIGHTED MRI IMAGING IN PREDICTING THE RESPONSE TO CONCURRENT CHEMORADIOTHERAPY IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA"** is a bonafide work done by Dr. Koti. Krishna Amulya, Post Graduate Student in the Department of Radiotherapy, Christian Medical College, Vellore during the period from April 2016 to March 2018 and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfilment of the MD Branch IX Radiotherapy examination conducted in May 2018.

Dr. Koti. Krishna Amulya

PG REGISTRAR,

DEPARTMENT OF RADIOTHERAPY,

CHRISTIAN MEDICAL COLLEGE,

VELLORE

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

October 25, 2016

Dr. Koti Krishna Amulya,
PG Registrar,
Department of Radiotherapy Unit I,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Grant NEW PROPOSAL:**
To study the role of diffusion weighted MRI in predicting response to concurrent chemoradiotherapy/ neoadjuvant chemotherapy in nasopharyngeal malignancies.
Koti Krishna Amulya, Employment No 21089, PG Registrar, Dr Simon Pavamani, Employment Number: 50669, Professor, Department of Radiotherapy Unit I, Dr. Aparnia I, Professor, Employment Number: 28382, Department of Radiology.Dr. Visalaikshi J, Lecturer, Department of Biostatistics.

Ref: IRB Min No: 10259 [OBSERVE] dated 05.09.2016

Dear Dr Koti Krishna Amulya,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "To study the role of diffusion weighted MRI in predicting response to concurrent chemoradiotherapy / neoadjuvant chemotherapy in nasopharyngeal malignancies" on September 05th 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Consent Form and Information Sheet
3. No. of documents 1-2.

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on September 05th 2016 in the C K Job Hall, Paul Brand Building, Christian Medical College, Bagayam, Vellore 632002.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC,Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist &Epidemiologist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Rajesh Kannangai	MD, PhD.	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Sneha Varkki	MBBS, DCH, DNB	Professor, Paediatrics, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Sathish	MBBS, MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS, MCh	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "To study the role of diffusion weighted MRI in predicting response to concurrent chemoradiotherapy/ neoadjuvant chemotherapy in nasopharyngeal malignancies" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:
A sum of 1,00,000/- INR (Rupees One Lakh Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an Ist Installment. The rest of the 50,000/- INR (Rupees Fifty Thousand only) each will be released at the end of the first year as 2 nd Installment.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min No: 10259 [OBSERVE] dated 05.09.2016

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

October 25, 2016

Dr. Koti Krishna Amulya,
PG Registrar,
Department of Radiotherapy Unit I,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Grant NEW PROPOSAL:**
To study the role of diffusion weighted MRI in predicting response to concurrent chemoradiotherapy/ neoadjuvant chemotherapy in nasopharyngeal malignancies. Koti Krishna Amulya, Employment No 21089, PG Registrar, Dr Simon Pavamani, Employment Number: 50669, Professor, Department of Radiotherapy Unit I, Dr. Aparnia I, Professor, Employment Number: 28382, Department of Radiology.Dr. Visalaikshi J, Lecturer, Department of Biostatistics.

Ref: IRB Min No: 10259 [OBSERVE] dated 05.09.2016

Dear Dr Koti Krishna Amulya,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr Simon Pavamani, Dept. of Radiotherapy Unit I, CMC, Vellore

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

URKUND

Document	EDITED FINAL VERSION.docx (D31375079)
Submitted	2017-10-16 21:43 (+05:0-30)
Submitted by	Koti Krishna Amulya (amulya2090@gmail.com)
Receiver	amulya2090.mgrmu@analysis.urkund.com
Message	Dr MGR University PG thesis - MD radiotherapy Show full message
	18% of this approx. 43 pages long document consists of text present in 9 sources.

[Urkund] 19% similarity - amulya2090@gmail.com Inbox x

report@analysis.urkund.com 10:25 PM (2 hours ago)

to me

Document sent by: amulya2090@gmail.com
Document received: 10/16/2017 6:13:00 PM
Report generated 10/16/2017 6:55:16 PM by Urkund's system for automatic control.

Student message: Thesis in MD Radiotherapy 2018 by Dr. Amulya
Thesis titled " To study the role of diffusion weighted MRI imaging in predicting the response to concurrent chemoradiotherapy in patients with nasopharyngeal malignancies"

Contents

ACKNOWLEDGEMENT

I would like to express my heartful gratitude to all those who have directly or indirectly helped in conducting this study. To commence with, I thank God, Almighty for bestowing upon me good health, courage and inspiration.

I express my sincere and deepest gratitude to my guide, Dr Simon Pavamani, for his untiring efforts, patience, constant support and scientific inputs. His continual inspiration, helped me in all the time of research and writing of this thesis. It would have not been possible to complete this study without his encouragement. I am inspired by his zeal and enthusiasm for research.

I would like to my co-guide Dr Aparna, Professor, Department of Radiology for all the efforts and time that she had put in for providing me with the necessary data.

I thank my co-guide Dr Rajesh I, Professor, Department of RT for his able guidance and for having the faith in me.

I thank Dr Selvamani, Professor and Head of the Department, Radiotherapy and all the RT Consultants for their concern, care and encouragement.

I take the opportunity to thank all the senior residents and fellow Post Graduates special mentions to Dr Solly for helping me out in carrying out this study.

I am thankful to Dr Visalakshi, Department of Biostatistics, for her assistance during the statistical analysis of this research work. I am also thankful to Radiology technicians for accepting my study requests and extend all their co-operation and support to help in carrying out this study

I wish to thank all my patients for their co-operation in this study.

And finally, last but by no means least, I thank my wonderful husband, my loving mother and others in the family for their prayers, love, encouragement and support

AIM

"To study the role of diffusion weighted MRI imaging in predicting the response to concurrent chemoradiotherapy in patients with nasopharyngeal carcinoma

OBJECTIVE

Primary Outcome: To study the role of diffusion weighted MRI derived parameters i.e. ADC as an imaging biomarker in nonmetastatic nasopharyngeal carcinoma.

Secondary Outcome: Validating the role of diffusion weighted in detection and characterization of nasopharyngeal cancers as well as for monitoring the response to radiotherapy and chemotherapy.

HYPOTHESIS

Diffusion weighted imaging plays a key role in prediction of treatment response to chemo-radiotherapy in patients diagnosed with nasopharyngeal malignancies

INTRODUCTION

According to the Globocan fact sheet, worldwide there are approximately 60,896 new nasopharyngeal cases and a reported of 35,756 deaths annually. In India, there are about 3947 cases being reported annually with nasopharyngeal malignancy.

Carcinomas of Nasopharynx are known to be radio-responsive and are treated using radiation therapy with or without chemotherapy. The standard of care for the treatment of patients with non-metastatic nasopharyngeal cancer is radiotherapy with or without chemotherapy. Based on the stage, they receive radiation alone or concurrent chemoradiotherapy followed by adjuvant chemotherapy. Some patients receive chemotherapy prior to Radiation to decrease the size of the tumor or lymph nodes especially if they lie close to critical structures in the head & neck region e.g. optic apparatus brainstem & the spinal cord. However, nearly in 7%–13% of cases residual disease persists after treatment. Moreover, the appearance of local or distant relapse determines a less favorable prognosis for these patients. Salvage treatment options are with limited success. Thus, it is essential to be able to predict and monitor the therapeutic response of patients with Carcinoma Nasopharynx. Hence attempts are being made to predict response to radiation therapy with various functional and metabolic imaging.

Anatomic imaging (CT and MR imaging) is focused on diagnosing and/or characterizing the disease, defining its local extent, and evaluating distant spread. While the accurate assessment of the biologic status of the cancer (cellularity, growth rate, response to chemoradiation therapy) with functional imaging modalities like dynamic contrast enhancement MRI, diffusion weighted MRI, FDG PET can be essential for prognostication, planning therapy, and follow-up of lesions after therapy. The combination of anatomic and biologic imaging

techniques can thus provide a more comprehensive evaluation of the patient helping in better understanding of the pathophysiology of the disease and allowing better evaluation of treatment strategies.

This study is mainly focused on evaluating the role of Diffusion-weighted Magnetic Resonance Imaging (DW MRI) in predicting early response to chemoradiation in nasopharyngeal malignancies. DW MRI explores the random motion of water molecules in the tissue. Water molecules are in a constant random movement called the Brownian motion. The Diffusion Weighted signal in biologic tissues is derived from the motion of water molecules in the intracellular space, the extracellular space, and the intravascular space. The degree of restriction to water diffusion in biologic tissue is inversely correlated to the tissue cellularity and the integrity of cell membranes. The motion of water molecules is more restricted in tissues with a high cellular density associated with numerous intact cell membranes (e.g., tumor tissue). The lipophilic cell membranes act as barriers to motion of water molecules in both the extracellular and intracellular spaces. By contrast, in areas of low cellularity or where the cellular membrane has been breached, the motion of water molecules is less restricted. A less cellular environment provides a larger extracellular space for diffusion of water molecules, and these molecules may also freely.

Effective anticancer treatment results in tumor lysis, loss of cell membrane integrity, increased extracellular space, and, therefore, an increase in water diffusion. Impediments such as cell membranes, organelles, and macromolecules interferes with the free movement of water molecule, this diffusion in biological tissue is quantified by means of an APPARENT DIFFUSION COEFFICIENT (ADC).

Malignant tissues have more densely packed cells as compared to their nonmalignant counterparts. Thus, the "diffusion" of water molecules is restricted due to high cellularity in malignant tissue. With radiation therapy, there is cell death and increased water movement across tumor and thus increased diffusion which in turn is expressed in increase in ADC values. Therefore, as treatment progresses, the ADC values are expected to rise as the tumour cells respond to the chemoradiation. Thus, the serial monitoring of the ADC values before radiation, during radiation and at 6 weeks after radiation will help in correlating the ADC values of the responders and non-responders. We chose the time periods for assessment as

1. Pre-RT: Prior to initiation of radiation therapy
2. Week 1: At 1 week of radiation therapy
3. Follow up: At 4-6 weeks after completion of RT

This response evaluation can be utilized for tailoring treatment for patients in the future. Therefore, patients showing response utilizing Diffusion weighted imaging may not need further chemotherapy. The purpose of this study was to evaluate the usefulness of DW MRI with ADC values in predicting the responses to radical chemoradiotherapy in nasopharyngeal malignancies

REVIEW OF LITERATURE

Epidemiology

Nasopharyngeal carcinoma(NPC) is a rare malignancy worldwide but is seen in high incidence in Sothern China, Hongkong and South-east Asia. These areas are termed “High-risk” or “Endemic” for NPC. According to the Globocan fact sheet, worldwide there are approximately 60,896 new nasopharyngeal cases and a reported of 35,756 deaths annually.

According to the Indian data there are about 3947 cases being reported annually with nasopharyngeal malignancy(1)

Estimated incidence, mortality and 5-year prevalence: both sexes

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	300373	2.1	4.0	145353	1.8	1.9	702149	2.2	13.5
Nasopharynx	86691	0.6	1.2	50831	0.6	0.7	228698	0.7	4.4
Other pharynx	142387	1.0	1.9	96105	1.2	1.3	309991	1.0	6.0
Oesophagus	455784	3.2	5.9	400169	4.9	5.0	464063	1.4	8.9
Stomach	951594	6.8	12.1	723073	8.8	8.9	1538127	4.7	29.6
Colorectum	1360602	9.7	17.2	693933	8.5	8.4	3543582	10.9	68.2
Liver	782451	5.6	10.1	745533	9.1	9.5	633170	2.0	12.2
Gallbladder	178101	1.3	2.2	142823	1.7	1.7	205646	0.6	4.0
Pancreas	337872	2.4	4.2	330391	4.0	4.1	211544	0.7	4.1
Larynx	156877	1.1	2.1	83376	1.0	1.1	441675	1.4	8.5
Lung	1824701	13.0	23.1	1589925	19.4	19.7	1893078	5.8	36.5
Melanoma of skin	232130	1.7	3.0	55488	0.7	0.7	869754	2.7	16.8
Kaposi sarcoma	44247	0.3	0.6	26974	0.3	0.3	80395	0.2	1.5

Table 1: The WORLD Incidence, mortality and 5year prevalence – adopted from the Globocan

Estimated incidence, mortality and 5-year prevalence: both sexes

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	77003	7.6	7.2	52067	7.6	4.9	118902	6.6	13.5
Nasopharynx	3947	0.4	0.3	2836	0.4	0.3	9967	0.6	1.1
Other pharynx	38691	3.8	3.7	32784	4.8	3.1	56754	3.2	6.4
Oesophagus	41774	4.1	4.1	38683	5.7	3.8	22157	1.2	2.5
Stomach	63097	6.2	6.1	59041	8.6	5.7	45390	2.5	5.1
Colorectum	64332	6.3	6.1	48603	7.1	4.6	86650	4.8	9.8
Liver	27416	2.7	2.7	26763	3.9	2.6	13089	0.7	1.5
Gallbladder	18787	1.9	1.8	15866	2.3	1.5	22892	1.3	2.6
Pancreas	11936	1.2	1.2	10828	1.6	1.1	6730	0.4	0.8
Larynx	25446	2.5	2.5	17560	2.6	1.7	50494	2.8	5.7
Lung	70275	6.9	6.9	63759	9.3	6.3	32464	1.8	3.7
Melanoma of skin	2103	0.2	0.2	1122	0.2	0.1	5314	0.3	0.6
Kaposi sarcoma	19	0.0	0.0	14	0.0	0.0	26	0.0	0.0

Table 2: The INDIAN Incidence, mortality and 5year prevalence of nasopharyngeal cancers – adopted from the Globocan

Though NPC is a rare malignancy in the Indian subcontinent, the North-eastern tribes are reported to be an intermediate risk population with an average incidence of 4.3 per 100,000 people/year(2). NPC is often misdiagnosed and underreported. Hence the actual incidence can be higher than reported. Highest incidence in our country is reported from the Imphal district of Manipur, closely followed Manipur and Sikkim.

ESTIMATED BURDEN – 2020

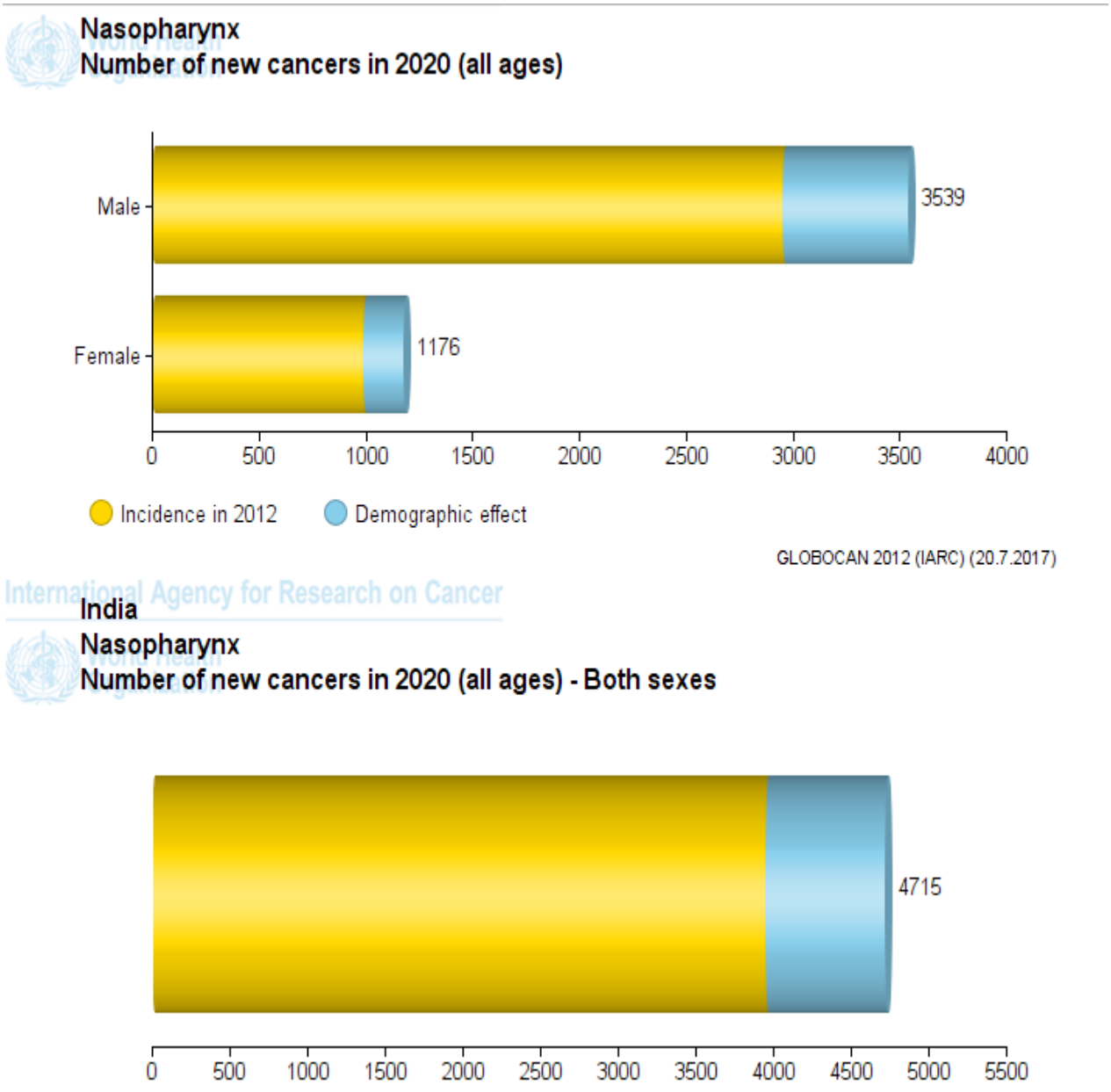


Fig 3: Estimated incidence of Nasopharyngeal malignancies by 2020 in India

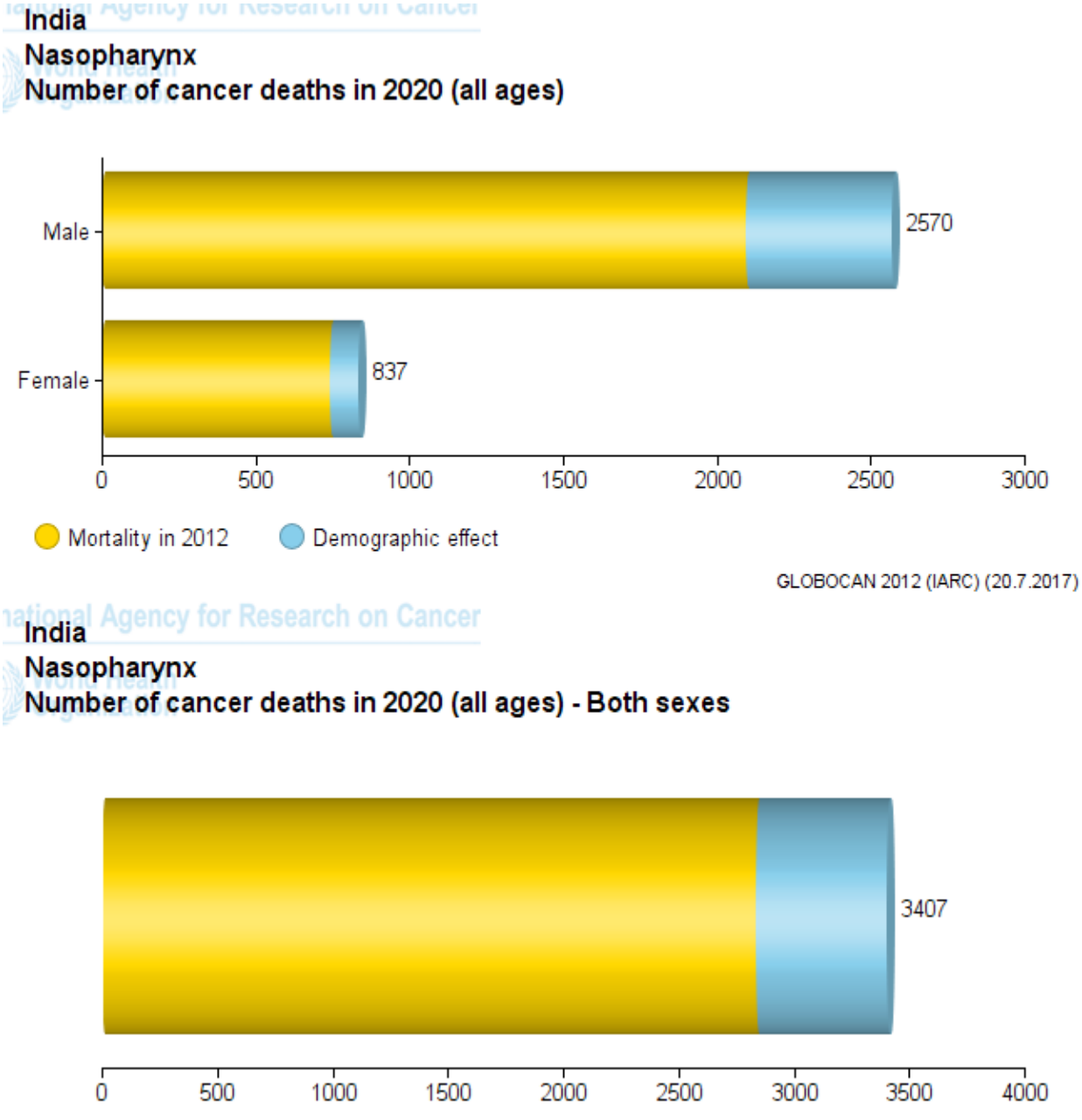


Fig 6: Estimated deaths due to Nasopharyngeal malignancy by 2020 in India

Anatomy of nasopharynx

The nasopharynx is a tubular space situated below the base of the skull. It is a part of the Waldeyer ring. It is lined by stratified squamous epithelium and ciliated epithelium. NPC is commonly developing from the lateral wall of nasopharynx, particularly at the fossa of Rosenmuller.

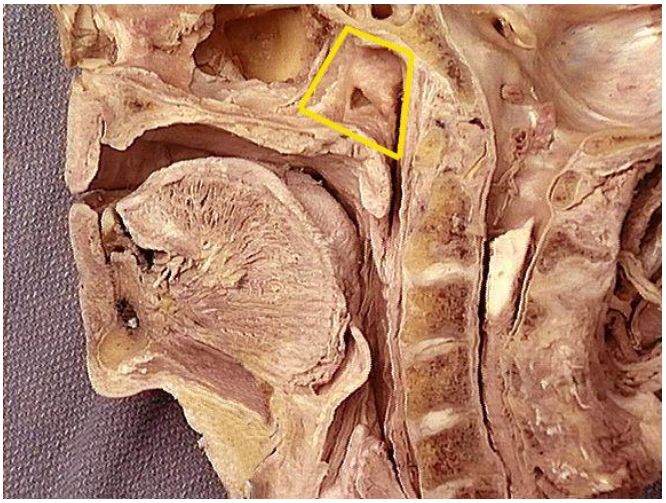


Figure 7: Sagittal section of human head showing Nasopharynx (Highlighted in yellow)

BOUNDARIES OF NASOPHARYNX	
Anterior	Posterior nares and posterior nasal septum
Posterior	C1 and C2 vertebral bodies Retropharyngeal space
Superior	Basi-sphenoid and Basi-occiput
Inferior	Anteriorly: Soft palate Posteriorly: Communicates with Oropharynx via Nasopharyngeal isthmus
Lateral	Contains opening of Eustachian tube

NEUROVASCULATURE

Arterial supply	Ascending pharyngeal Artery
	Facial Artery
	Ascending cervical artery
Venous drainage	Pterygoid and Pharyngeal Plexus
Lymphatic drainage	Lateral lymphatic channels → Lateral retropharyngeal, deep cervical and posterior triangle nodes
	Medial lymphatic channels → Median retropharyngeal nodes
Nerve innervation	Sensory – V & IX cranial nerve branches
	Motor – Pharyngeal plexus

Synonyms for NPC: The first description of NPC as "Skull base tumor" dates to 1845. In 1921, it was termed "lymphoepithelioma" by Regaud and Schmincke.

Risk Factors

The risk factors most frequently associated with nasopharyngeal carcinoma are ethnicity, smoking and Epstein Barr Virus (EBV) infection.

Ethnicity – Nasopharyngeal carcinoma (NPC) is a very common neoplasm in Southern Chinese and south-east Asians. China along with southeast Asia is considered an endemic region for NPC. Southern Chinese who have migrated to non-endemic regions are found to have a decline in incidence of NPC compared to their counterparts residing at homeland. Yet,

they continue to have higher incidence rate compared to other ethnic groups residing in the same geographical regions.(3) Ethnicity shadows genetic susceptibility.

Genetic Predisposition – There has been much debate over genetic predisposition in nasopharyngeal malignancies. A review of Genome-wide association studies (GWAS) showed association of immune related genes with NPC. DNA repair genes, Classical and Non-classical HLA genes are found to have a strong association with NPC in the Chinese (4). The association in the non-endemic region needs to be proven yet.

Familial aggregation of NPC has also been reported.

Epstein Barr virus infection – EBV infection is a well-known causal factor in NPC. Epstein-Barr virus (EBV) infection has been linked with the non-keratinising subtypes of nasopharyngeal cancers. High pre-treatment plasma EBV DNA titres correlate with higher stage of disease and persistent EBV DNA titres after treatment are associated with poor prognosis. EBV DNA is now an established biomarker for prognosticating outcomes after treatment.

Smoking – Smoking tobacco products (cigarettes, cigars, pipes) is an important risk factor for the development of NPC. It is a major factor in development of NPC in non-endemic areas. Association of smoking was found with well differentiated histology rather than an undifferentiated histology. Furthermore, those with > 30 pack-years had double the incidence of NPC than those with < 30 pack-years. From a recent Metanalysis, the pooled risk estimate for nasopharyngeal malignancy associated with each 1-pack-year increment of smoking was 1.019 (5).

Alcohol — Like smoking, alcohol intake was also found to have increased the risk of well differentiated NPC. The quantitative relationship is however complex. Results from a Systematic review showed a J shaped pooled dose response curve indicating that risk of NPC decreases up to 15 drinks/week and thereafter increases with further increase in alcohol intake. Confounding factors like smoking and salted fish could have led to such a conclusion.(6)

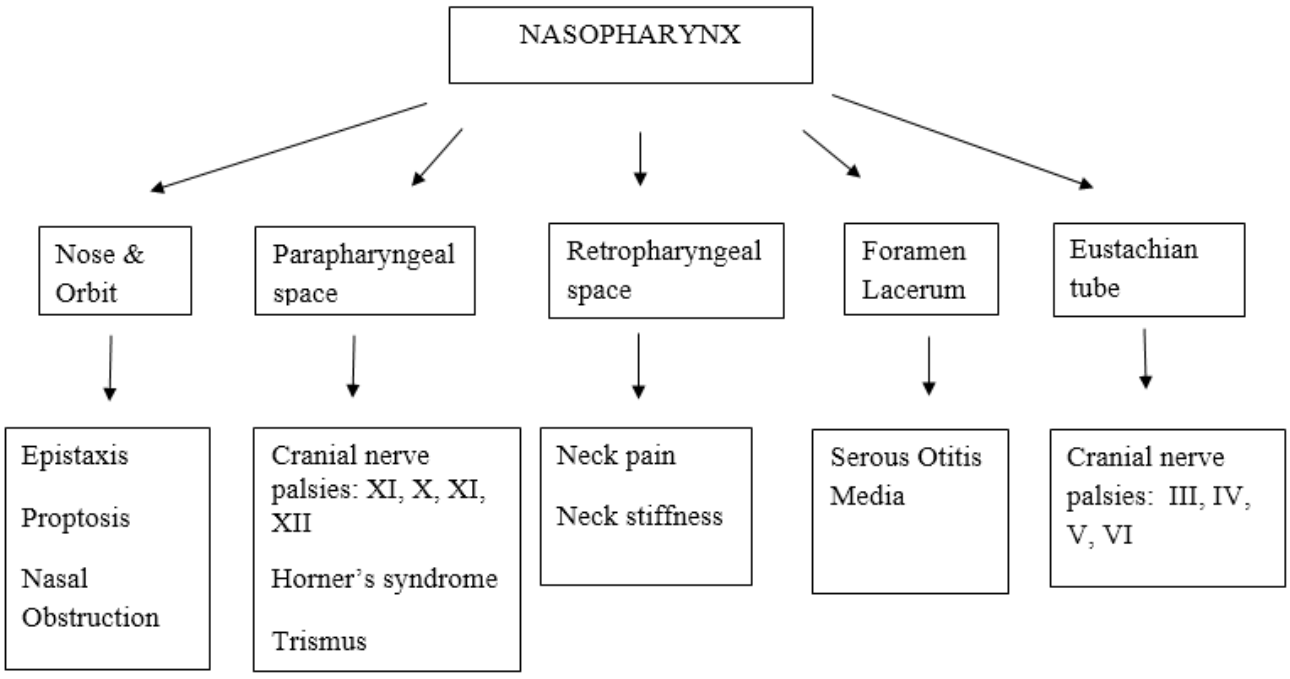
Occupational exposure — Multiple other occupational or environmental toxins have been studied for potential relationship with NPC. Formaldehyde, wood dust and fumes are known carcinogens(7).

Radiation — Prior irradiation for either malignant or benign disease has been linked to thyroid cancer, salivary gland tumors, squamous cell cancers, and sarcomas. Although this relationship appears to be real, its relevance in NPC is unclear.

Diet — Some dietary factors may have a role in protecting individuals from head and neck cancer, while others may increase susceptibility for specific diseases. Salted fish and preservatives in food items are for long thought to be one of the causal factors of NPC

Clinical presentation

Nasopharyngeal malignancies can spread through local, lymphatic and hematogenous pathways. Symptoms and its severity varies according to the site and extent of involvement. Owing to its proximity to base of skull and sinuses, it can often present with cranial nerve involvement. Common symptoms secondary to **local spread** are described below as a flow diagram



Lymphatic spread assumes great significance in NPC as nasopharynx has a rich lymphatic network. The retropharyngeal group of lymph nodes are believed to be the first echelon nodes and the risk of involvement of deep cervical nodes unilaterally or bilaterally is the highest in NPC in comparison to any other head and neck tumor. As high as 70% of patients present with nodal involvement at presentation and lymph node enlargement is the most common clinical presentation. It also is an important prognostic factor in NPC.

Distant metastases are not very uncommon in NPC. The common sites of involvement are bone, liver and lung. Nodal involvement and the site of lymphadenopathy predicts distant metastatic potential.

Diagnostic Evaluation

NASOPHARYNGOLARYNGOSCOPE (NPL): The flexible fibreoptic Nasopharyngolaryngoscopy is a very valuable tool that can visualise Nasopharynx and structures around it

It helps in

- Identifying the site and extent of the disease
- Biopsy and
- Stage the disease.

BIOPSY: The histopathology is the gold standard for diagnosis of NPC. ls called squamous cells. The WHO classification of NPC began in 1978 and has had multiple revisions since then. The most recent classification in 2005 divides NPC into three histological subtypes:

1. Keratinizing squamous cell carcinoma

- Well differentiated / Moderately differentiated / Poorly differentiated

2. Non-Keratinizing carcinoma

- Undifferentiated / Differentiated

3. Basaloid carcinoma

Non-keratinizing carcinoma is the most common (~90%) variant in endemic areas (high risk areas). Keratinizing is relatively rare and is seen in high incidence in patients with smoking and alcohol abuse. Basaloid is the rarest variety (~1%). Association with EBV was found in Non-keratinizing and Basaloid types.

IMAGING: The anatomy of nasopharynx presents structural and functional variations, making precise diagnosis and staging a challenging task. NPL scopy will not be able to exactly stage disease, Example: Intracranial extension which is identified on cross-sectional imaging may be missed in a routine NPL scopy. There is a greater need for precise staging of the disease as survival varies with each stage and so is the treatment planning.

Cross-sectional imaging was revolution since its invention in the mid seventies. Anatomical imaging techniques such as Computerized Tomography (CT) and Magnetic resonance imaging (MRI) provide morphological information while the evaluation of biological characteristics of tumors is by the functional imaging modalities.

1. **Computed Tomography**: CT can identify tumor in the nasopharynx based upon anatomic distortion and/or specific tumor enhancement. In general, tumors enhance more than normal structures except for mucosa, extraocular muscles, and blood vessels. Compared with MRI, CT provides greater spatial resolution, and can be performed faster, thereby eliminating motion artefact, and it is better for the evaluation of bone destruction such as skull base erosion seen in T3 disease. Modern multidetector CT technology allows scanning to be performed with slice thickness less than 1 mm. Slice thickness of 3 mm is generally optimal.

- **Primary site** — For primary site, contrast-enhanced CT can help determine the extent of tumor infiltration into soft tissue and bone. CT can provide information on invasion

of the para-pharyngeal space, sinuses and skull base invasion. The modern technology of dual energy and multispectral CT has demonstrated improved accuracy for assessing bone invasion compared with conventional CT. Asymmetry is a feature suggestive of malignant process in nasopharynx in the initial stages. However, clinical relevance of such asymmetry is difficult to interpret on CT because of inflammatory process, lymphoid tissue and secretions in nasopharynx. Presence of minor asymmetry is often mistaken for disease and results in false positivity. A modified Valsalva manoeuvre which opens collapsed lateral pharyngeal recess can be tried during CT. Also, occasionally CT may fail to depict an early cortical erosion of the skull base that is better depicted on MRI.

- **Regional nodes** — Imaging by CT or MRI is complementary to the clinical examination for the staging of the neck lymph nodes. CT evaluation of regional lymph nodes primarily relies upon size criteria as well as the appearance of lymph nodes to differentiate involved from uninvolved lymph nodes. The use of size criteria alone results in frequent false positive and false negative assessment of regional nodes. CT is also highly sensitive for detection of extracapsular spread of tumor.

  Pathologic lymphadenopathy is usually identified radiologically as a node greater than 10 to 11 mm in minimal axial diameter or presence of central necrosis. In general, criteria based on measurement of minimal axial diameter are considered the most accurate, effective and probably most reproducible. Other features pointing towards lymph nodal involvement by malignancy include rounded shape, loss of normal fatty hilum, and increased or heterogeneous contrast enhancement. Although CT is superior to clinical examination, the implementation of size criteria and presence of central necrosis limit detection of borderline-sized nodes, non-necrotic nodes. CT cannot

differentiate between reactive and normal nodes. This is a critical issue since microscopic or occult lymphadenopathy is very common in NPC which is known for its high lymphatic spread.

1. **Magnetic Resonance Imaging(MRI)** : MRI provides superior soft tissue definition compared with CT and can often provide information that is complementary to CT. Moreover, there is no use of non-ionizing radiation with MRI. Most important imaging sequences for include non-contrast enhanced T2-weighted images and contrast T2 and T1 sequences. Images in axial and coronal plane are the most useful. For general purpose, slice thickness should be no more than 5 mm. Some applications, such as evaluation of skull base and perineural spread, may require thinner slice thickness, typically around 3 mm.

- **Primary site** – As the soft tissue is better seen on MRI than CT, it adds to the information generated from CT. MRI is also better than CT for discriminating tumor from mucus and in detecting bone marrow invasion. MRI is superior to CT for evaluation of perineural spread, para-pharyngeal extension, skull base invasion, and intracranial extension. MRI may also provide additional benefits compared with CT in the evaluation of the base of tongue involvement and parotid glands.

- **Regional nodes -** Fat surrounding the nodes decreases their prominence on the MRIs. Fat-suppressed contrast-enhanced sequences are the optimal sequences for detecting nodal metastasis. The retropharyngeal nodes, which are the echelon nodes, are easily detected on MRI.

2. **18 Flurodeoxyglucose PET (FDG PET):** With PET, injected positron-emitting radionuclides, such as fluorine-18, are taken up by metabolically or functionally active

tissues. PET images are created by detecting these emissions by an array of detectors and then using reconstruction techniques to create a three-dimensional image. The most commonly used agent is 18F-flourodeoxyglucose (FDG), which is taken up into cells in different concentrations depending on the relative metabolism of different tissues. It is specific for tumors because metabolic rates are very high in many tumors.

Imaging of the primary tumor site and regional lymph nodes with PET is limited by its poor spatial resolution, which can make it difficult to localize the anatomic location of the FDG uptake. These issues can be at least partially addressed with integrated PET-CT imaging, in which PET and CT are performed sequentially during a single visit on a hybrid PET-CT scanner. The images are then co-registered using fusion software, enabling the physiologic data obtained on PET to be localized according to the anatomic CT images.

- **Primary site** - Historically, CT images obtained from integrated PET-CT scanners had lower spatial resolution compared with dedicated CT scanners. This problem is now being overcome by new generation of PET-CT scanners that offer volumetric CT capability. Thus, currently PET appears to be at least as sensitive and specific as CT and MRI in detecting primary head and neck tumors.

- **Regional nodes** - More importantly, PET is superior to both CT and MRI for detecting regional nodal metastases, as well as second primary tumors(10) Data indicates that PET/CT is accurate for detecting occult cervical nodal metastases, although it does not have the sensitivity to replace neck dissection. However false negatives of PET may be seen in lymph nodes less than 5 mm, necrotic or cystic lymph nodes, and tumors of low metabolic activity.

- **Distant metastases** -Its main utility is in finding distant metastases, unknown primary lesions, and synchronous second primary tumors.

An updated Metanalysis comparing CT Vs MRI Vs PET-CT showed the following results(11)

	CT		MRI		PET CT	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Local site – T staging	0.84	0.80	0.95	0.76	0.85	0.91
Nodal site – N staging	0.92	0.93	0.88	0.95	0.88	0.95

Authors have concluded by stating that MRI was more accurate than CT or PET-CT in local staging and fairly comparable in nodal staging. PET-CT is preferred for detecting occult neck nodes, metastatic disease, synchronous second primaries and recurrences**.**

Staging of the Disease

Currently we are following the 7th edition of AJCC/UICC staging system. However, the 8th edition which would come into effect from January 2018 has major modifications in NPC staging. We had followed the 7th edition in our study.

The 7th and 8th editions are both presented below:

7th EDITION AJCC STAGING	**T stage**	**8th EDITION AJCC STAGING**
Tumor confined to Nasopharynx or extension to oropharynx / nasal cavity	**T1**	Unchanged

Extension to: - Para-pharyngeal space	**T2**	Extension to: - Para-pharyngeal space - ***Pterygoid muscle (Medial / lateral)*** - ***Prevertebral structure***
Invading: - Skull base - Paranasal sinuses	**T3**	Invading: - Skull base - Paranasal sinuses - Pterygoid structures - Cervical vertebrae
Any invasion into - ***Infratemporal fossa*** - ***Masticator space*** - Hypopharynx - Orbit - Intracranial extension - Cranial nerve involvement	**T4**	Any invasion into: - ***Parotid gland*** - ***Beyond lateral surface of lateral pterygoid*** - Hypopharynx - Orbit - Intracranial extension - Cranial nerve involvement

Changes are highlighted in Bold Italics

7th EDITION AJCC STAGING	**Nodal**	**8th EDITION AJCC STAGING**
< 6 cms in greatest dimension, above supraclavicular fossa - Unilateral metastases, in cervical lymph nodes (or) - Unilateral / Bilateral metastases in retropharyngeal nodes	**N1**	< 6 cms in greatest dimension, ***above the caudal border of cricoid cartilage*** - Unilateral metastases, in cervical lymph nodes (or) - Unilateral / Bilateral metastases in retropharyngeal nodes
< 6 cms in greatest dimension, above supraclavicular fossa - Bilateral cervical nodes	**N2**	< 6 cms in greatest dimension, ***above the caudal border of cricoid cartilage*** - Bilateral cervical nodes
>6 cms in greatest dimension (and / or)	**N3**	>6 cms in greatest dimension (and / or)
In the supraclavicular		***Below the caudal border of cricoid cartilage***

Changes are highlighted in Bold Italics

7th EDITION AJCC STAGING	STAGE GROUP	8th EDITION AJCC STAGING
T1 N0 M0	**I**	T1 N0 M0
T1 N1 M0	**II**	T1 N1 M0
T2 N0/1 M0		T2 N0/1 M0
T1/2 N2 M0	**III**	T1/2 N2 M0
T3 N1/2 M0		T3 N1/2 M0
T4 N0/1/2 M0	**IV A**	T4 N0/1/2 M0
		Any T N3 M0
Any T N3 M0	**IV B**	***Any T Any N M1***
Any T Any N M1	**IV C**	***No longer exists***

Treatment of Non-Metastatic Nasopharyngeal malignancies

EARLY DISEASE (T1 N0 M0): Radiotherapy alone is treatment for early disease. According to Song et al. use of chemotherapy has not shown additional benefit in stage I NPC(12). In another study, the 10-year disease specific survival, recurrence free survival and distant metastasis free survival rates were all over 95% with radiation alone(13). Guidelines by the European Society for Clinical Oncology -ESMO (14), the Spanish Society of Medical Oncology -SEOM(15) and National Comprehensive Cancer Network - NCCN(16) suggest RT alone is an optimal modality of therapy for T1N0M0 NPC.

LOCALLY ADVANCED DISEASE (T1, N1–3; T2–4, Any N, M0): Addition of chemotherapy both concurrently and as adjuvant was found to survival advantage in locally advanced NPC in multiple studies. Landmark Intergroup study by South-west Oncology Group

(SWOG) showed increased survival with concurrent chemoradiotherapy (CRT) followed by adjuvant chemotherapy compared to radiotherapy alone in stage III and IV carcinoma nasopharynx patients(17). The benefit combined therapy in Stage III and IV is undebated.

Stage II NPC has remained an enigma for most clinicians with conflicting evidence on addition of chemotherapy to radiation. Most studies on CRT excluded stage II NPC. Cheng et al. (18) showed that disease-free survival in stage II NPC with CRT is equal to that of patients with stage I disease with radiation alone. While SEOM(15) recommends radiation alone for stage II, both ESMO(14) and NCCN(16) recommend CRT.

Metanalysis of 2138 stage II NPC patients by Cheng Xu et al. had shown chemoradiation to have significantly higher overall survival and locoregional relapse free survival compared to RT alone(19). But there was no difference in distant metastases free survival. Moreover, the equivalence of RT alone with chemoradiation was seen when IMRT was used in subgroup analysis. Also grade 2/3 toxicities were lesser in IMRT group compared to chemoradiation group. This lead the authors to the conclude that chemoradiation was superior to 2D radiotherapy but the same does not hold true for IMRT in stage II NPC.

ROLE OF INDUCTION / NEOADJUVANT CHEMOTHERAPY: A pooled data analysis was conducted by Chua et al. of two phase III studies (n=784). It showed that the addition of platinum-based induction chemotherapy to radiation had caused decrease in relapse by 14.3%. The cancer-related deaths reduced by 12.9 percent at 5 years. However, there was no improvement in overall survival (61.9 % Vs. 58.1 %, p=0.092). This could be attributed to more late intercurrent deaths in both the groups(20)

Other benefit of Induction chemotherapy is downsizing tumor which could be very useful in a complex structure like nasopharynx where the tumor can lie close to many critical structures

making the dose delivery to tumor a challenge without limiting the organs at risk (OAR) dose. In our institution, we follow induction/neoadjuvant chemotherapy whenever there is high tumor bulk or when the lesion is close to critical OARs.

Role of Intensity Modulated Radiation Therapy (IMRT)

Tumor control for carcinoma nasopharynx highly correlates with the tumor dose. In a retrospective review of 85 patients with NPC, an improved local control was seen when the tumor received > 67 Gy(21). In another series having 118 patients, the improved tumor control was not just due to higher doses delivered to tumor, but also due to improvements in technical accuracy(22). As nasopharynx is surrounded by many critical structures, accuracy in dose delivery is very important in dose escalation.

Intensity-modulated radiation therapy allows very high dose to be delivered to the tumor while sparing the surrounding critical structures. These critical structures include the salivary glands, optic apparatus, brainstem, spinal cord and the auditory apparatus. In addition, IMRT can deliver a higher dose per fraction which yields a biologically more effective dose to the tumor. Therefore, IMRT offers a significant advantage over conventional radiotherapy. Nasopharynx is a site where IMRT can play a key role in improving the therapeutic ratio which can translate into better tumor control. Several studies have proved that IMRT results in improved survival in NPC along with reduced long term toxicities(23) (24) (25) (26) (27). A high dose can be given to the nasopharynx while sparing critical normal structures such as the brainstem, the spinal cord, the optic chiasm, and salivary glands.

At our institute, non-metastatic nasopharyngeal malignancies are treated with IMRT and we had employed the same for our study.

Lacunae in Current Knowledge and Need for Treatment Response Assessment

Response prediction in Nasopharyngeal cancers is very essential as it helps in:

DETECTING EARLY RELAPSES: Although NPC is very radiosensitive, in nearly 7%–13% of cases residual disease persists after treatment(28). Moreover, the appearance of local or distant relapse determines a less favorable prognosis for these patients. Salvage treatment with radiosurgery or brachytherapy has been shown to give excellent tumor control in residual disease(29). Salvage surgery was also proved to achieve long-term survival in patients with local persistent or recurrent NPC who could achieve long-term survival(30). Thus, it is essential to be able to predict and monitor the therapeutic response of patients with NPC.

After treatment, local findings of clinical examination may be unreliable as nasopharyngeal site is not completely accessible at clinical examination. The residual tumor may be sub-mucosal making it unsuitable for biopsy. Moreover, CT imaging may be equivocal or inconclusive for detection of residual NPC due to the presence of diffuse soft-tissue inflammation and edema post radiation therapy at primary site which is often reported as merely an increase or decrease in soft tissue thickening. False-positive findings in CT regarding local persistence of disease detection are mainly correlated with inflammatory changes of the nasopharyngeal mucosa and sub mucosa. Nodal persistence also signifies a poorer prognosis if not detected and appropriately treated with salvage neck dissection. MR imaging is reported as more sensitive in depicting retropharyngeal lymph nodes(31),(32) which are the most frequent lymph node sites affected and not identifiable at clinical examination. Thus, CT imaging is inferior in detecting residual disease both at the primary site and neck nodal region in comparison to functional imaging modalities like PET/CT.

Functional imaging techniques using CT, MRI and positron emission tomography (PET) are increasingly being studied for the evaluation of tumors for staging, planning treatment volumes, assessment of response etc. These techniques exploit pathophysiological changes that occur within tumors such as altered blood flow, increased glucose metabolism, hypoxia and cellularity for tumor detection, monitoring of treatment response and to detect relapsed disease.

1. **TAILORED TREATMENT:** The entire treatment strategy for locally advanced nasopharyngeal cancer has been majorly drawn from the Intergroup 0099 study. With time, the focus has shifted from 'Cure alone' to 'Cure with better quality of life'. The intent of treatment is to achieve cure with least toxicities. Chen L et al. in a well conducted phase 3 randomized trial, found that adjuvant cisplatin and 5 FU (Fluorouracil) chemotherapy did not significantly improve failure-free survival following concurrent chemoradiotherapy (33). In the current era, the whole concept of adjuvant chemotherapy is being questioned for those small cohorts of patients with complete response following chemoradiotherapy. This would potentially prevent physicians form unnecessarily subjecting those 'Complete responders' to adjuvant chemotherapy and its toxicities. This hypothesis however needs to be proven through a well conducted study. Before planning any study on de-escalation therapy, it is important to have:
    1. An accurate predictive tool for response evaluation to therapy
    2. Stringent follow up

And our study is directed to find if Diffusion Weighted MRI is that predictive tool in question.

Role of Functional Imaging Modalities in response assessment

Various Functional imaging modalities have been described in literature, a few are described below:

1. Dynamic Contrast Enhanced Imaging
2. Diffusion Weighted MR Imaging
3. CT Perfusion Study
4. FDG PET
5. Bold Imaging
6. Imaging in Hypoxia

1. Dynamic Contrast-enhanced Imaging

Dynamic contrast-enhanced MR imaging is a non-invasive technique that helps characterize the microvasculature, thereby providing markers specific to perfusion, permeability of blood vessels, and the volume of extracellular space.

Newbold et al demonstrated a statistically significant correlation between various dynamic contrast-enhanced MR imaging parameters, particularly K_{trans} (which represents the permeability of blood vessels) and pimonidazole staining, an exogenous marker for hypoxia.(34) A pilot study done by Donaldson et al, supported the theory that more-hypoxic tumors have poorer vascular function, resulting in VEGF expression to increase blood flow to the tumor.(34) Hypoxia is known to limit the efficacy of radiotherapy and some chemotherapy agent. Non-invasive assessment of tumor micro vascularity with dynamic contrast-enhanced MR imaging could be incorporated in RT planning of Nasopharyngeal tumors, potentially allowing the selection of treatment strategies to combat radiation resistance associated with hypoxia.

2. **Diffusion-weighted Magnetic Resonance Imaging (DW MRI)**

Diffusion-weighted MR imaging is also another non-invasive imaging technique that facilitates tissue characterization on the basis of the molecular motion of water molecules. Diffusion is quantified by using the Apparent Diffusion Coefficient values (ADC). The ADC is inversely correlated with cellularity meaning the more cellular the tumor is, lesser is the space for water molecule motion leading to its restriction for diffusion in the tumor tissue. This limited diffusion of water molecules in a very cellular tumor tissue is represented by a lower ADC value. Subsequently, with treatment as the tumor gets kills, it becomes less cellular and there is higher degree of diffusion of water molecules in the tumor tissue now which would be represented as increase in the ADC value.

The increased density of cells within the primary tumor or malignant lymph nodes reduces their ADC at diffusion-weighted MR imaging.

Study by Kim et al included 33 patients with head and neck SCCs, the change in ADC was used as a marker of tumor response 1 week after the commencement of chemoradiation therapy. Change in tumor ADC after 1 week of treatment had a high sensitivity and specificity for identifying patients who would have a partial or complete response to treatment. The pre-treatment ADC value of complete responders was significantly lower ($P < 0.05$) than that from partial responders. A significant increase in ADC was observed in complete responders within 1 week of treatment ($P < 0.01$), which remained high until the end of the treatment(37). Dirix et al evaluated the usefulness of diffusion-weighted MR imaging for radiation therapy planning and found that patients with local-regional recurrence had lower ADC values within the tumor

after 4 weeks of radiation therapy. This finding suggests that diffusion-weighted imaging would be useful for early identification of responders to treatment.(38)

Multiple studies have been done in head and neck tumors evaluating the role of DW MRI as biomarker for response prediction and they had excluded Nasopharyngeal cancers(NPC). Hence there is a need for such studies in NPC.

3. **Perfusion CT**

Perfusion CT is based on the passage of iodinated contrast material through a region of interest to produce changes in attenuation, which may be used as markers of microvascular blood flow. A kinetic model analysis of these changes in attenuation allows the derivation of several physiologic parameters, including blood flow (BF) or perfusion, blood volume (BV), mean transit time (MTT), and permeability(39)

CT perfusion has been studied in patients with head and neck SCC for the diagnosis and characterization of disease and the prognostication and evaluation of its response to treatment. The development of new blood vessels (i.e. Neo-Angiogenesis), which is an adaptive response to hypoxia in the tumor, is an indirect marker that is demonstrated on perfusion CT as an increase in perfusion, BV, MTT, permeability, or a combination these. The results from numerous studies support the hypothesis that tumors with low perfusion have greater levels of hypoxia and therefore exhibit more resistance to treatment.

4. **FDG PET:**

FDG-PET imaging relies on transport of radiolabelled glucose into the cell, thus providing an indirect way of visualizing abnormal cells.

Treatment Response Assessment

FDG-PET/CT can be used to assess treatment response in tumors, with most studies indicating that the efficacy of treatment not be assessed fully for at least 8–10 weeks after completion due to treatment (Chemotherapy or Radiation) induced inflammation. It is generally accepted that FDG-PET be performed 10–12 weeks after treatment completion to reduce the false-positives

Evaluation for Residual or Recurrent Disease

FDG-PET/CT is one of the most accurate non-invasive modalities presently available for differentiating posttreatment changes from residual or recurrent disease. While there may be false-positives (brown fat, asymmetric muscular activity, inflammation from infection or previous therapy) or false-negatives (small tumor size, low glycolytic activity), the sensitivity and specificity of FDG-PET/CT has been fair (85% and 91%, respectively)

5. **Blood Oxygen Level Dependent Imaging (BOLD Imaging)**

BOLD imaging, also known as intrinsic susceptibility–weighted MR imaging, is a functional imaging technique that is primarily used to evaluate brain activity triggered by exercise or other external stimuli. In recent years, it also has been used as a hypoxia-specific imaging technique. Contrast at BOLD imaging depends on the quantity of paramagnetic deoxyhaemoglobin within red blood cells, which generates an MR signal. BOLD uses a T2 - sensitive sequence during oxygen inhalation to detect an increase in signal resulting from the reduced paramagnetic effect of a reduction in the blood deoxyhaemoglobin within a cancer. As with all functional MR techniques, BOLD presents challenges; the signal is not purely the result of oxygenation, the effects are short lived, and signal changes are small and may be difficult to reproduce.(40) However, despite these difficulties BOLD has been used successfully to detect decreases in the blood deoxyhaemoglobin in human cancers during

carbogen inhalation and shows promise for tailoring treatment for hypoxic cancers in the future. The use of BOLD MR imaging in patients with Nasopharyngeal cancer still under development, and further research must be performed before the technique may be validated and standardized to ensure reproducibility.

6. **Other Modalities of Hypoxia Imaging**

Hypoxia represents a negative prognostic factor for radiation treatment of Nasopharyngeal malignancies and is associated with significant resistance to chemoradiation. Hypoxic cells are resistant to cytotoxic effects of both chemotherapy and ionizing radiation. They require radiation doses much higher than those in the same cells under normoxic condition to achieve the same level of cell kill. Hence, there is growing need in diagnosing hypoxic areas before treatment in the hope of applying novel treatment strategies which might overcome resistance to conventional chemoradiation.

Potential tumor hypoxia imaging agents include ^{18}F-FMISO and copper 60 (II)-diacetyl-bis(N4-methylthiosemicarbazone). ^{18}F-FMISO is bound to cell constituents under hypoxic conditions with the level of hypoxia demonstrated by ^{18}F-FMISO before treatment. Treating patients with hypoxic primary tumors with additional cytotoxin is expected to result in significantly lesser local failures than treating patients with chemotherapy alone. Biologic imaging for hypoxia detection can be crucial for prognostication and tailored therapy.

Rationale for Choosing Diffusion Weighted MRI in our study

1. GOOD ACCURACY WITH MRI

As stated earlier, MRI is a better imaging modality than CT or PET in detecting tumor at primary site and retropharyngeal nodes(11). A study by Comoretto et al compared MRI and PET/CT in detecting residual/recurrent disease in 46 patients treated with chemoradiotherapy

in nasopharyngeal cancers(41). It concluded that MR demonstrated a trend toward higher accuracy than did FDG PET/CT (PPV of 87.1% Vs 85.2%, NPV of 96.9% Vs 86.1%, Overall accuracy of 92.1% Vs 85.7%) in depicting residual NPC at the primary tumor site and fairly well in detecting residual at nodal site (PPV of 83% Vs 95%, NPV of 95% Vs 97%, Overall accuracy of 91% Vs 96%).

2. DWI MRI – MORE ECONOMIC

Serial monitoring of response evaluation would need a minimum of imaging the patient thrice. PET would be much expensive compared to DWI MRI.

Cost of different functional imaging in the institute where this study was conducted:

PET CT – 3 x 22,000= Rs 66,000.00

Functional MRI – 3 x 2265 =Rs 6,795.00

MRI is cheaper with equivalent results as seen with PET.

3. HIGH FALSE POSITIVITY WITH PET IN THE IMMEDIATE POST RT PERIOD

PET imaging poses challenge during immediate post RT period, study performed too early may lead to false positive as well as false negative results. Post-treatment inflammation results in false positivity with resultant reduction in the specificity. Possible mechanism for false negative studies has been attributed to radiation induced vascular damage, which temporarily prevents concentration of radiotracer in the viable tumor cells(42). To strike a balance between misguiding PET results when study was done early and the drawbacks of imaging late, an interval of 12 weeks after completion of radiation is usually recommended. However, PET cannot be used for identifying complete response immediately following RT. MRI would be a more reliable indicator of response evaluation.

4. BETTER TUMOR DELINIATION IN RADIOTHERAPY PLANNING

MRI and PET CT images are often used to guide oncologist in delineating the tumor volume on the planning CT. However, tumor margins are indistinct on PET images because of movement, partial volume effects, and the lower spatial resolution of PET. The lesion appearance is influenced by the quality of the PET scanner, the reconstruction algorithm, and the image display threshold. Without standardization, apparent variations in tumor dimensions occur, making it difficult to ensure uniformity of contouring among different clinicians and facilities(43). MRI provides excellent soft tissue contrast resolution and helps in tumor and critical structure delineation for radiotherapy planning.

Diffusion Weighted Magnetic Resonance Imaging – Biophysical basis

Diffusion Weighted Imaging(DWI) explores the random motion of water molecules in the tissues. Water molecules are in a constant random movement called the Brownian motion. This uninhibited motion of water molecules is due to free diffusion. However, the movement of water molecules in tissues is restricted as their motion is limited ad modified by interactions with cellular membranes and macromolecules(44)

The DWI signal in biologic tissues is derived from the motion of water molecules in the intracellular space, the extracellular space, and the intravascular space. The degree of restriction to water diffusion in biologic tissue is inversely correlated to the tissue cellularity and the integrity of cell membranes. The motion of water molecules is more restricted in tissues with a high cellular density associated with numerous intact cell membranes (e.g., tumor tissue). The lipophilic cell membranes act as barriers to motion of water molecules in both the extracellular and intracellular spaces. By contrast, in areas of low cellularity or where the cellular membrane has been breached, the motion of water molecules is less restricted. A less

cellular environment provides a larger extracellular space for diffusion of water molecules, and these molecules may also freely(45)

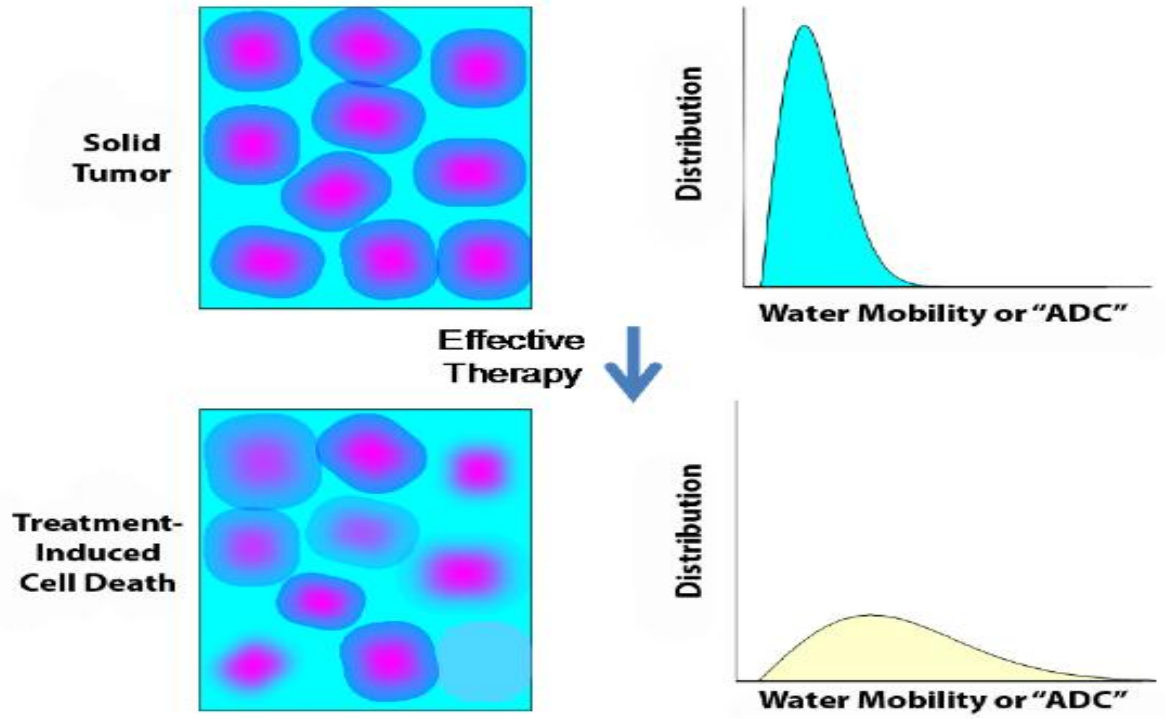


Figure 8: Relationship between change in cellular density following an effective therapy and the corresponding distribution of water diffusion values within tumor. The mean diffusion value of tumor increases early following the loss of cellular density.

Measuring Water Motion - Apparent Diffusion Coefficient (ADC)

The moving water molecules acquire different phase information from the first gradient, but because of their motion, their signal will not be completely rephased by the second gradient, thus leading to a signal loss. Hence, the motion of water molecules is detected as attenuation of the measured signal intensity at DWI. The degree of water motion has been found to be proportional to the degree of signal attenuation.

The sensitivity of the DWI sequence to water motion can be varied by changing the gradient amplitude, the duration of the applied gradient, and the time interval between the paired gradients. On clinical MR scanners, the diffusion sensitivity is easily varied by changing the parameter known as the "b value," which is proportional to these three factors. When the b value is changed, it is usually the gradient amplitude, rather than the duration or time intervals between gradients, that is altered.

Treatment response assessment using Diffusion Weighted MRI

Radiation therapy with chemotherapy as induction or concurrent or adjuvant is the standard of care for Carcinoma Nasopharynx. However, not all patients respond to chemoradiation therapy. Thus, it is important to develop prognostic imaging biomarkers that can accurately predict treatment outcome before initiation of treatment. These imaging biomarkers may help in stratifying patients who would benefit from chemoradiation therapy from those who would not. With the use of Diffusion Weighted MRI (DW MRI), the ADC measurements will be able to predict the response of tumor to chemotherapy and radiation treatment

Effective anticancer treatment results in tumor lysis, loss of cell membrane integrity, increased extracellular space, and, therefore, an increase in water diffusion. Impediments such as cell membranes, organelles, and macromolecules interferes with the free movement of water molecule, this diffusion in biological tissue is quantified by means of an APPARENT DIFFUSION COEFFICIENT (ADC).

With the use of Diffusion Weighted MRI (DW MRI), the ADC measurements will be able to predict the response of tumor to chemotherapy and radiation treatment. Two major factors in predicting response are:

1. Baseline ADC values
2. Magnitude of serial change in ADC values

BASELINE ADC VALUES: Cellular tumor having low baseline ADC values respond better to chemotherapy or radiation treatment than tumors with high baseline ADC values. One possible explanation is that tumors with high baseline ADC values are likely to be more necrotic than those with low values. Necrotic tumors frequently are hypoxic, acidotic, and poorly perfused, leading to diminished sensitivity to chemotherapy and to radiation therapy. Studies in cerebral gliomas and breast cancers have also shown that an early increase in the ADC after commencing treatment was predictive of better treatment outcome.(46)

MAGNITUDE OF SERIAL CHANGE: Diffusion weighted images with quantitative ADC (Apparent diffusion Coefficient) values have shown promise in predicting response to chemo radiation by assessing pre-treatment ADC values and monitoring their magnitude of change serially during treatment at different time frames. This diffusion restriction of water molecules can be assessed quantitatively by using ADC by obtaining two or more images with different gradient duration and amplitudes (which are referred to as different b values).

The term apparent refers to the dependence and modulation of these coefficients/diffusion processes on multiple factors in tissues such as restriction in closed spaces, tortuosity etc. ADC values are calculated automatically by the software and then displayed as a parametric map that reflects the degree of diffusion of water molecules through

different tissues. Then, by use of a dedicated workstation, ADC measurements are recorded for a given region by drawing regions of interest (ROIs) on the ADC map. An ADC of a tissue is expressed as a value in first decimal place x10-3 in units of mm2/sec (Eg: 1.1x10-3 mm2/sec).

Rate of change of ADC values during the course of treatment have also been predictive of response to chemo radiation. Increase in ADC values as seen on subsequent scans with ongoing chemo radiation reflects treatment response as opposed to an inital rise followed by a fall in ADC values which would indicate no response to chemo radiation.

Hence at the start of treatment, tumors are anticipated to be densely cellular, posing a restricted diffusion with a diffusion histogram reflective of this. Shortly after initiation of the treatment, there is breakdown of cellular membranes, which is detectable with a rise in the ADC values. Finally, after the completion of an effective treatment, tumor death leading to further breakdown of cells leading to a further rise in the ADC values. However, the poor or non-responders would not show any significant rise in the ADC values during the course of their treatment owing to the less cellular breakdown resulting in poor response to the treatment to Chemoradiotherapy. These tumors may show an initial rise in ADC values followed by a drop in the same. Thus, the serial monitoring of the ADC values at baseline, 1st week, 4th week and at 6 weeks follow up will help in correlating the ADC values of the responders and non-responders. If the ADC values are found to help in predicting treatment response, this valuable outcome could be utilized for tailoring the treatment care for this group of patients in the future.

Diffusion Weighted MR Imaging in Nasopharyngeal carcinoma: A Predictive Biomarker

Studies conducted in squamous cell carcinoma of head and neck to establish DW MRI as predictive biomarker for response assessment have shown promising results. However, they have excluded Nasopharyngeal malignancies as it forms a distinct entity among the Head and Neck malignancies (37) (47) (48) (49). Studies on DW MRI in Carcinoma Nasopharynx are very limited. Two studies looked at response assessment using DWI-MRI in patients Carcinoma Nasopharynx undergoing chemoradiation. They had showed similar results as seen with other sites in Head and Neck suggesting the usefulness of DW MRI for response prediction in Nasopharynx. Jinsheng Hong, et al proved role of magnetic resonance diffusion-weighted imaging in predicting radiosensitivity in NPC (50) (51). Guo-Yi Zhang et al. showed that pretreatment ADCs could be used as a new pretreatment imaging biomarker of response to neoadjuvant chemotherapy in nasopharyngeal malignancies (52).

There has been no consensus as to an ideal follow-up time for imaging during and post chemoradiation. In a paper published on consensus of DWI imaging as a biomarker in cancers; it was emphasized that if DWI is used as a biomarker, imaging follow-up should be at a time before changes in size become appreciable (53). Study by King AD et al, showed that ADC post-treatment was a marker for local failure. Serial change in ADC was an even stronger marker (54) . Long term time frames may normalize ADC values as liquefactive necrosis resolves and becomes replaced by fibrosis. However, no uniform consensus has been formulated regarding an ideal time for follow. All patients routinely undergo a CT scan at the end of Chemoradiation (i.e. at 4- 6 weeks) to assess response to treatment. As the lesion may be sub mucosal, the NPL scopy may not show a growth. CT scan may show a response which may be reported as a decrease in the thickness in the nasopharyngeal region as well as a

reduction in the size of the nodes. An MRI with DWI and increase in ADC values may in turn give additional evidence of response.

The eventual goal of this line of research is to use DW imaging and its parameters like ADC values at the various stages of treatment to prospectively identify patient who would benefit from concurrent chemoradiotherapy and classify them as responders and nonresponders. This valuable information can be further utilized for the modification of the treatment process, such as a boost of radiation therapy at the end of initial treatment, additional targeted therapies.

MATERIALS AND METHODS

Place of study: Christian Medical College, Vellore, Tamil Nadu, India

Department Registry: Department of Radiotherapy in our Institute, on an average has 14-17 patients of Carcinoma Nasopharynx treated per year

Study Design: Prospective Study

Study Type: Observational

Inclusion Criteria: Patients with biopsy proven nonmetastatic carcinoma nasopharynx and fulfilling the following were be asked to enroll in the study after informed consent.

1. Female or male patients aged 18-70 years

2. ECOG Performance Status of 0 to 2

3. Histologically confirmed carcinoma (Keratinizing, Non- keratinizing or Basaloid)

4. Non- metastatic disease

5. No previous chemotherapy or radiotherapy for any neoplasm/tumor

6. Weight > 35kgs

7. Adequate bone marrow function: WBC > 4000/mm3; Absolute Neutrophil count > 2000/cc platelets > 100,000 mm3

8. Estimated creatinine clearance > 50ml/min/1.73m2

9. Total bilirubin ≤ 1.5 times upper limit of normal (ULN), SGOT and SGPT ≤ 2 times ULN

Exclusion Criteria:

1. Presence of severe or uncontrolled systemic disease

2. Pregnant or breastfeeding mother

3. Contraindication to MRI like MRI incompatible pacemaker / aneurysm clip

Institutional Review Board Approval and Funding:

Institutional Review Board (IRB) approval and fund grant was obtained prior to the commencement of the study (IRB No 10259 dated 05.09.2016) (attached in Appendix 4)

Sample Size Calculation:

The required sample size to show the proportion of response of about 80% with a precision of 15% was found to be 27 subjects who underwent chemoradiotherapy. However due to logistic issues and limited study period, we decided to include 20 patients. (Ref: Jinsheng Hong et al. Value of Magnetic Resonance Diffusion-Weighted Imaging for the prediction of Radiosensitivity in Nasopharyngeal Carcinoma. Otolaryngology – Head and Neck Surgery 149(5) 707–713) with 95% confidence limits.

Single Proportion - Absolute Precision

Expected proportion		0.8	0.8
Precision (%)	1	10	15
Desired Confidence level (1- alpha) %		95	95
Required sample size		61	27

Formula:

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

Where,

p : Expected proportion

d : Absolute precision

1- α/2 : Desired Confidence level

Reference: Lemeshow S, Hosmer DW, Klar J, Lwanga SK. Adequacy of Sample Size in Health Studies. John Wiley and Sons, 1990.

Sampling and Consent: The prospective study patients were seen in the outpatient department of Department of Radiotherapy, Christian Medical College Hospital from September 2016 to September 2017. All patients who fulfilled the inclusion criteria were included in the study. No specific sampling strategy was employed to enrol the patients. The baseline data was entered in a numbered proforma (Annexure 3). Informed written consent was obtained from the patient/ patient relatives prior to the baseline diffusion weighted MRI imaging. The consent form along with the Patient Information Sheet is (attached in Annexure 1 and 2).

Treatment Protocols: Patients diagnosed to have Carcinoma Nasopharynx fulfilling the criteria were assessed based on the clinical examination findings Nasopharngolaryngeal scopy findings and a baseline CT scan and the suitable patients would be subjected to Diffusion weighted MRI imaging which is a non-invasive stud requiring less than 6 minutes to acquire a baseline ADC value. Subsequently the patients received their planned therapy with radical radiotherapy with 66-70 Gy in 33-35 fractions with concurrent 3 weekly Cisplatin spanning over 6 -7 weeks. As part of the study, ADC values were measured at baseline, 1 week, and 4-6 weeks of follow up were compared and analysed for their changes to determine the response to the treatment. At 6 weeks follow up clinical examination, NPL Scopy and a follow up DW

MRI was repeated for evaluation of treatment response. Patients receiving induction chemotherapy were also included in the study.

Data acquisition: MRI imaging was performed on a 3T Philips Achieva scanner with a neck coil. An axial T2HR sequence will be done in the neck from ventricles to clavicle with TE: 90; TR: 3500 and slice thickness of 5mm and slice gap of 5.6 mm. Matrix size used was 362 x 292. DWI images were acquired with b values of 0 and 1000s/mm2 with slice thickness of 5mm.

Data analysis: ADC values are calculated automatically by the software and then displayed as a parametric map that reflects the degree of diffusion of water molecules through different tissues. Then, by use of a dedicated workstation, ADC measurements are recorded for a given region by drawing regions of interest (ROIs) on the ADC map. The DW MR and conventional T2-weighted images were reviewed by a senior radiologist. The radiologist blinded to the treatment outcome. Regions of interest (ROI) were placed on the primary lesions and target metastatic lymph nodes including most of the substantial area and avoid the necrotic area. Metastatic lymph nodes were chosen as per imaging criteria (a minimal axial diameter of 10 mm threshold, including most of the substantial area and avoiding the necrotic area. ADC values were calculated using different b-values, which measures the degree of diffusion weighting applied. A useful rule of thumb is to choose the b value such that (b X ADC) is nearly equal to 1. ADC values were derived from the ROI's drawn over the metastatic nodes and tumor using a free handed drawn setting. Both mean and minimum ADC value were taken into consideration. The difference between Complete Response (CR) and Partial Response (PR)/ non- responders was assessed by Mann Whitney U test. ROC analysis was done to calculate predictive value of ADC as a marker to distinguish responders from nonresponders.

Outcome

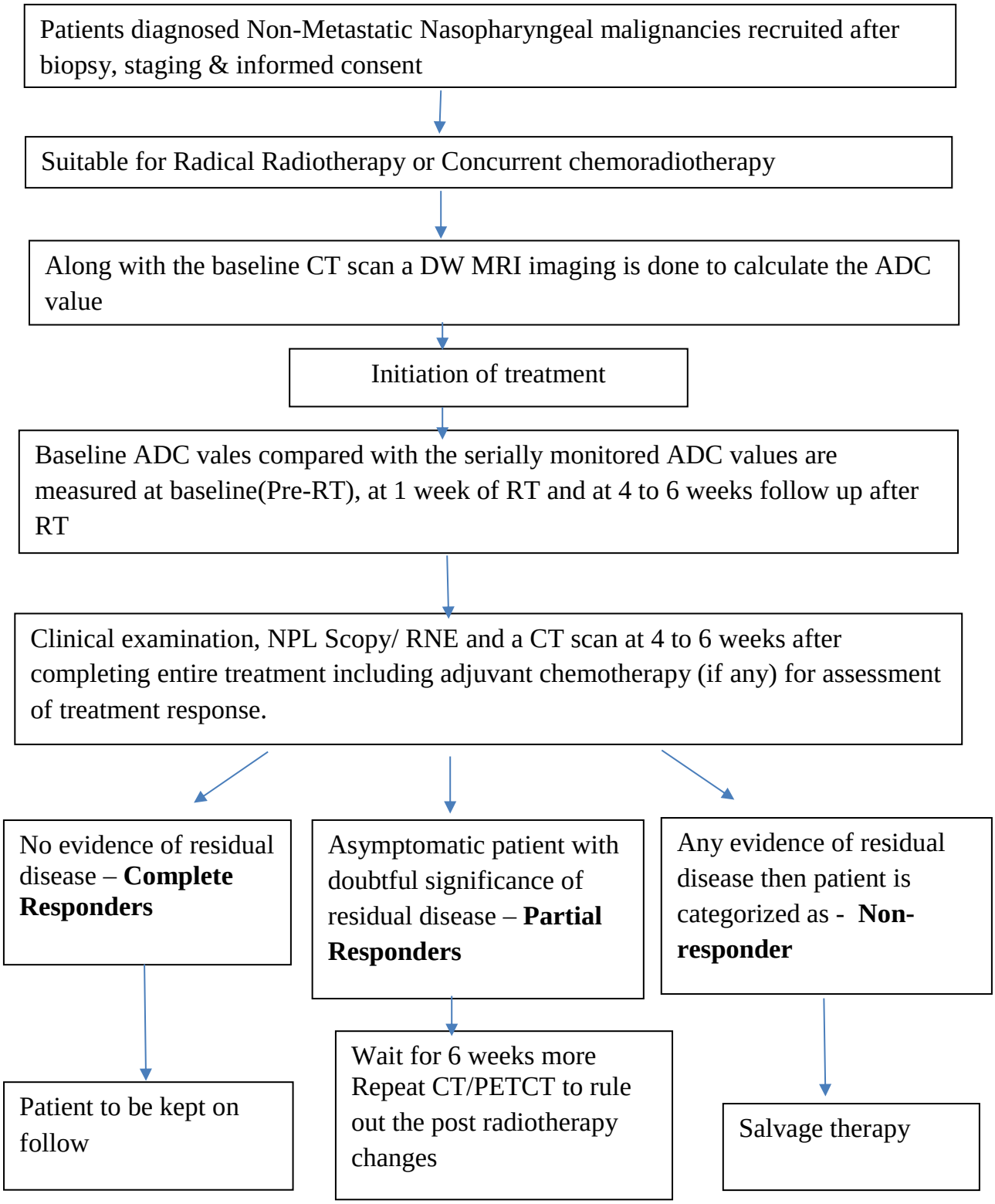
1. Primary Outcome: To study the role of diffusion weighted MRI derived parameters i.e. ADC as an imaging biomarker in non-metastatic nasopharyngeal carcinoma.
2. Secondary Outcome/s: Validating the role of diffusion weighted in detection and characterization of nasopharyngeal cancers as well as for monitoring the response to CRT.

Timing of DW MRI acquisition:

A series of 3 diffusion weighted MRI scans were obtained serially at

1. **Pre- RT:** Prior to initiation of radiotherapy
2. **Week 1:** At 1 week after initiation of Radiation
3. **Follow Up**: On 4-6 weeks follow up after Radiation

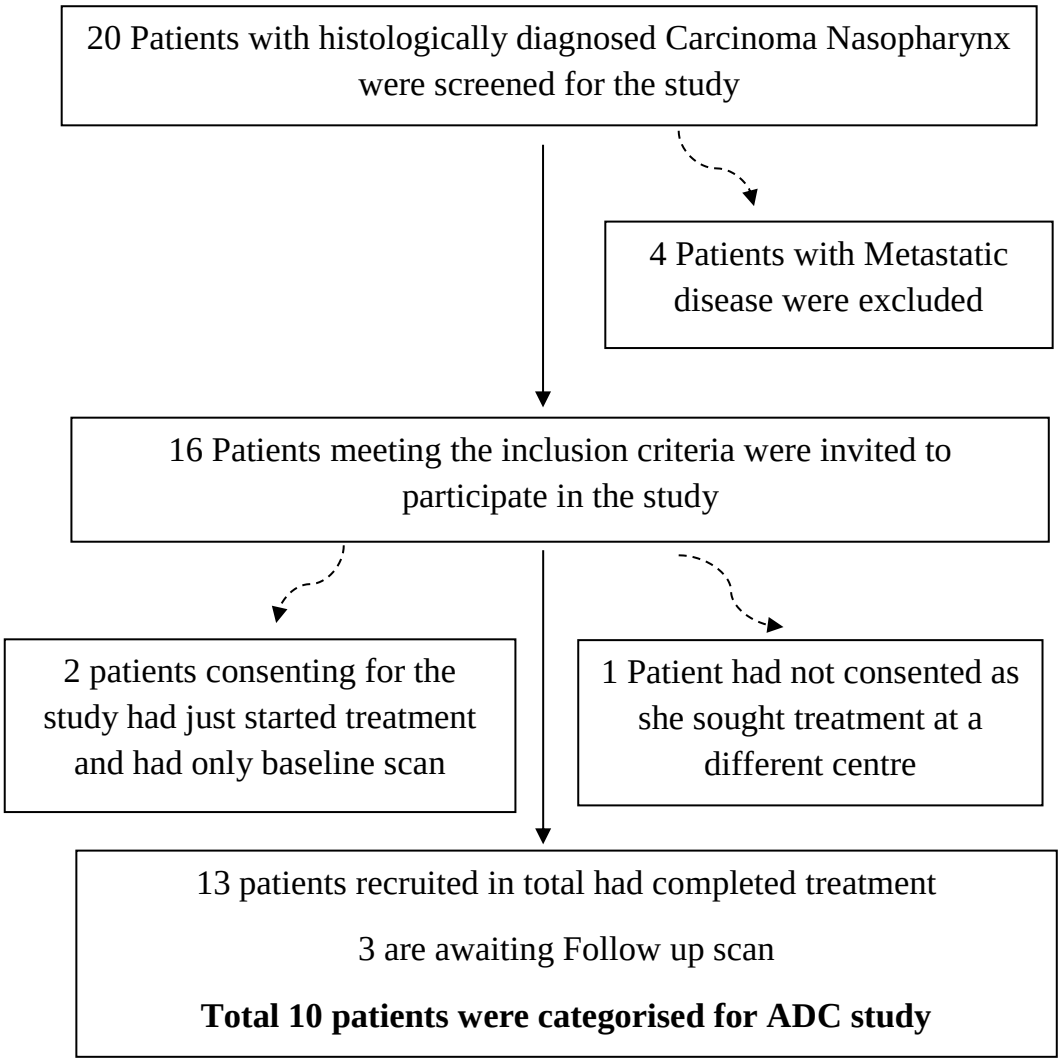
Detailed diagrammatic Algorithm of the study:



RESULTS

Social Demographics

20 patients with histologically proven Carcinoma Nasopharynx were screened and 4 were excluded after reviewing the inclusion criteria. One patient had defaulted treatment. 2 other patients were enrolled into the study at the time of this write up, However, they were included for analysis. 13 were enrolled in this prospective study after informed consent. Pre-treatment diagnostic examinations included Endoscopy, biopsy and baseline contrast-enhanced CT in all patients.



Flow chart: Consort diagram explaining the recruitment of patients for the study

Table 4: Baseline characteristics of patients in the study

CHARACTERISTIC	Category	Number of patients
1. Age	18 – 30 years	5 (38.4%)
	31 – 40 years	3 (23%)
	41 – 50 years	2 (15.3%)
	51 - 60 years	3 (23%)
2. Sex	Male	13 (100%)
	Female	0
3. Comorbidities	Diabetes	3 (23%)
	Hypertension	5 (38.4%)
	Nil comorbidities	7 (53.8%)
4. Histology	Undifferentiated Non-Keratinizing Carcinoma	9 (69.2%)
	Poorly differentiated Carcinoma	4 (30.7%)
	Basaloid	0
5. T stage	T1	2 (15.3%)
	T2	1 (7.6%)
	T3	5 (38.4%)
	T4	5 (38.4%)
6. Node	N0	0
	N1	4 (30.7%)
	N2	7 (53.8%)

	N3	2(15.3%)
7. Stage	Stage I	0
	Stage II	1 (7.6%)
	Stage III	5 (38.4%)
	Stage IV A	5 (38.4%)
	Stage IV B	2 (15.3%)
8. Induction chemotherapy	No Induction chemotherapy	4 (30.7%)
	3 Cycles of Docetaxel, Cisplatin and 5 FU (DCF)	7 (53.8%)
	3 Cycles of Cisplatin and Paclitaxel	2 (15.3%)
9. Radiation therapy (Volumetric Arc Therapy with Simultaneous Integrated Boost)	66 Gray in 33 fractions	1 (8%)
	70 Gray in 33 fractions	10 (76.9%)
	70 Gray in 35 fractions	2 (15.3%)
10. Concurrent chemotherapy	Cisplatin – 40mg/m2 Weekly schedule	2 (15.3%)
	Cisplatin – 100mg/m2 Three Weekly schedule	11 (84.6%)

Age and Sex distribution: 10 of 13 patients were below 50 years of age. 3 of them were in their 6th decade at the time of diagnosis. All thirteen patients were male.

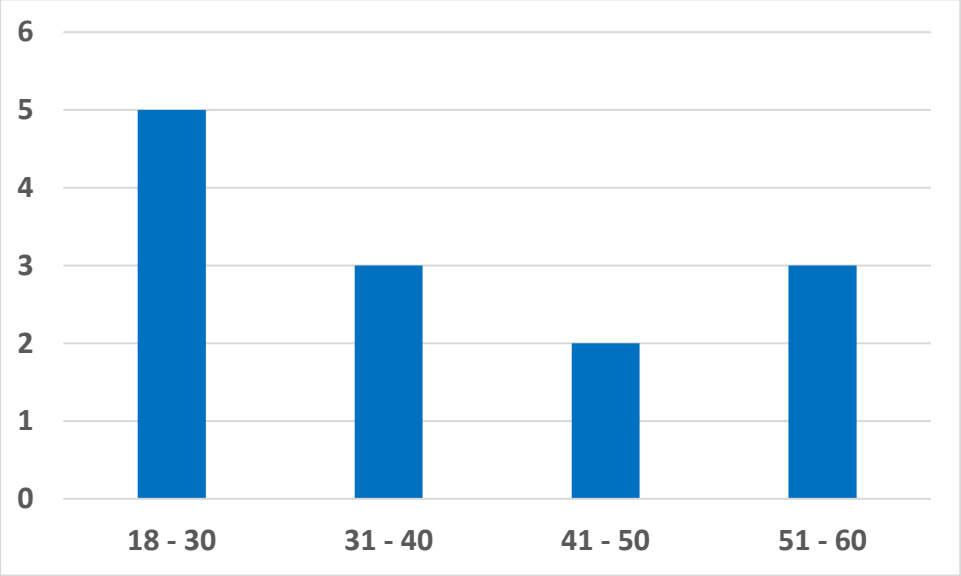


Figure 9: Frequency of Age distribution

Majority of the patients were in stage III and IV A with 5 patients each. Two were of stage IV B and one had stage II disease. None of the patients were in stage I.

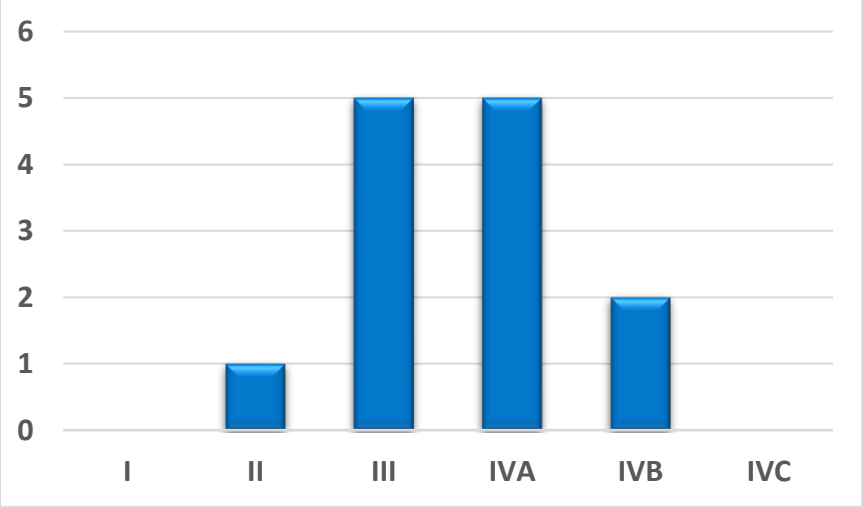


Figure 10: Stage wise grouping of patients

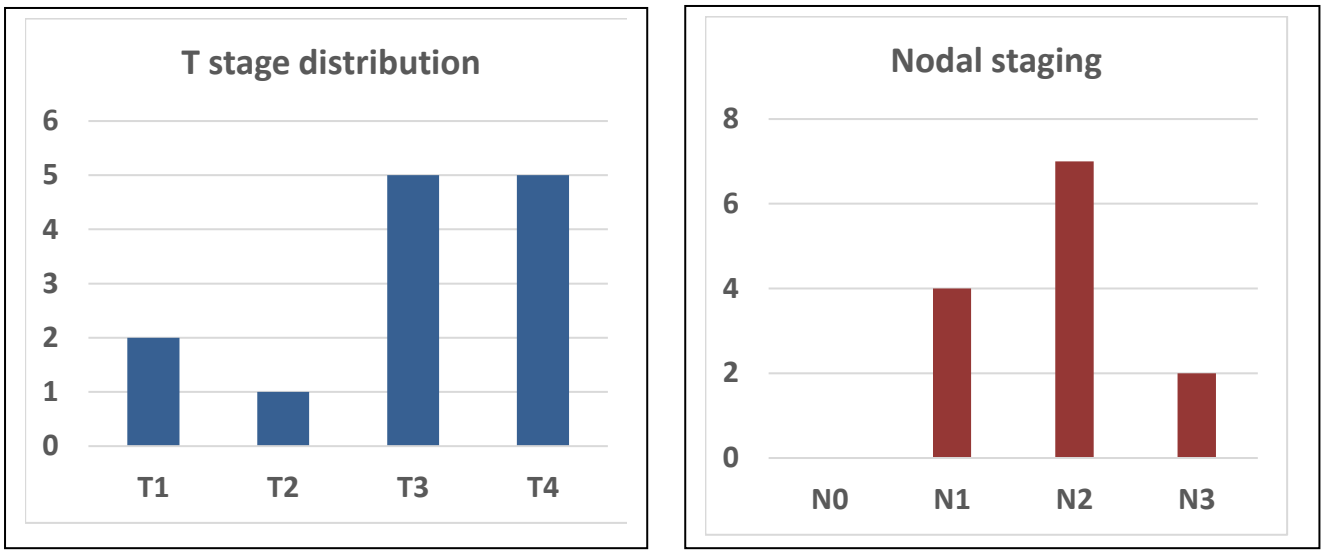


Figure 11: T and N stage of the patients are summarized

Induction Chemotherapy: Induction chemotherapy was given for 9 of 13 patients. Three of them were in stage III and six were in Non-Metastatic Stage IV (four in IVA and two in IVB. Seven out of nine patients received 3 cycles of three drug regimen (Triplet) with Docetaxel, Cisplatin and 5FU. Other two received 3 cycles of two drug regimen (Doublet) with Cisplatin and Paclitaxel. Age, comorbidities were taken in to consideration before choosing between the two Induction chemotherapy schedules.

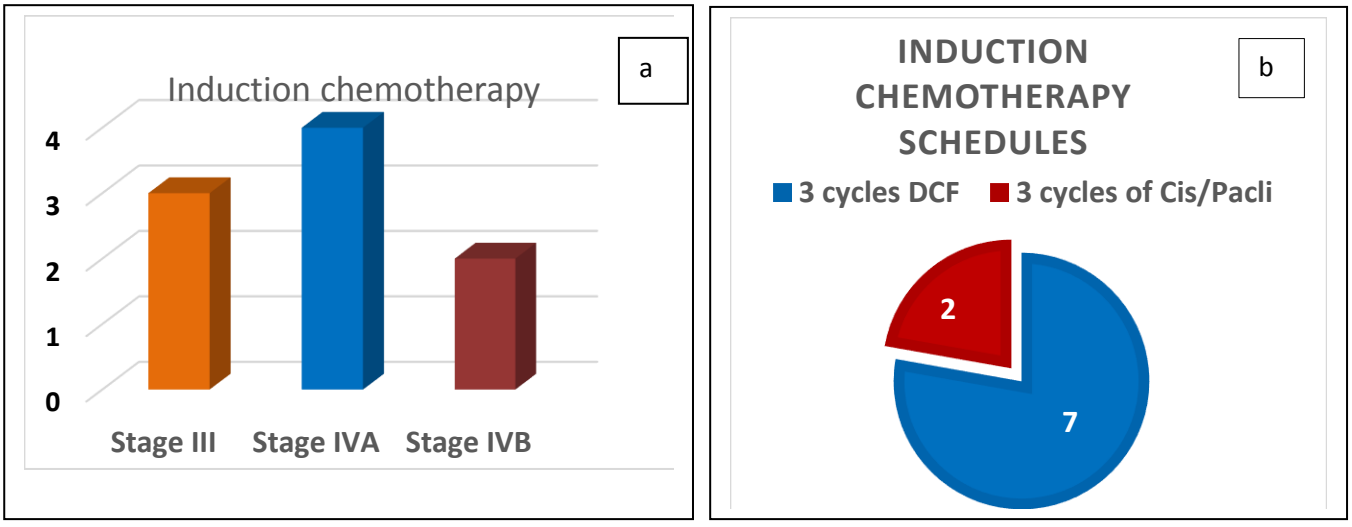


Figure 12a: Patients receiving induction therapy-Stage wise numbers b. Type of Induction chemotherapy

Radiation Schedules: The radical radiotherapy doses ranged from 66-70 Gy in 33-35 fractions using Volumetric Modulated Arc Therapy. Simultaneous Integrated Boost was employed for all patients. They were treated 5 days a week. Mean treatment duration was 7.2 weeks. All of them had completed radiation therapy by around 7 weeks with treatment break of less than 5 days except 2 patients. One of them had a treatment break of 8 days due to grade 3 mucositis and completed RT by 8 weeks and other patient had defaulted treatment for 35 days due to personal reasons and completed RT by 12 weeks.

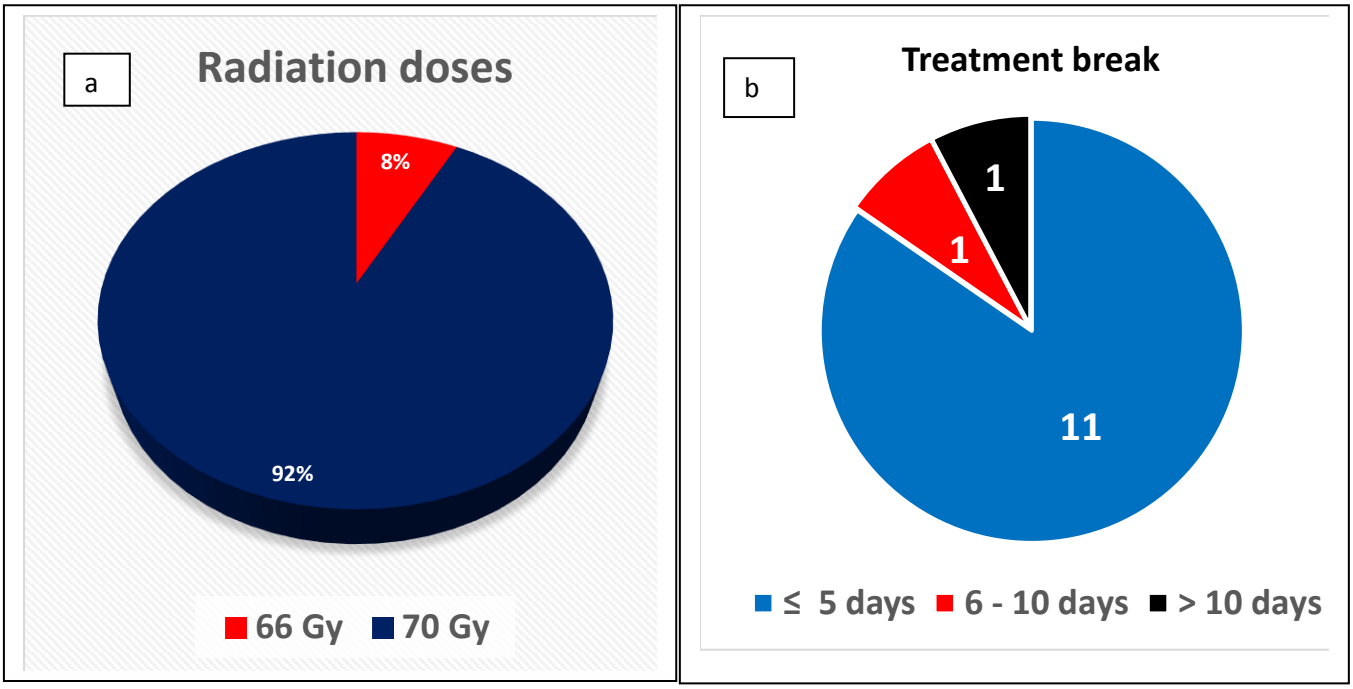


Figure 13a: Pie chart depicting doses received by patients

Figure 13b: Pie chart showing number of days of break in RT

Concurrent Chemotherapy: All patients received concurrent chemotherapy with Cisplatin(CDDP), the schedules followed were:

1. 3-Weekly Cisplatin at 100mg/m2 given every 21 days (CDDP-100mg/m2)
2. Weekly Cisplatin at 40mg/m2 given every 7 days (CDDP-40mg/m2)

11 of 13 received 3 weekly schedules with 100 mg/m2 while the other 2 patients had weekly Cisplatin at 40mg/m2.

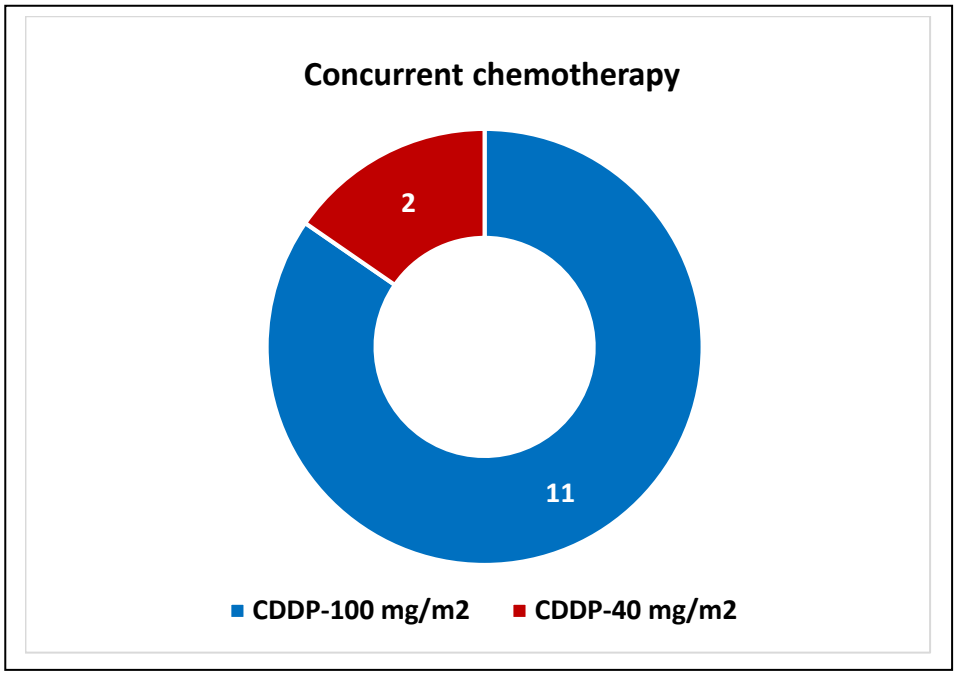


Figure 14: A Doughnut pie chart depicting two different schedules of concurrent Cisplatin(CDDP) and number of patients in each.

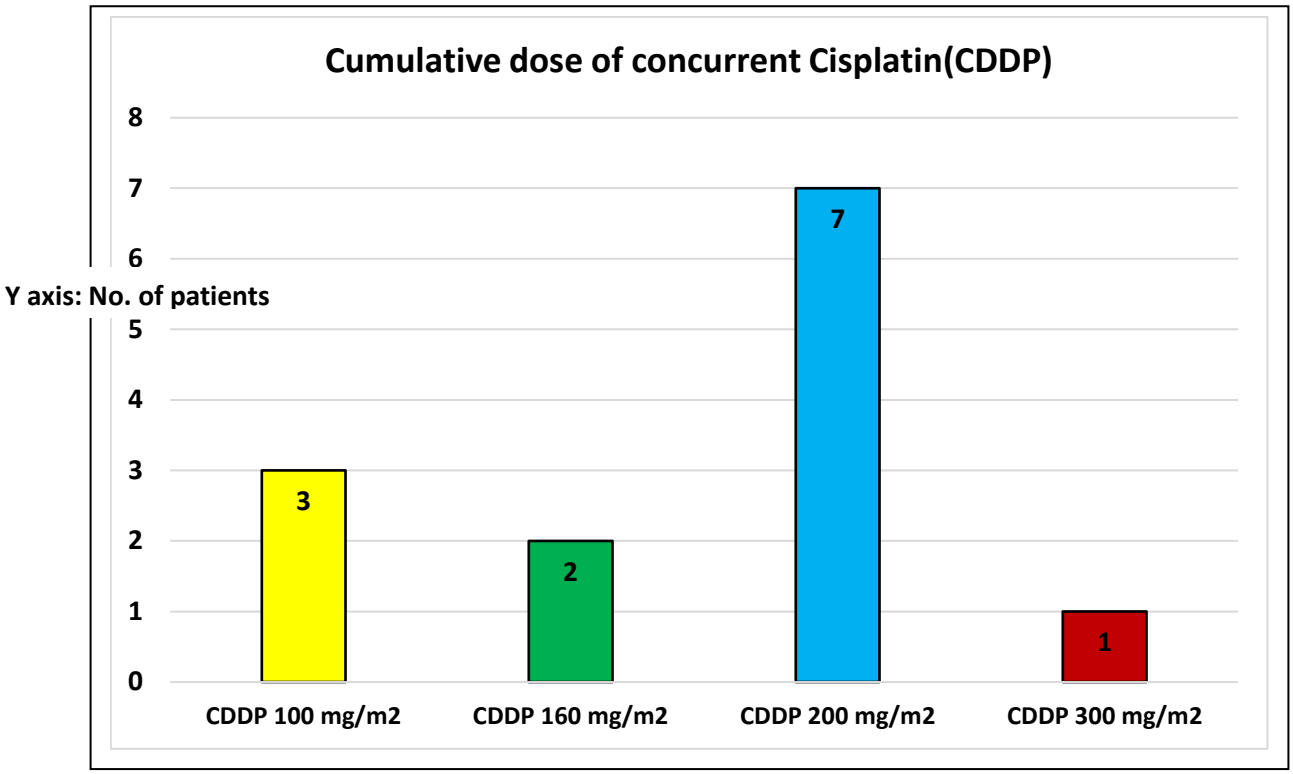


Figure 15: Bar diagram showing Cumulative dose of Concurrent Cisplatin.

X axis indicates total cumulative dose received, Y axis shows number of patients receiving it.

Of the eleven patients who received 100 mg/m2 3-weekly Cisplatin, seven patients had completed two cycles, three patients had received one cycle and one patient had 3 cycles concurrently. Two patients with multiple comorbidities were planned for weekly Cisplatin with 40 mg/m2 and both had received 4 cycles each concurrently.

Table 5: Overview of each patient's treatment

Patient No.	Age / Sex	Stage	Induction chemotherapy	RTdose/Number of fractions	Concurrent chemotherapy
1	18/Male	T3N1	No	66 Gy / 33 fractions	2 cycle of three weekly Cisplatin 100mg/m2
2	45/Male	T3N2	No	70 Gy / 33 fractions	1 cycle of three weekly Cisplatin 100mg/m2
3	58/Male	T4N1	No	70 Gy / 33 fractions	4 cycles of weekly Cisplatin 40mg/m2
4	20/Male	T4N2	3cycles of Docetaxel, Cisplatin and 5FU	70 Gy / 33 fractions	1 cycle of three weekly Cisplatin 100mg/m2
5	50/Male	T1N1	No	70 Gy / 33 fractions	2 cycle of three weekly Cisplatin 100mg/m2
6	40/Male	T3N3	3cycles of Docetaxel, Cisplatin and 5FU	70 Gy / 33 fractions	2 cycle of three weekly Cisplatin 100mg/m2

Continued in next page

Patient No.	Age / Sex	Stage	Induction chemotherapy	RTdose/Number of fractions	Concurrent chemotherapy
7	38/Male	T2N3	3cycles of Docetaxel, Cisplatin and 5FU	70 Gy / 33 fractions	2 cycle of three weekly Cisplatin 100mg/m2
8	22/Male	T3N1	3cycles of Cisplatin and Paclitaxel	70 Gy / 33 fractions	2 cycle of three weekly Cisplatin 100mg/m2
9	57/Male	T4N2	3cycles of Cisplatin and Paclitaxel	70 Gy / 33 fractions	2 cycle of three weekly Cisplatin 100mg/m2
10	34/Male	T4N2	3cycles of Docetaxel, Cisplatin and 5FU	70 Gy / 35 fractions	4 cycles of weekly Cisplatin 40mg/m2
11	29/Male	T1N2	3cycles of Docetaxel, Cisplatin and 5FU	70 Gy / 33 fractions	3 cycles of three weekly Cisplatin 100/m2
12	52/Male	T3N2	3cycles of Cisplatin and Paclitaxel	70 Gy / 35 fractions	1 cycle of three weekly Cisplatin 100mg/m2
13	18/Male	T4N2	3cycles of Docetaxel, Cisplatin and 5FU	70 Gy / 33 fractions	2 cycle of three weekly Cisplatin 100mg/m2

The Diffusion-Weighted Imaging: All MR examinations were performed on a 1.5-T MRI machine. Conventional MRI was performed by using T2-weighted HR axial and diffusion weighted MR imaging. DWI was acquired in 5-6 minutes and ADC was calculated. DWI was performed at three-time points: Pre-radiation, Week one of radiation and on follow up at 6 weeks after the end of treatment. At each assessment, DWI was performed on the same lesion, both for the primary site and the node.

Image Analysis: The ADC was measured on ADC maps by drawing a region of interest (ROI) around the largest area of solid tumour on a single slice identified with the aid of the T2-weighted MR images. The ROIs were drawn by a radiologist blinded to treatment outcome. In addition, the ADC pattern over three-time points was evaluated for the trend with the mean and minimum ADC values to determine response was assessed.

Statistical analysis: Statistical analysis was performed by using SPSS software. ADC values Pre-RT, Week 1 and 6 weeks follow up were expressed as a mean and minimum with a standard deviation. The treatment response assessment was done by evaluating the changes seen in the ADC values. Analysis with ANOVA was done to compare the mean and minimum ADC values and correlation was derived between the Pre-RT ADC, Week 1 ADC and the follow up ADC for Mean and Minimum ADC values. Subsequently the sensitivity and specificity was assessed. Receiver operating characteristic curve (ROC) analysis was performed to determine the Mean and Minimum Pre-RT ADC value that best predicted locoregional failure. All statistical tests were two-sided, and p values less than 0.05 were considered statistically significant.

DWI – MRI OF COMPLETE RESPONDER: Primary lesion

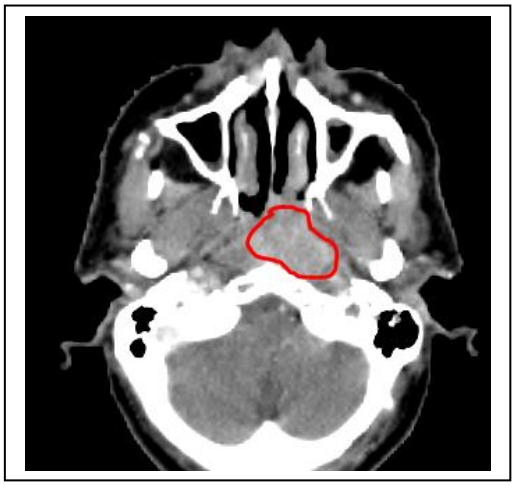
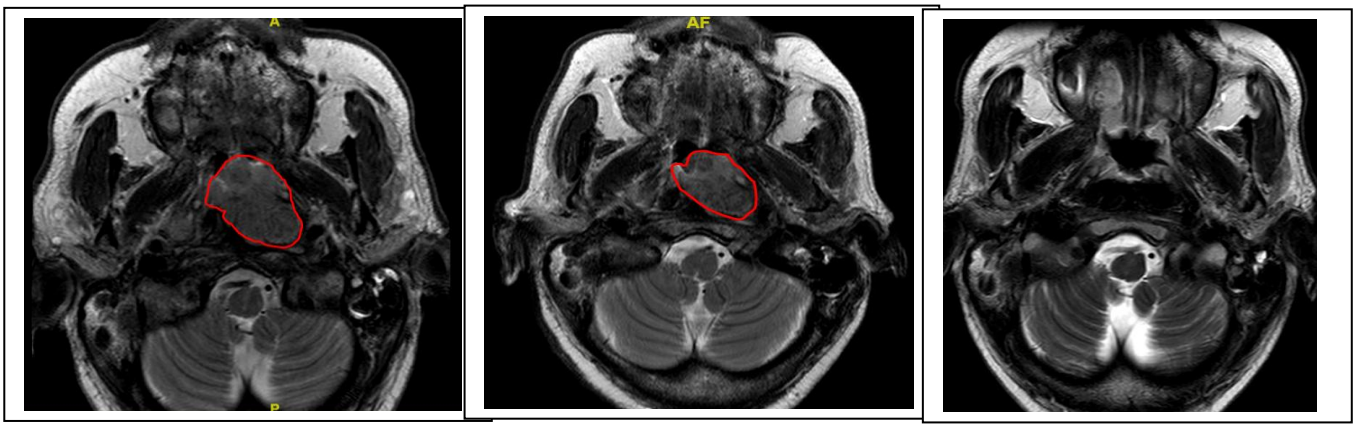
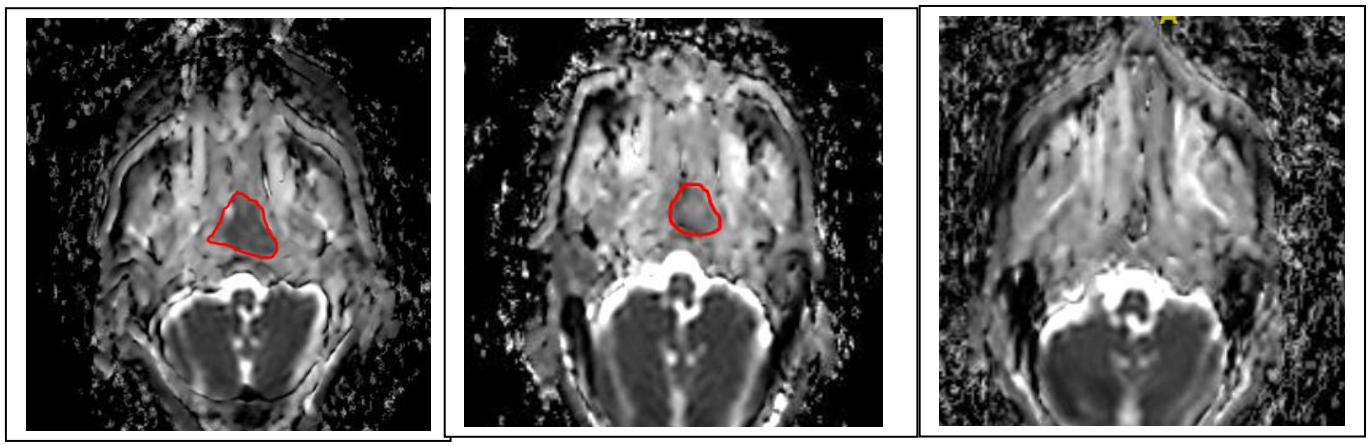


Figure 16: CT Imaging of a Complete responder showing primary lesion at Diagnosis



A. Pre-RT B. Week 1 of RT C. Follow up

Figure 17 A, B &C: T2 Weighted Imaging of the primary lesion of the same patient (Complete Responder) over the three-time periods



A. Pre-RT B. Week 1 of RT C. Follow up

Figure 18 A, B & C: ADC map of primary lesion of the same patient (Complete Responder) over three-time periods

DWI – MRI OF COMPLETE RESPONDER: Node

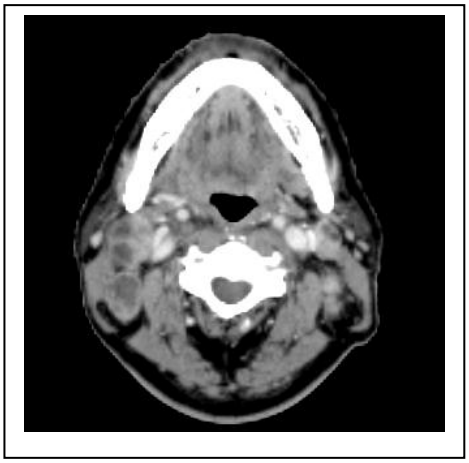
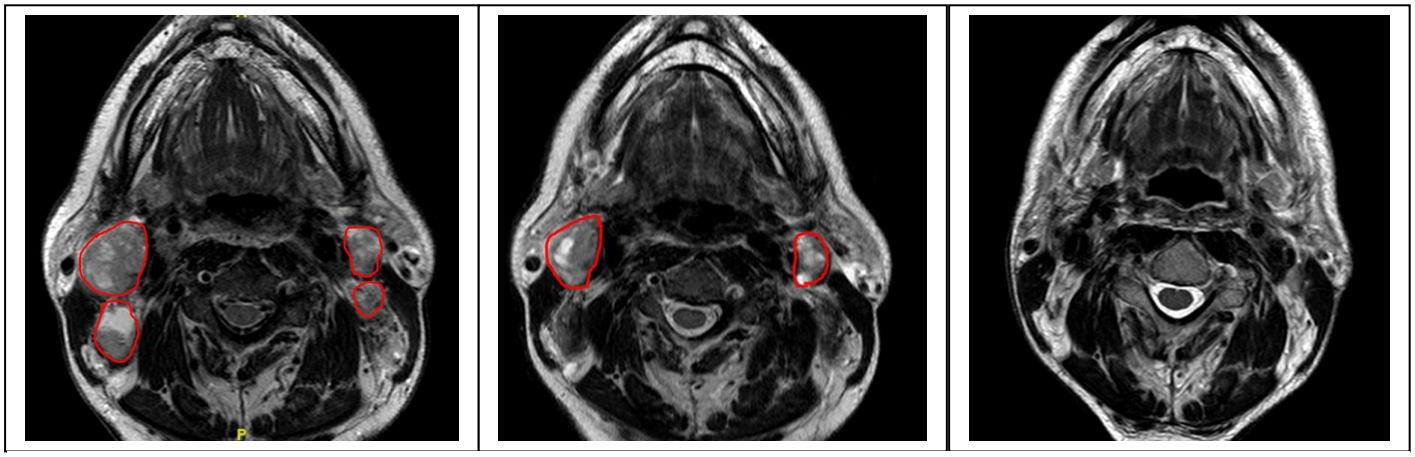
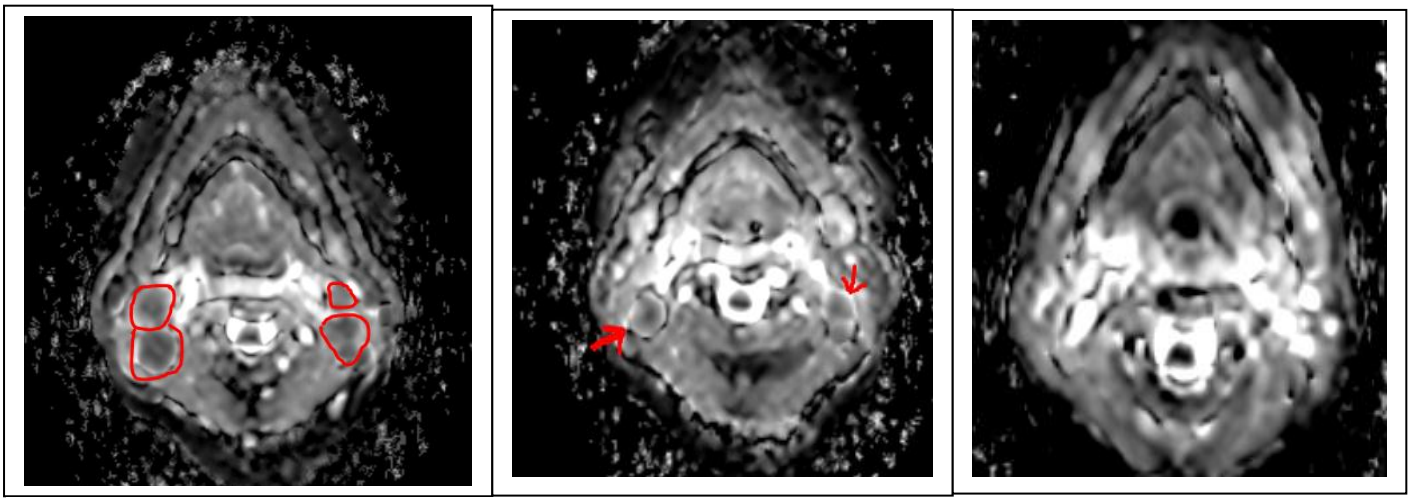


Figure 19: CT scan of a Complete responder showing multiple level II nodes



A. Pre-RT B. Week 1 of RT C. Follow up

Figure 20 A, B &C: T2 Weighted Imaging of the Node of the same patient (Complete Responder) over the three-time periods



A. Pre-RT B. Week 1 of RT C. Follow up

Figure 21 A, B &C: ADC of the Node of the same patient (Complete Responder) over the three-time periods

DWI OF A PARTIAL RESPONDER: Primary

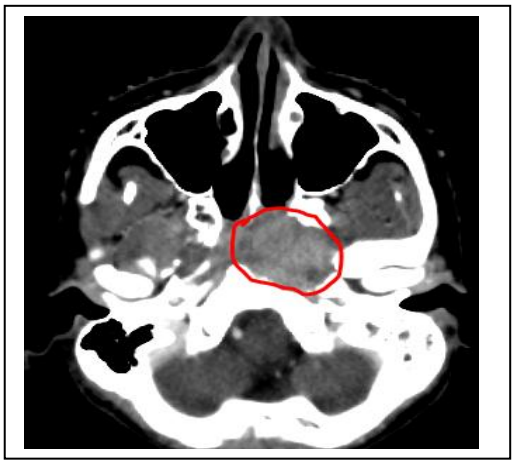
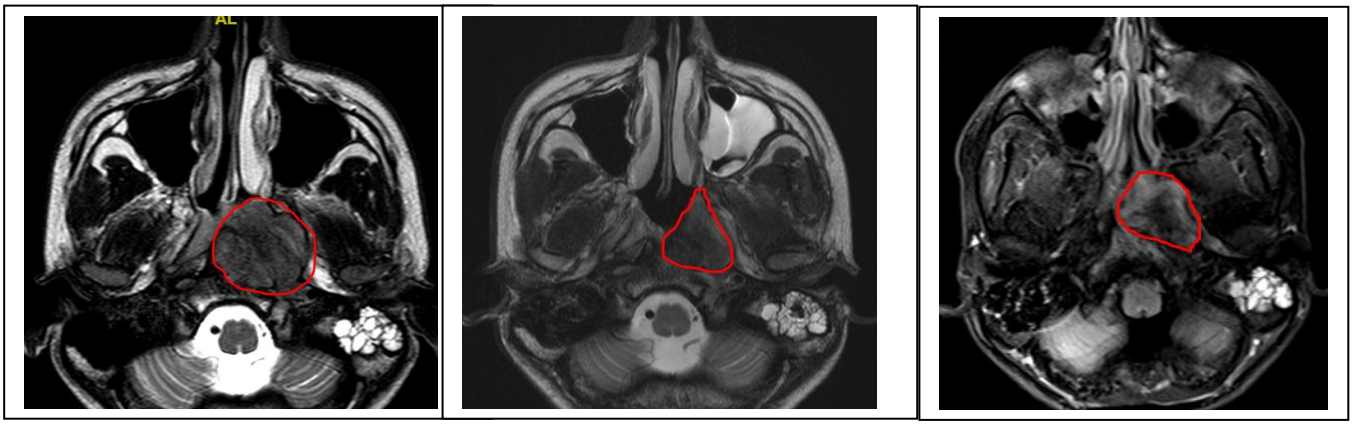
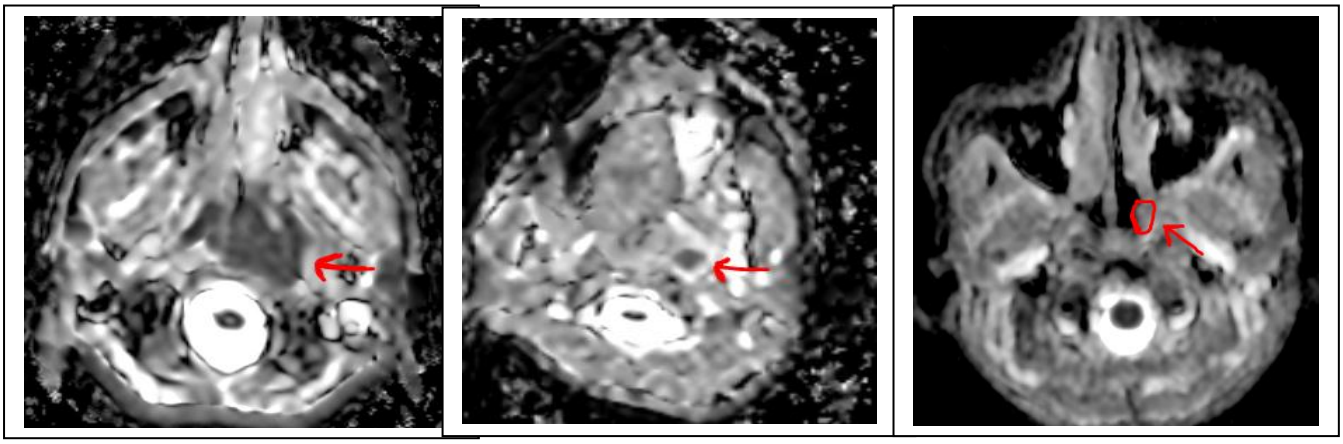


Figure 22: CT Imaging of a Partial responder showing primary lesion at Diagnosis



A. Pre-RT B. Week 1 C. Follow up

Figure 23 A, B &C: T2 Weighted Imaging of the primary of the same patient (Partial Responder) over the three-time periods



A. Pre-RT B. Week 1 C. Follow up

Figure 24 A, B &C: ADC map of the primary of the same patient (Partial Responder) over the three-time periods

DWI – MRI IN PARTIAL RESPONDER: Node

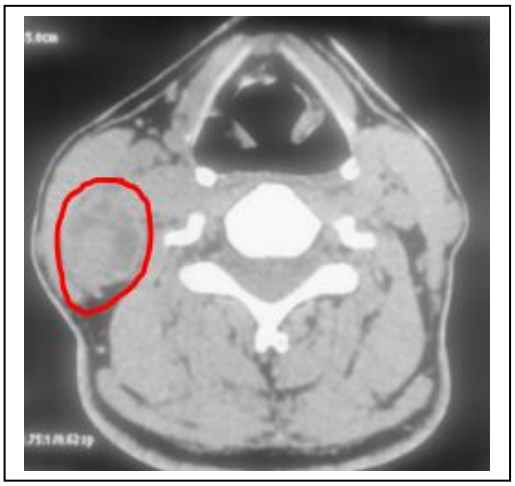
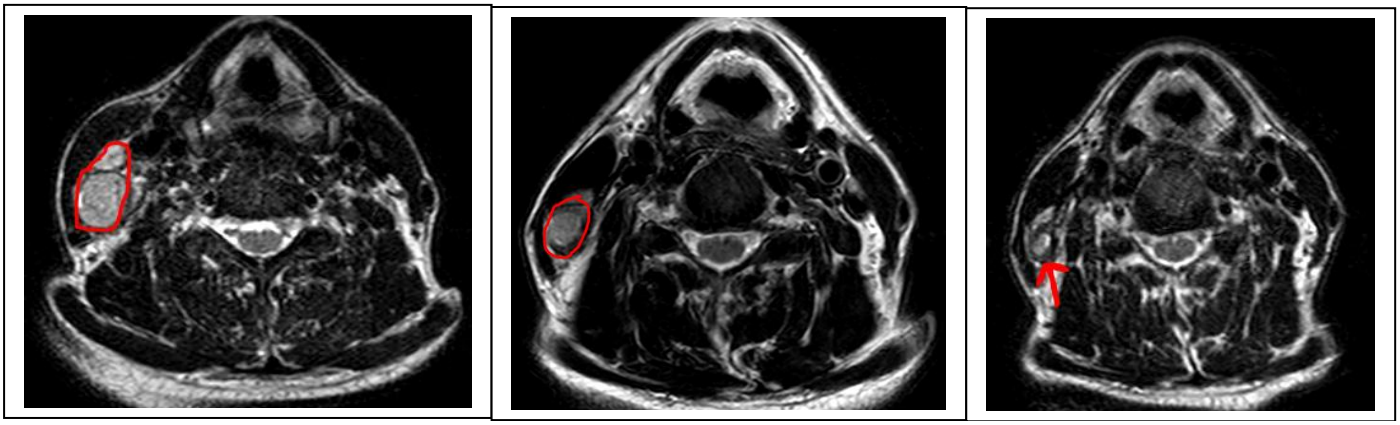
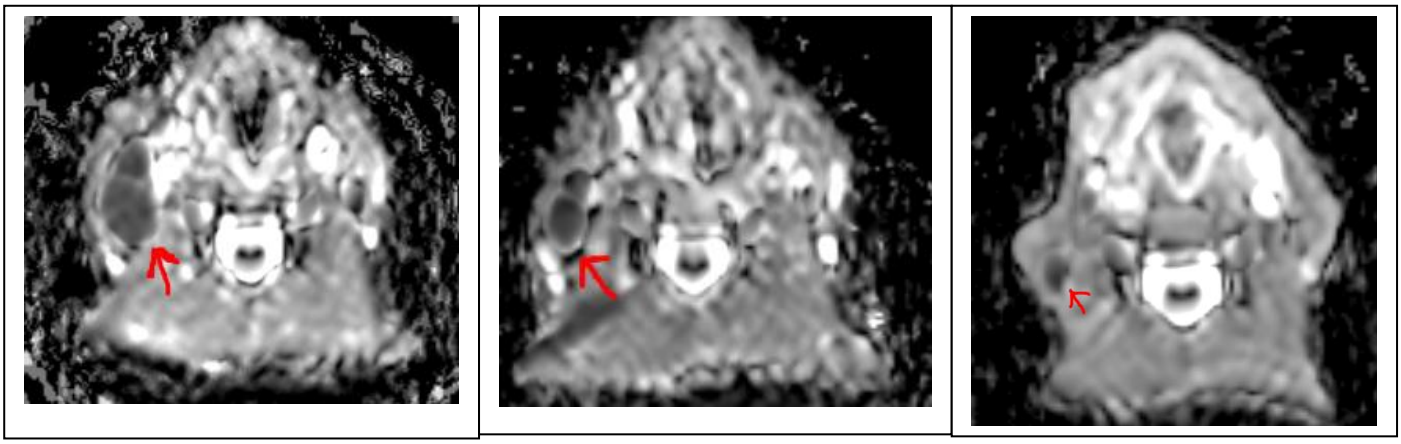


Figure 25: CT image of a Partial responder showing right level II node



A. Pre-RT B. Week 1 of RT C. Follow up

Figure 26 A, B & C: T2 Weighted Imaging of the primary of the same patient (Partial Responder) over the three-time periods



A. Pre-RT B. Week 1 of RT C. Follow up

Figure 27 A, B & C: ADC map of a Node of the same patient (Partial Responder) over three-time periods

STACK DIAGRAM:

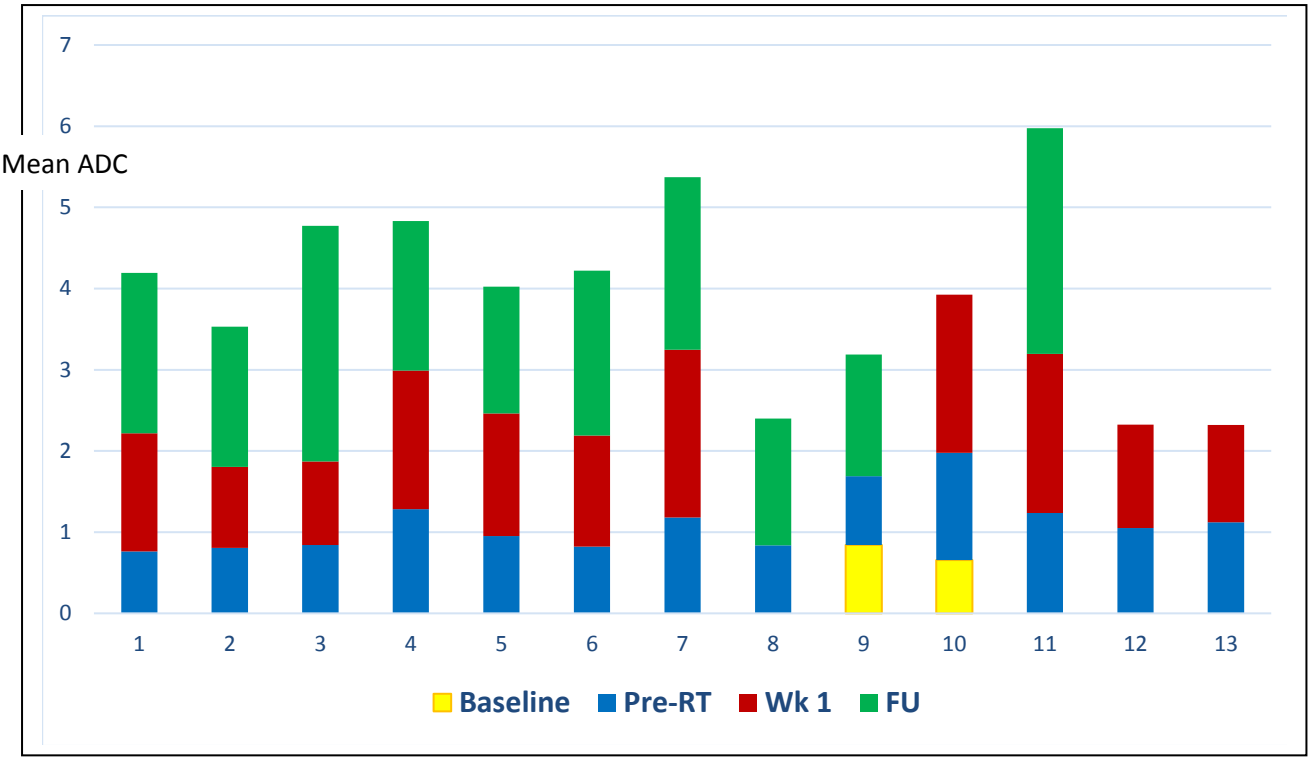


Figure 28: Stack diagram showing Mean ADC distribution of our patient cohort

This stack graph is representative of the Mean ADC distribution of our patient cohort. In our study group patient 8 and 9 did not have Week 1 Imaging due to technical issues and hence the ADC couldnot be calculated at these timepoints. All the 13 patients, an increasing trend in the ADC values at three different time points was observed. Patient 10, 12 and 13 had just completed treatmet at the time of analysis and their follow up scans were awaited. Hence we analyssed with total of 10 patients. They were categorised at the end of the treatmet as Completed Responders and Partial Responders based on clinical, Endoscopy or CT scan findings.

COMPLETE RESPONDERS	PARTIAL RESPONDERS
5 patients	5 patients

Complete Responders: The absence of any residual lesion on clinical examination, Endoscopy (Rigid nasal endoscope) or by CT scan was defined as complete response.

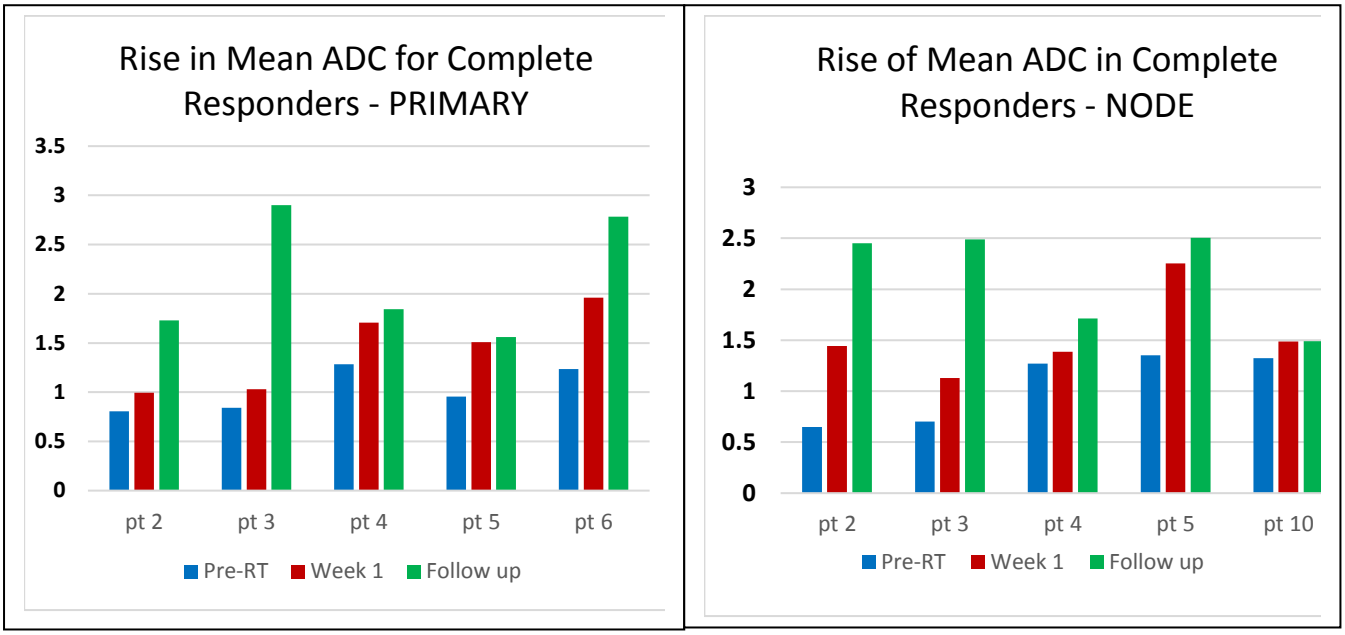


Figure 29: Bar diagram representing rise in MEAN ADC values for COMPLETE RESPONDERS for both Primary and the Node. ADC values in: (x 10-3 mm^2/s)

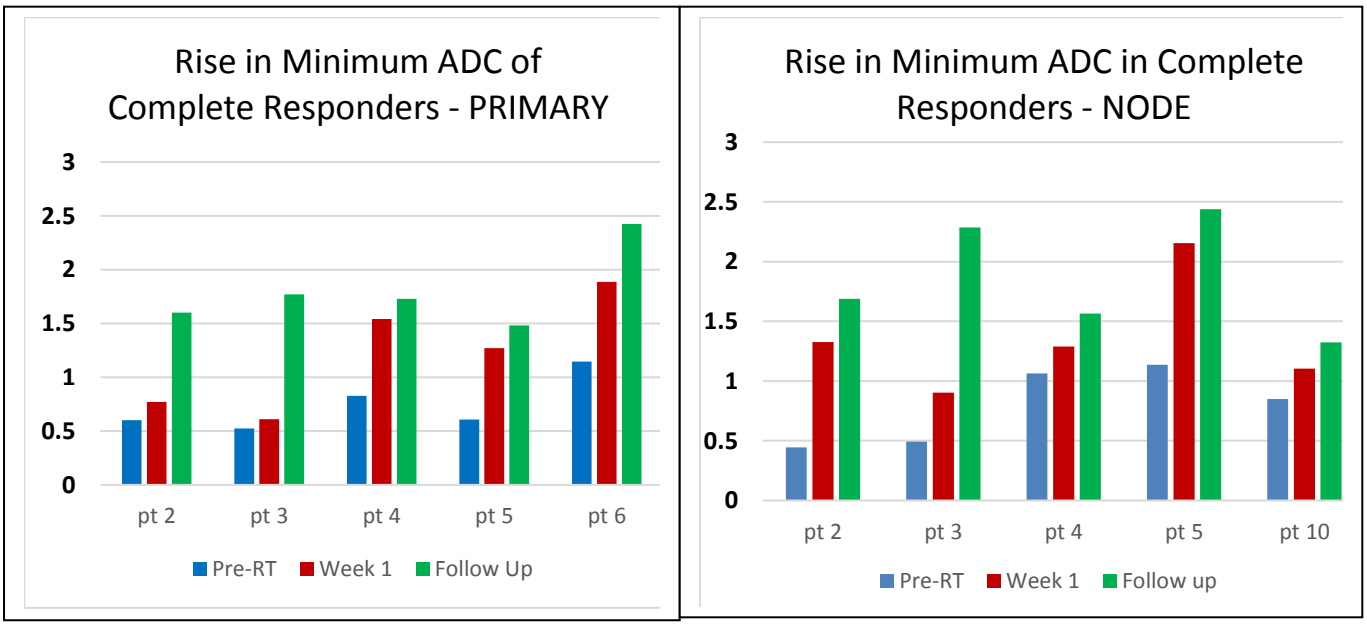


Figure 30: Bar diagram representing rise in MINIMUM ADC values for COMPLETE RESPONDERS for both Primary and the Node. ADC values in: (x 10^{-3} mm^2/s)

Complete Responders: The study of the general trend of the mean and minimum ADC variation in these subset of patients revealed an increase in the ADC values among the subsequent dWMR imaging. In our study, 5 patients had complete response by 6 weeks follow up. Among these 5 patients, the Week 1 DWI-MRI did not show any visible disease for 4 patients.

Visual Restriction: The diffusion restriction as seen on ADC map is termed Visual restriction. It is a qualitative expression of diffusion restriction. We had used visual restriction for Response predication. We found that the 4 patients in complete responder had no visual restriction on the ADC mapping at Week 1 DWI-MRI.

Impact of Stage, Histology, Radiation and Chemotherapy: Three patients belonged to Undifferentiated histology. Two out of five patients were in Stage IVA with poorly differentiated histology. All 5 had received RT doses of 70 Gy. Only two had induction chemotherapy

Patient no.	**Stage**	**Histology**	**Radiation doses**	**Induction chemotherapy**
2	III	Undifferentiated	70 Gy / 33 #	No
3	IV A	Poorly differentiated	70 Gy / 33 #	No
4	IV A	Poorly differentiated	70 Gy / 33 #	3 Cycles of Docetaxel, Cisplatin and 5 FU (DCF)
5	II	Undifferentiated	70 Gy / 33 #	No
11	III	Undifferentiated	70 Gy / 33 #	3 Cycles of Docetaxel, Cisplatin and 5 FU (DCF)

Table 6: Overview of treatment and patient factors in complete responders

Partial Responders: The presence of any residual lesion on clinical examination, Endoscopy(RNE) or by CT scan was defined as partial response.

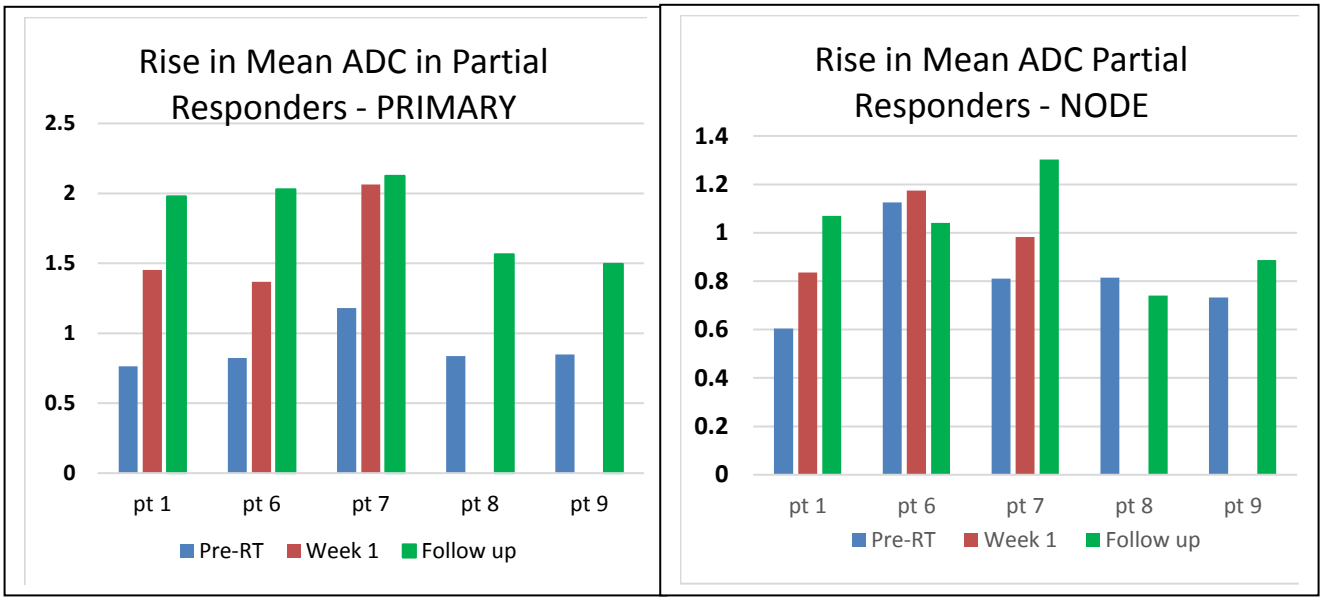


Figure 31: Bar diagram representing rise in MEAN ADC values for PARTIAL RESPONDERS for both Primary and the Node. ADC values in: (x 10^{-3} mm^2/s)

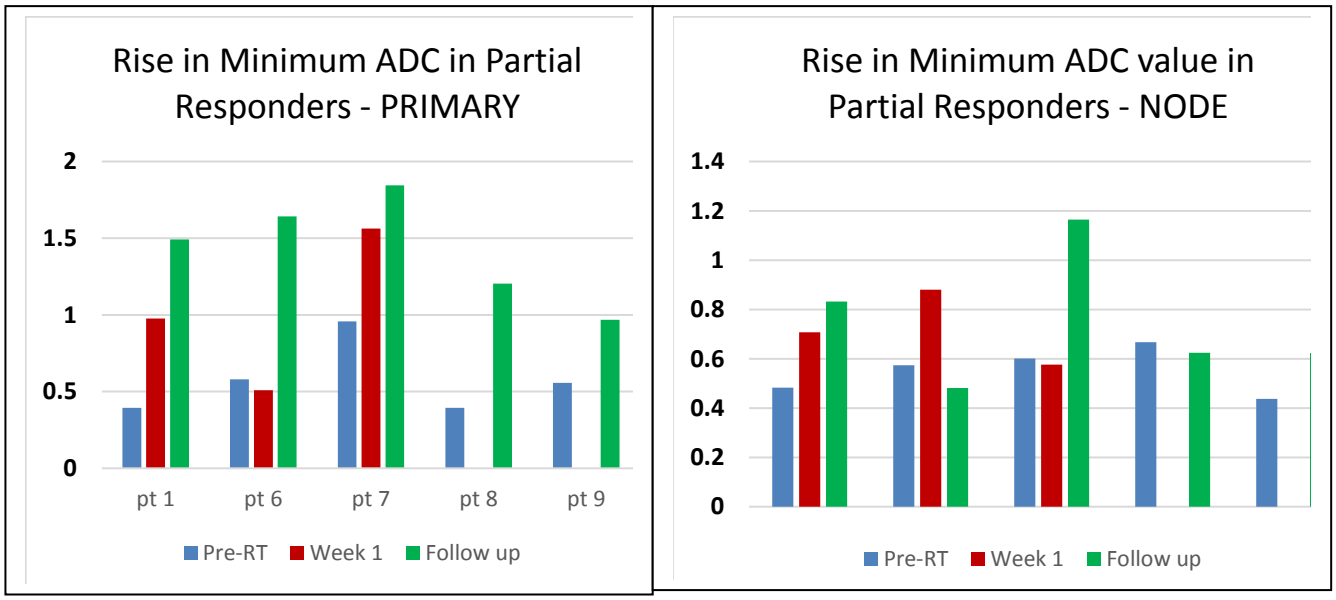


Figure 32: Bar diagram representing rise in MIMIMUM ADC values for PARTIAL RESPONDERS for both Primary and the Node. ADC values in: (x 10^{-3} mm^2/s)

Partial Responders:

In our study, 5 patients had residual disease by 6 weeks follow up. The study of the general trend of the mean and minimum ADC variation in partial responders also had revealed an increase in the ADC values among the subsequent DWI-MR imaging. Among these 5 patients, the Week 1 DWI-MRI had shown residual disease for 3 patients.

Visual Restriction: Visual restricted was used for partial responers for response prediction. Visual restriction was present for primary for 3 and all 5 of them at visual restriction at node on ADC mapping on DWI-MRI at Week 1.

Impact of Stage, Histology, Radiation and Chemotherapy: There were 3 patients with Undifferentiated histology and 1 with Poorly differentiated histology. Two of them had N3 disease putting them in stage IV B. Two patients were in stage III and the other one was stage III. Four out of five patients received induction chemotherapy except one. Four had received RT doses of 70 Gy. Only one patient who had received 66 Gy in the study was found to have residual at primary.

Correlation of response with Other modalities: Patients categorised as partial responder also had either PET-CT or biopsy of the residual to validate the results and they were depicted in table 7. Three patients who were classified as Partial responders also had proven residual on PET-CT and two other patients were false positives.

False Positives:

1. Patient 8 : This patient was found to have a residiual node as on clinical examination at follow up. MRI and CT performed had releaved residual at right level II which had increased in size as compared to Pre-RT. His case was discussed in Multidiscplinary tumoe board and he underwent salvage neck dissection as per decision. Histopathology was reported as necrotisng granulomatous inflammation with acid fast bacilli suggestive of Tuberculous lymphadenitis and was started on antituberculosis therapy (ATT) soon after that.

2. Patient 9 : This patient had residual at primary site on rigid nasal endoscopy. Biopsy from the site reported chronic inflammation. On CT, he was found to have extensive infective ethmoidal and maxillary sinsitis . He underwent FESS for the same.

We had inferred that conditions like tuberculous lymphadenitis would mimic residual at nodal site. Also infective conditions of the surronding structures in the region of Nasopharynx would lead to the suspicion of recurrence. These would have a bearing on our study as these patients in real sense were responders to therapy who were classeifed as Partial responders based on RNE, Clinical and CT findings.

We suggest confirmation by biopsy remains the gold standard for diagnosing residual disease as these would result in a false positive result.

Table 7 continued in next page

Table 7: Overview of treatment and patient factors in partial responders

Patient	**Stage**	**Histology**	**Radiation doses**	**Induction chemo**	**Site of failure on DWI-MRI**	**Residual on as seen on PET-CT**	**Biopsy**
1	III	Undifferentiated	66 Gy / 33 #	No	Primary	Primary	No biospy
6	IV B	Undifferentiated	70 Gy / 33 #	3 Cycles of DCF	Node	Node	No biopsy
7	IV B	Poorly differentiated	70 Gy / 33 #	3 Cycles of DCF	Primary & Node	Priamry & Node	No biopsy
8	III	Undifferentiated	70 Gy / 33 #	3 Cycles of DCF	Node	No PET	Necrotising granulomatous inflammation postivie for acid fast bacilli
9	IV A	Poorly differentiated	70 Gy / 33 #	3 Cycles of DCF	Primary	No PET	Necrosis with Chromic inflammation, artefacts present.

Complete Responder Vs Partial Responder

1. **Mean Baseline ADC:** Correlation was made between the Mean Pre-RT ADC and the nature of response obtained. The Mean ADC values were higher for Complete responders for the minimum, maximum and median values. In the primary lesion, the complete responders had a minimum Pre-RT ADC of $0.8x10^{-3}$ and a maximum of $1.2x10^{-3}$. When compared to the partial responders in whom the mean Pre-RT ADC values ranged from $0.7x10^{-3}$ to $0.8x10^{-3}$ as seen in the table below. Similarly, for the node, the Pre-RT ADC values were higher for complete responder than Partial responder in terms of minimum, maximum and median values.

PRIMARY TUMOR	Minimum Pre-RT ADC (In mm2/s)	Median Pre-RT ADC (In mm2/s)	Maximum Pre-RT ADC (In mm2/s)
Complete Responders	**0.8×10^{-3}**	**1×10^{-3}**	**1.2×10^{-3}**
Partial Responders	**0.7×10^{-3}**	**0.8×10^{-3}**	**1.1×10^{-3}**

NODE	Minimum Pre-RT ADC (In mm2/s)	Median Pre-RT ADC (In mm2/s)	Maximum Pre-RT ADC (In mm2/s)
Complete Responders	**0.6×10^{-3}**	**1×10^{-3}**	**1.3×10^{-3}**
Partial Responders	**0.4×10^{-3}**	**0.6×10^{-3}**	**1.1×10^{-3}**

2. **Visual Restriction:** The diffusion restriction as seen on ADC map is termed Visual restriction. It is a qualitative expression of diffusion restriction. We had used visual restriction for Response predication. We found that the 4 patients in complete responder had no visual restriction on the ADC mapping at Week 1 DWI-MRI. Whereas in Partial Respnders, Visual restriction was present for primary for 3 and all 5 of them at visual restriction at node. This proves that Visual restriction has the potential to predict reposnse to treatment as early as 1 week.

VR Wk1 * Response

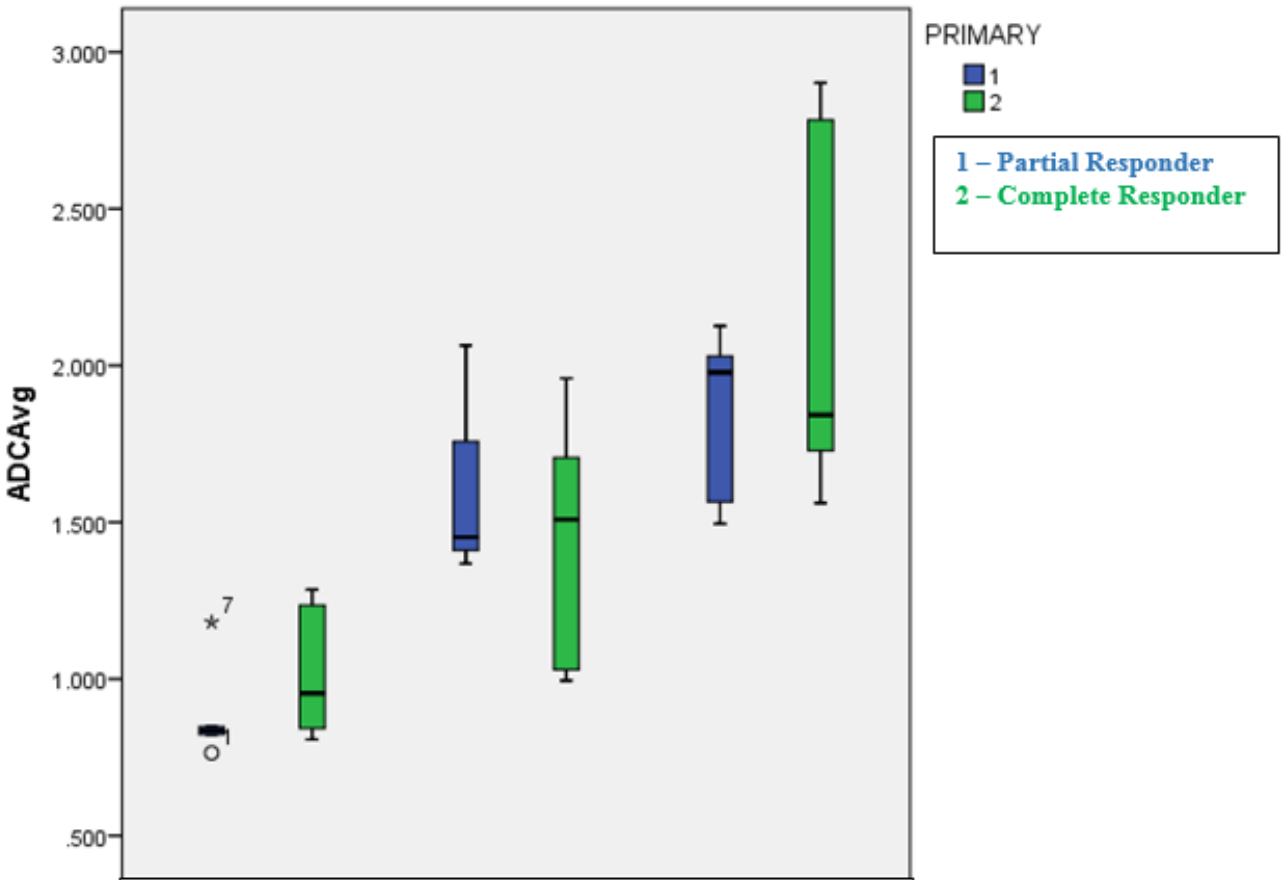
Crosstab

			Response		Total
			Complete Responders	Partial Responders	
VRW1	Absent	Count	4	2	6
		% within VRW1	66.7%	33.%	100.0 %
		% within resp	80.0%	40%	75.0%
	Present	Count	1	3	4
		% within VRW1	25%	75%	100.0 %
		% within resp	20.0%	60%	25.0%
Total		Count	5	5	10
		% within VRW1	50%	50%	100.0 %
		% within resp	100.0%	100.0%	100.0 %

Figure 33: Cross table showing presence or absence of Visual restriction of primary tumor on ADC map of DWI-MRI at Week 1 and its correlation with response assessment (p value: 0.6)

3. Rate of change in ADC values

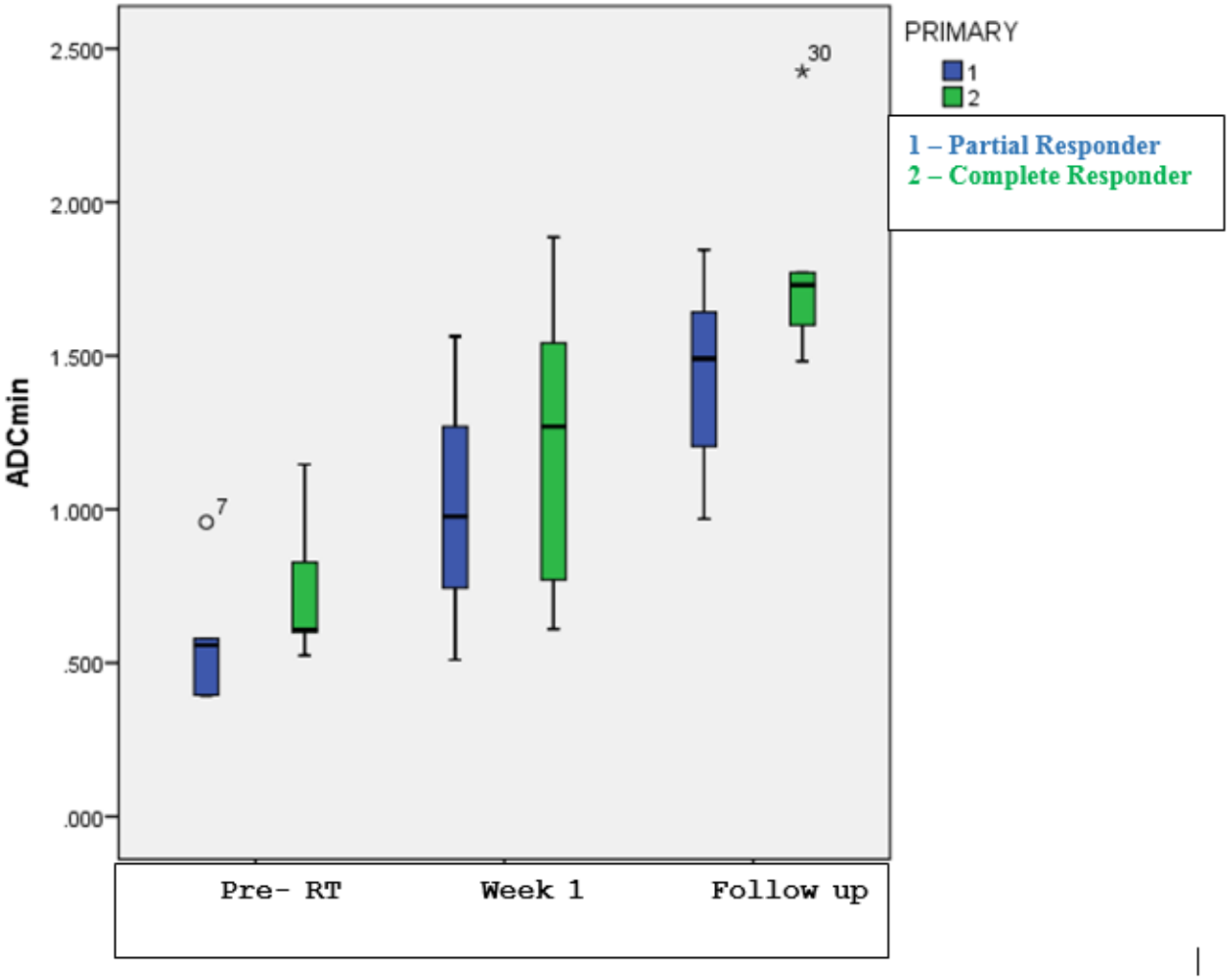
A. Box plot comparing Mean ADC value of complete responders and partial responders over the three-time points for PRIMARY TUMOR



Box plot 1: This Box plot compares the Mean ADC values of primary tumor in Complete Responders and Partial responders over the different time points (Pre-RT, Week 1 and Follow up). ADC in (10^{-3} mm^2 /sec)

The complete responders had a higher mean ADC values at baseline (Pre-RT) compared to partial responder. Among partial responder patient 7 had a high increase in mean ADC by Week 1 and thus remained an outlier in the box plot. Hence at week 1, the partial responder box plot had the highest mean value because of the plot appear at a higher level for partial responders. Otherwise, complete responders had a greater rise in mean ADC values with radiation in comparison to partial responders at follow up.

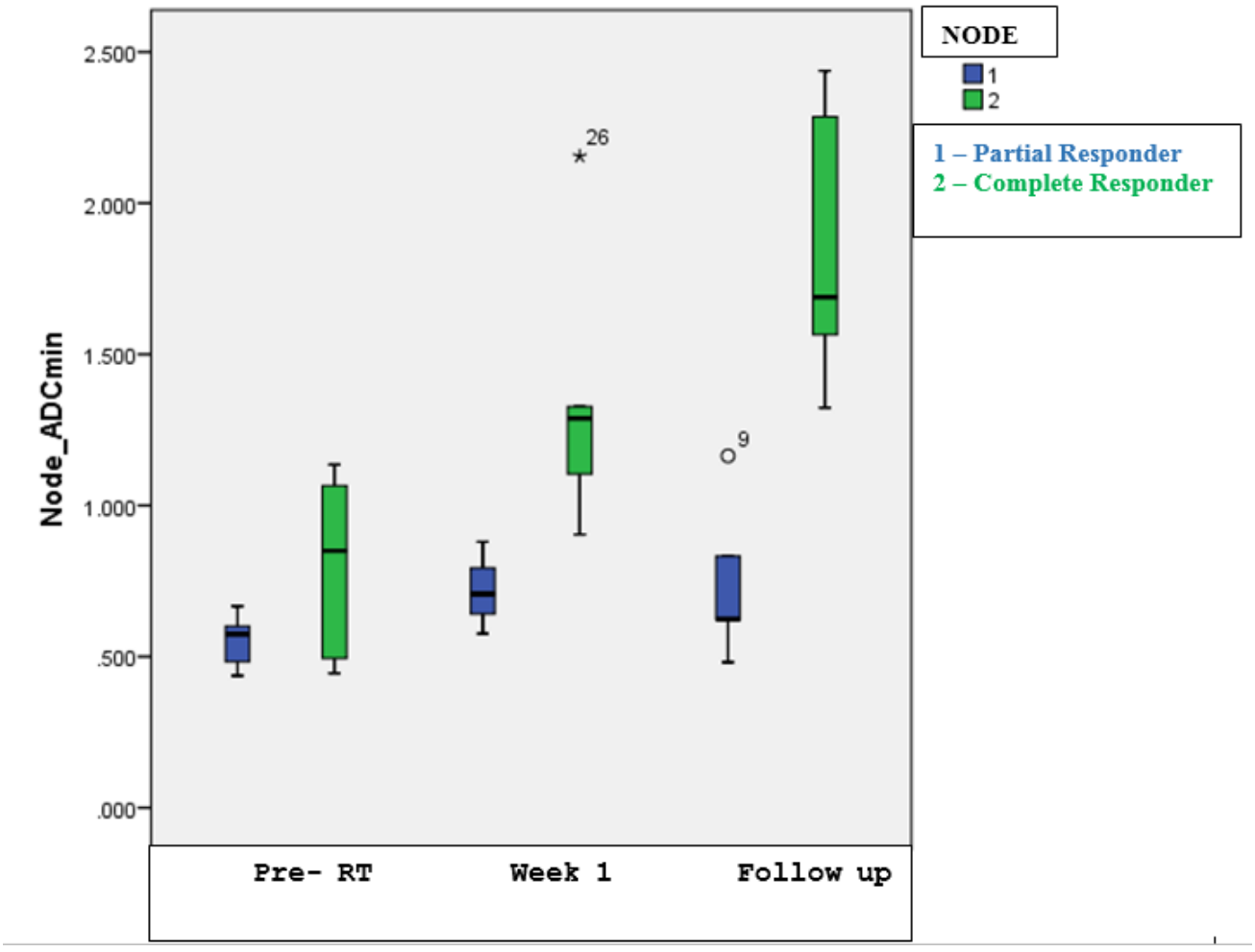
B. Box plot comparing MINIMUM ADC value of complete responders and partial responders over the three-time points for PRIMARY



Box plot 2: This Box plot compares the Minimum ADC values of primary tumor in Complete Responders and Partial responders over the different time points (Pre-RT, Week 1 and Follow up). ADC in (10^{-3} mm^2 /sec)

The complete responders had a higher Minimum ADC values at baseline (Pre-RT) compared to partial responder. Also, complete responders had a greater rise in Minimum ADC values with radiation in comparison to partial responders at all time points

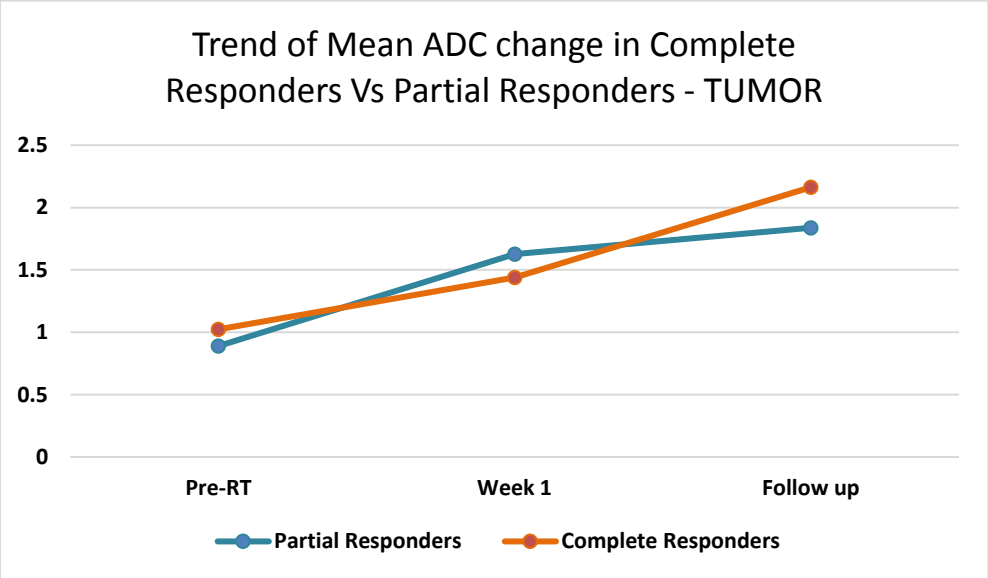
C. Box plot comparing MINIMUM ADC values of complete responders and partial responders over the three-time points for NODE



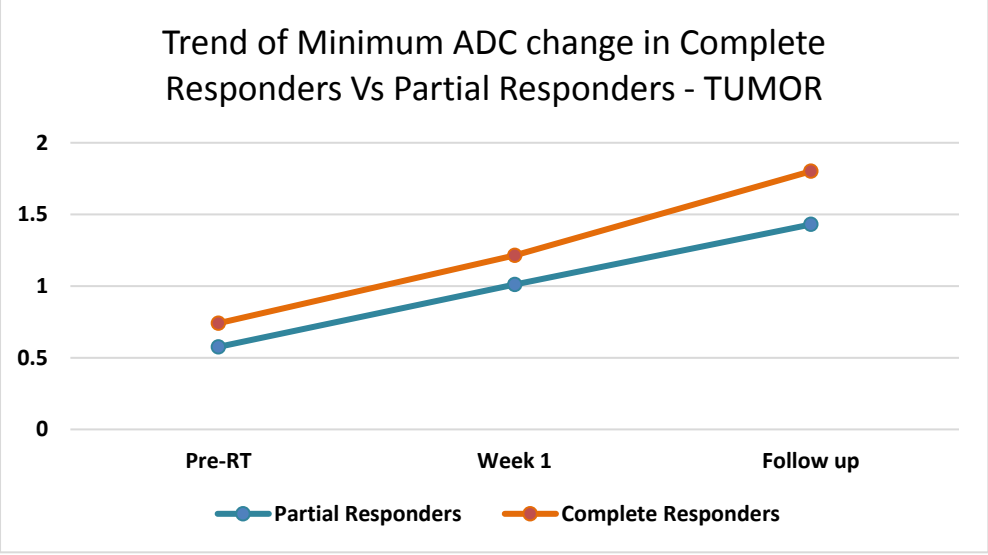
Box plot 3: This box plot compares the Minimum ADC values of Node in Complete Responders and Partial responders over the different time points (Pre-RT, Week 1 and Follow up). ADC in (10^{-3} mm^2 /sec)

The complete responders had higher minimum Pre-RT ADC values compared to partial responder. The rate of increase in Minimum ADC values over three-time points was greater among complete responders in comparison to partial responders at all time points

D. Line graph comparing complete responders and partial responders – TUMOR

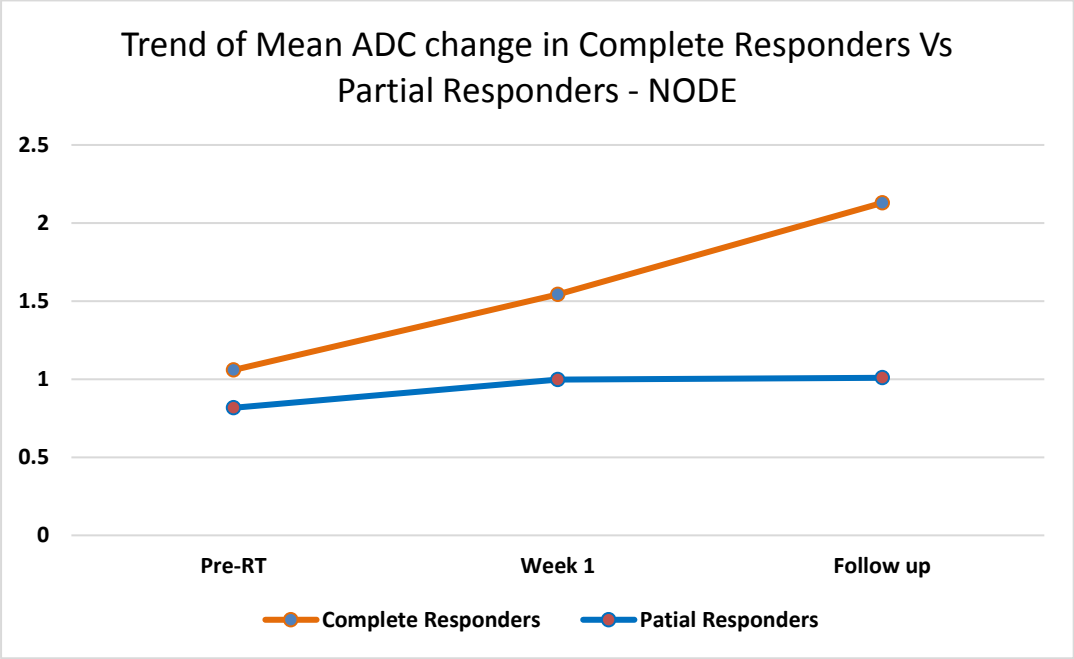


Line graph1: The lines depicting change in mean ADC values over three-time points for complete responders (Orange line) and partial responders (Blue line) were seen crossing each other at week 1. This was due to patient 7 in the partial responder category had a very high increase in mean ADC by Week 1 and thus was an outlier. This had led to increase in average mean ADC for partial responder resulting in an erroneous interpretation of this line graph. However, at follow up the complete responder had a higher rise in ADC values than partial responders (ADC in 10^{-3} mm^2 /sec)

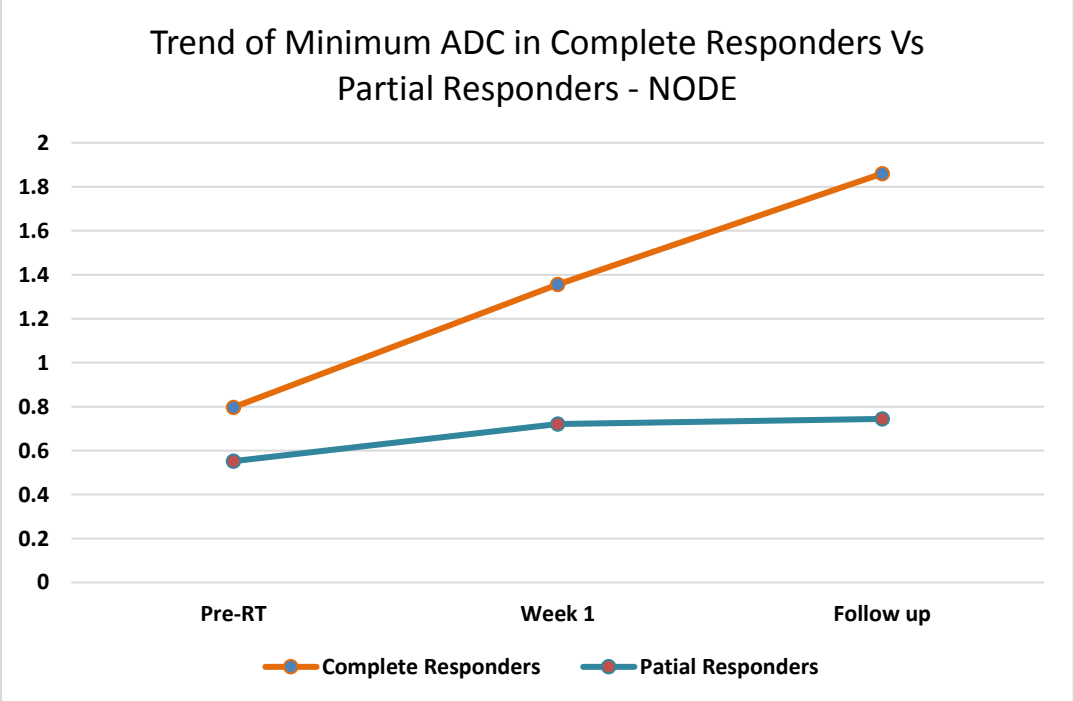


Line graph2: The rate of increase in Minimum ADC values over three-time points was greater among complete responders in comparison to partial responders at all time points

E. Line graph comparing complete responders and partial responders – NODE

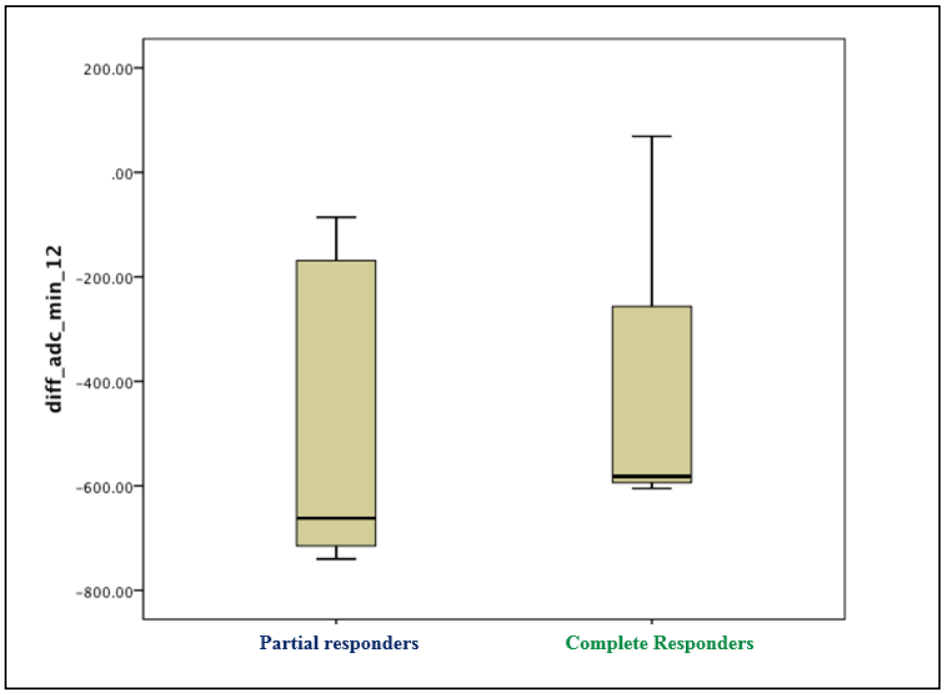


Line graph 3: This line graph shows the change in Mean ADC values over three-time points was greater for Complete Responders than Partial Responders in the node. ADC in (10^{-3} mm^2 /sec)



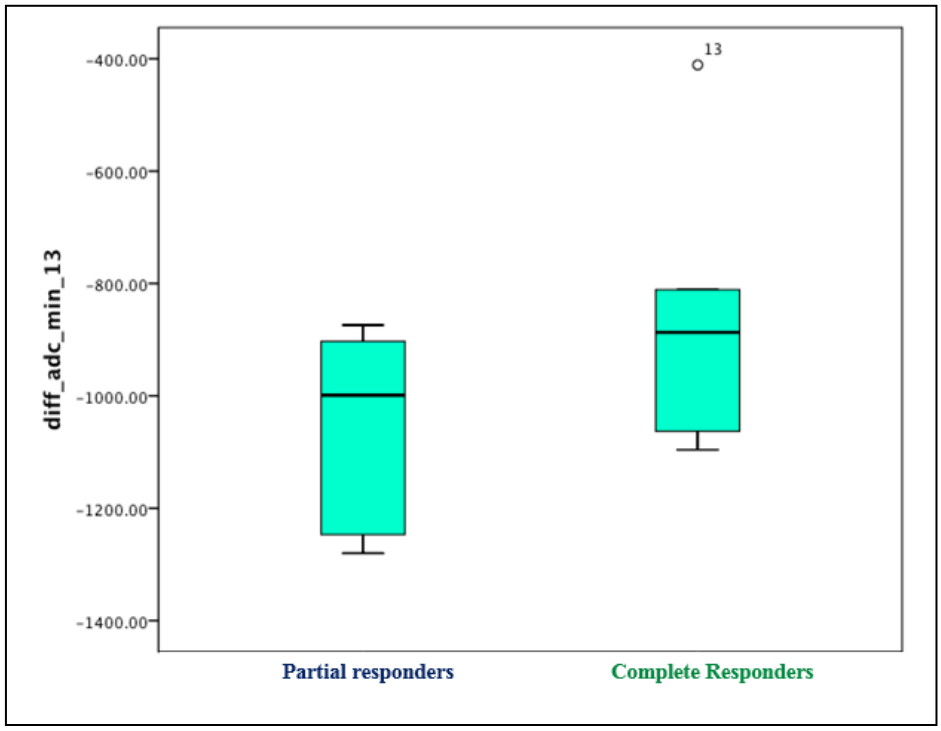
Line graph 4: This line graph shows the minimum ADC(ADCmin) values for Complete Responders and Partial Responders was well separated with higher increase in ADCmin over time in the node.
ADC in (10^{-3} mm^2 /sec)

F. Difference in Minimum ADC between Pre-RT and Week 1 (ADCmin12)



Box Plot 4: The difference between Pre-RT minimum ADC and Week 1 ADC (ADCmin12) was greater among Complete Responder. However, the p value was not significant

G. Difference in Minimum ADC between Pre-RT and follow up (ADCmin13)



Box Plot 5: The difference between Pre-RT minimum ADC and Follow up ADC i.e. (ADCmin13) was greater among Complete Responders in node.

The p value was significant

(p = 0.03)

Correlations:

1. Correlation of Mean Pre-RT ADC and Week 1 ADC

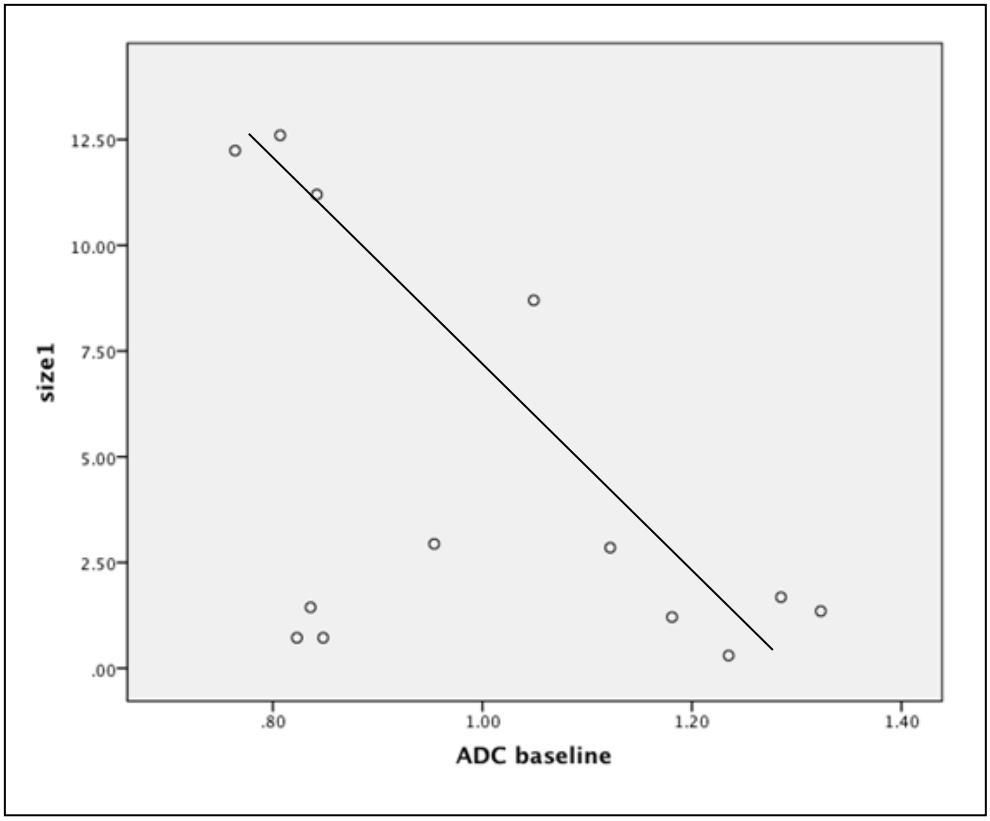
Correlations

Reso				ADC1avg	ADC2avg	ADC3avg
.0	Spearman's rho	ADC1avg	Correlation Coefficient	1.000	.500	.
			Sig. (2-tailed)	.	.667	.
			N	3	3	0
		ADC2avg	Correlation Coefficient	.500	1.000	.
			Sig. (2-tailed)	.667	.	.
			N	3	3	0
		ADC3avg	Correlation Coefficient	.	.	.
			Sig. (2-tailed)	.	.	.
			N	0	0	0
Complete Responder	Spearman's rho	ADC1avg	Correlation Coefficient	1.000	.900*	.100
			Sig. (2-tailed)	.	.037	.873
			N	5	5	5
		ADC2avg	Correlation Coefficient	.900*	1.000	.200
			Sig. (2-tailed)	.037	.	.747
			N	5	5	5
		ADC3avg	Correlation Coefficient	.100	.200	1.000
			Sig. (2-tailed)	.873	.747	.
			N	5	5	5
Partial Responder	Spearman's rho	ADC1avg	Correlation Coefficient	1.000	.500	.100
			Sig. (2-tailed)	.	.667	.873
			N	5	3	5
		ADC2avg	Correlation Coefficient	.500	1.000	.500
			Sig. (2-tailed)	.667	.	.667
			N	3	3	3
		ADC3avg	Correlation Coefficient	.100	.500	1.000
			Sig. (2-tailed)	.873	.667	.
			N	5	3	5

Figure 34: Non-Parametric tests showing correlation between ADC over different time periods

We had also looked at Correlation between mean Pre-RT ADC, Week 1 ADC and follow up ADC. It showed positive correlation for Mean Pre-RT with Mean Week 1 ADC in complete responders.

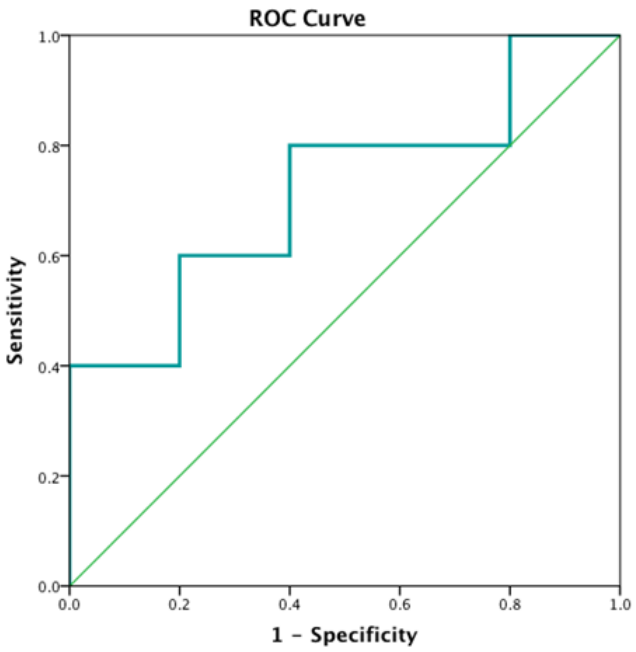
2. Correlation between Primary tumor size and mean ADC value



Scatter plot 1: This plot shows Negative correlation between primary tumor size and ADC value. This means that greater the tumor size lesser is the mean ADC value suggestive greater possibility of being a partial responder.

Sensitivity and Specificity

1. Pre-RT mean ADC



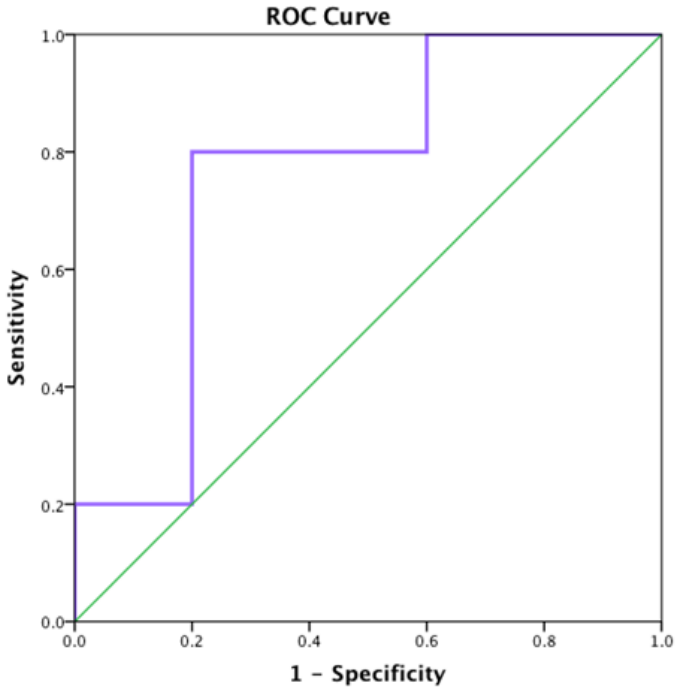
Test Result Variable(s): ADC1avg

Positive if Greater Than or Equal To[3]	Sensitivity	1 - Specificity
763.000	1.000	1.000
785.500	1.000	.800
815.000	.800	.800
829.500	.800	.600
839.000	.800	.400
845.000	.600	.400
901.000	.600	.200
1067.500	.400	.200
1208.000	.400	.000
1260.000	.200	.000
1286.000	.000	.000

Figure 35: ROC log regression analysis table with Sensitivity and Specificity determining tables- log regression analysis for Mean Pre-RT ADC values

Based on the ROC curve, the sensitivity and specificity of the Pre-RT mean ADC to determine the treatment response was assessed which revealed a sensitivity of about 80% and a specificity of about 60%. The rest of the sensitivity and specificity could be determined from the table above

2. Pre-RT minimum ADC



Coordinates of the Curve

Test Result Variable(s): ADC1min

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
393.000	1.000	1.000
394.500	1.000	.800
459.500	1.000	.600
541.000	.800	.600
568.500	.800	.400
590.000	.800	.200
604.500	.600	.200
717.500	.400	.200
892.500	.200	.200
1052.000	.200	.000
1147.000	.000	.000

Figure 36: ROC log regression analysis table with Sensitivity and Specificity determining tables- log regression analysis for Minimum Pre-RT ADC values

The primary objective of this study was to determine a correlation between the Pre-RT ADC and the prediction of treatment response. Based on the ROC curve the sensitivity and specificity of the Pre-RT minimum ADC to determine the treatment response was assessed which revealed a sensitivity of about 80% and a specificity of about 80%. The rest of the sensitivity and specificity could be determined from the table above.

DISCUSSION

In this study, we investigated the role of ADC for prediction and early detection of treatment response to chemoradiation therapy in Nasopharyngeal Carcinoma. The ADC values at various time points were calculated and were correlated with treatment response.

Patient population: The patient population in our study were predominantly stage III and non-metastatic stage IV, similar to other trials which also had the majority of patients in the locally advanced stage. The median age in our study was 40 years was also in concurrence with other studies. A male predilection was seen in all studies, and our study had all male patients.

Induction chemotherapy: There has been an increasingly growing evidence for Induction chemotherapy with platinum-based agents. In a pooled analysis, induction chemotherapy was found to have decreased relapse and increase in disease-specific survival (55) Studies conducted for prediction of response assessment to treatment using DWI in Nasopharyngeal carcinoma had the majority of patients receiving Induction chemotherapy. Our study also had 70% of patients receiving platinum-based induction chemotherapy.

Radiation therapy: All patients had radiation delivered by Volumetric Modulated Arc Therapy(VMAT) using Simultaneous Integrated Boost technique (SIB). Doses ranged from 66-70 Gy in 33-35 fractions as seen with other studies. All patients received 70Gy except patient 1 in our cohort, who received 66 Gy and he had residual disease at first follow up and was further categorized as a partial responder.

Concurrent chemotherapy: All our study patients had received concurrent Cisplatin. Patients in this study had treatment was in concurrence with the standard of care for Carcinoma Nasopharynx (17)

Data acquisition: The imaging protocols and measuring ADC values were as described in our methods were similar to two other studies - Chen et al. and J Hong et al. (50) (51). We contoured regions of interest with free hand technique and made sure the necrotic regions were avoided as they tend to have an abnormally high ADC due to free water movement. This could result in erroneous results.

Results: We found that two major factors predicting response were:

1. Difference in serial ADC values
2. Pre-RT ADC

The difference in serial ADC values:

Studies by Chen et al. and Hong et al. also found that change in mean ADC was independent factor in predicting response to chemoradiation in carcinoma Nasopharynx. Though our study showed greater difference of mean ADC for Complete responders in comparison to Partial responders, it was not statistically significant. The difference between Pre-RT minimum ADC and Follow up ADC was greater among Complete Responders. The p-value was significant. ($p = 0.03$). We inferred that ADC minimum value represents an area of densely packed tumor tissue and possibly could be the more radio resistant region with in the tumor. We feel it is more prudent to consider minimum ADC values along with mean ADC values form the region of interest. To our knowledge, we are the first to find Minimum ADC to be more sensitive than Mean ADC.

This can have clinical utility in dose painting in that it could use these areas of minimum ADC and visual restriction for dose escalation. Also, regions with a very high ADC are seen within necrotic areas which could also be treated to a higher dose

Comparison with other studies:

	YunBin Chen et al.	**Jinsheng Hong et al.**	**Current study**
No of patients, n	31	121	13 (10 analysed)
Stage	Stage III and IV (Non-metastatic)	All stages	All stages (Non-metastatic)
DWI-MRI time points	1. Baseline 2. Day 3 post chemo 3. Day 20, post chemo 4. Day 50, 6 days after RT 5. At completion of chemoRT	1. Baseline 2. Week 2 after initiation of RT 3. Follow up at 3 months	1. Pre-Radiation 2. Week 1 after initiation of RT 3. Follow up at 6 weeks
Induction chemotherapy	All received platinum based chemotherapy (2-4 cycles)	Platinum based chemotherapy (80% received chemo)	9 (69.2%) patients had 3 cycles of platinum based chemotherapy
RT doses	70 Gy in 35 fractions	66 -74 Gy in 30 to 33 fractions	70 Gy in 33-35 fractions (66 Gy for 2 patients)
Concurrent chemotherapy	67% received concurrent chemotherapy - 3 weekly Cisplatin 100mg/m2 (21) - Immunotherapy (2)	60% patients received chemotherapy - Cisplatin – 80 mg three weekly	All received concurrent chemo - Three weekly Cisplatin (85%) - Weekly Cisplatin (15%)
Results	Change in mean ADC from Baseline to Day 20 is significant for Response prediction ($p = 0.017$)	Change in mean ADC from Baseline to Week 2 is significant for Response prediction ($p = 0.002$)	Change of difference in Minimum ADC difference from Pre-RT to Follow up is significant for Response prediction ($p = 0.03$)

Table 10: This table shows comparison of our data with similarly conducted studies

Response prediction with Pre-RT ADC: In our study, the ADC variation observed were as follows across the complete responders and partial responders

PRIMARY TUMOR	Minimum Pre-RT ADC (In mm2/s)	Median Pre-RT ADC (In mm2/s)	Maximum Pre-RT ADC (In mm2/s)
Complete Responders	**0.8×10^{-3}**	**1×10^{-3}**	**1.2×10^{-3}**
Partial Responders	**0.7×10^{-3}**	**0.8×10^{-3}**	**1.1×10^{-3}**

Similar finding was observed for metastatic cervical nodes as well. However, the p values were not significant.

NODE	Minimum Pre-RT ADC (In mm2/s)	Median Pre-RT ADC (In mm2/s)	Maximum Pre-RT ADC (In mm2/s)
Complete Responders	**0.6×10^{-3}**	**1×10^{-3}**	**1.3×10^{-3}**
Partial Responders	**0.4×10^{-3}**	**0.6×10^{-3}**	**1.1×10^{-3}**

This finding is in unison with the study by Zheng. D et al. who had compared the mean ADC values (lowest, highest and average) of complete responders and partial responders.(56) They found Mean ADC in effective groups was significantly ($P < 0.05$) higher than that in the ineffective group. Average and minimum ADC demonstrated higher sensitivity than maximum

ADC for predicting response to treatment. The sensitivity and the specificity for Pre-RT mean ADC value to predict response was 80% and 60% respectively.

Similarly, the calculated sensitivity was 80%, and the specificity was also 80% for Pre-RT minimum ADC value to predict response.

	Group	n	Mean (SD) ($\times 10^{-3}$mm^2/s)	*t*	*P*
ADC_Avg	ineffective	16	0.882 (0.145)	2.485	0.016
	effective	38	0.996 (0.157)		
ADC_Max	ineffective	16	0.956 (0.172)	2.111	0.040
	effective	38	1.074 (0.193)		
ADC_Min	ineffective	16	0.818 (0.137)	2.517	0.015
	effective	38	0.918 (0.131)		

Figure 37: Zheng. D et al: The average, minimum and maximum ADC values in their study and its significance in predicting response to treatment.

Our study showed that patients with high Mean and Minimum ADC showed a trend towards complete response with a reasonable sensitivity and specificity. However, the p-value was not significant. From the observations made from our study we recalculated sample size required to prove significance.

Two Means - Hypothesis testing for two means		
Standard deviation in group I	222	222
Standard deviation in group II	222	222
Mean difference	43	200
Effect size	0.193693694	0.900900901
Alpha error (%)	5	5
Power (1- beta) %	80	80
1 or 2 sided	2	2
Required sample size per group	419 ADCmean	19 ADCminimum

Using ADC_{min}, we need 19 patients in either of complete responder or partial responders group, to find significance. This would require studying at least 40 patients. And using Mean ADC, it is 419 patients in each group.

We are continuing the study to reach the required sample size for proving significance for Minimum ADC.

Problems with sample size: As explained earlier, of the 20 patients screened 4 were excluded as they had metastatic disease. One did not consent to participate in the study. T two patients had only started treatment at the time of this analysis, and only Pre-RT MRI was available and therefore were not included. Of the thirteen patient who had completed treatment, 2 had completed treatment in last week of September 2017 and hence were awaiting at the 6 weeks follow up scan. One patient from overseas did not return for follow after completing chemoradiotherapy and is continuing his further treatment in his home country. Hence, we had only 10 patients for complete analysis.

LIMITATIONS OF THE STUDY

1. Short Study Period: This study was done as a part of requirement for a 2-year MD dissertation and therefore there was a difficulty in accruing the number planned at the outset of the study. There were eligible patients but who could not be recruited into the study for reasons mentioned before. This simulates real life situation which we encounter every day in our clinics while trying to conduct clinical trials. However, we plan to continue recruiting patients to reach the calculated sample size. This will enable us to draw a meaningful conclusion at the end of the study, and we hope to present the findings at a scientific conference and publish in a scientific journal as we feel these findings are clinically significant and will add to the limited literature available on this subject.

Although we could prove our hypothesis that Diffusion Weighted Imaging plays a key role in the prediction of early treatment response in patients diagnosed with Carcinoma Nasopharynx, we need a larger sample size to yield a better outcome.

2. Short Follow Up: The study patients need to be followed up for longer period of time to establish role of Diffusion-weighted imaging in predicting long term disease control.
3. False Positive: One patient classified as a partial responder with persisting neck node was found to have T.B Lymphadenitis after salvage neck dissection. Another patient was suspected to have residual primary had Maxillary and Ethmoidal sinusitis.

FUTURE DIRECTIONS

1. Dose Painting using DWI-MRI: Radiotherapy treatment planning incorporating DWI-MRI may a tool of the future for dose painting and radiotherapy dose escalation. This modality may aid in identifying and contouring necrotic areas and the diffusion restricted areas. This may eventually help in better tumor control and thus translates into a superior locoregional control and survival.

2. Biological Adaptive Radiotherapy (BiGART): With the introduction of MR-LINAC (MRI Linear Accelerator) for clinical use, the possibility of incorporating DW imaging may find its utility in Adaptive Radiotherapy using Biological Imaging.

3. De-escalating therapy in Complete responders: With evidence from studies showing no improved failure-free survival from adjuvant chemotherapy following concurrent

chemoradiotherapy in Carcinoma Nasopharynx, there is an increase in the need to develop a tool to predict response to concurrent chemoradiation before omitting it and thereby reducing treatment related toxicity (33). We feel that DWI-MRI may be an additional tool to aid in response assessment and de-scalation of therapy.

CONCLUSIONS

- Serial DWI-MRI is a potential tool for response prediction in carcinoma nasopharynx treated with chemoradiotherapy.
- Quantitatively, the difference in Minimum ADC values from baseline to follow up was statistically significant to predict response to chemoradiation.
- Qualitatively, Visual diffusion restriction is a potential tool to explore in DWI-MRI for response prediction.
- Mean and Minimum Pre-RT values could predict response.
- This study needs to be continued and a larger sample size and long term follow up may help in establishing its role in clinical practice.

REFERENCES

1. Globocan 2012 - Home [Internet]. [cited 2017 Jul 21]. Available from: http://globocan.iarc.fr/Default.aspx

2. BUSEPT03 - BUSEPT03.pdf [Internet]. [cited 2017 Jul 26]. Available from: http://icmr.nic.in/BUSEPT03.pdf

3. Tsao SW, Yip YL, Tsang CM, Pang PS, Lau VMY, Zhang G, et al. Etiological factors of nasopharyngeal carcinoma. Oral Oncol. 2014 May 1;50(5):330–8.

4. Hildesheim A, Wang C-P. Genetic Predisposition Factors and Nasopharyngeal Carcinoma Risk: A Review of Epidemiological Association Studies, 2000–2011. Semin Cancer Biol. 2012 Apr;22(2):107–16.

5. Xue W-Q, Qin H-D, Ruan H-L, Shugart YY, Jia W-H. Quantitative Association of Tobacco Smoking With the Risk of Nasopharyngeal Carcinoma: A Comprehensive Meta-Analysis of Studies Conducted Between 1979 and 2011. Am J Epidemiol. 2013 Aug 1;178(3):325–38.

6. Chen L, Gallicchio L, Boyd-Lindsley K, Tao X (Grant), Robinson KA, Lam TK, et al. Alcohol Consumption and the Risk of Nasopharyngeal Carcinoma: A Systematic Review. Nutr Cancer. 2009;61(1):1–15.

7. Yu MC, Yuan J-M. Epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol. 2002 Dec 1;12(6):421–9.

8. Sakata K, Hareyama M, Tamakawa M, Oouchi A, Sido M, Nagakura H, et al. Prognostic factors of nasopharynx tumors investigated by MR imaging and the value of MR imaging in the newly published TNM staging. Int J Radiat Oncol. 1999 Jan 15;43(2):273–8.

9. Anzai Y, Brunberg JA, Lufkin RB. Imaging of nodal metastases in the head and neck. J Magn Reson Imaging JMRI. 1997 Oct;7(5):774–83.

10. Ng S-H, Chan S-C, Yen T-C, Chang JT-C, Liao C-T, Ko S-F, et al. Staging of untreated nasopharyngeal carcinoma with PET/CT: comparison with conventional imaging work-up. Eur J Nucl Med Mol Imaging. 2009 Jan 1;36(1):12.

11. Chen W-S, Li J-J, Hong L, Xing Z-B, Wang F, Li C-Q. Comparison of MRI, CT and 18F-FDG PET/CT in the diagnosis of local and metastatic of nasopharyngeal carcinomas: an updated meta analysis of clinical studies. Am J Transl Res. 2016 Nov 15;8(11):4532–47.

12. Song CH, Wu H-G, Heo DS, Kim KH, Sung M-W, Park CI. Treatment Outcomes for Radiotherapy Alone are Comparable With Neoadjuvant Chemotherapy Followed by Radiotherapy in Early-Stage Nasopharyngeal Carcinoma. The Laryngoscope. 2008 Apr 1;118(4):663–70.

13. Chua DTT, Sham JST, Kwong DLW, Au GKH. Treatment outcome after radiotherapy alone for patients with Stage I–II nasopharyngeal carcinoma. Cancer. 2003 Jul 1;98(1):74–80.

14. Chan ATC, Grégoire V, Lefebvre J-L, Licitra L, Hui EP, Leung SF, et al. Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2012 Oct;23 Suppl 7:vii83-85.

15. Pastor Borgoñón M, Mesía Nin R, Cruz Hernández JJ, Isla Casado D, SEOM (Spanish Society for Medical Oncology). SEOM clinical guidelines for the treatment of nasopharyngeal carcinoma. Clin Transl Oncol Off Publ Fed Span Oncol Soc Natl Cancer Inst Mex. 2010 Nov;12(11):749–52.

16. NCCN - Evidence-Based Cancer Guidelines, Oncology Drug Compendium, Oncology Continuing Medical Education [Internet]. [cited 2017 Jul 26]. Available from: https://www.nccn.org/

17. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol. 1998 Apr;16(4):1310–7.

18. Cheng: Concomitant radiotherapy and chemotherapy... - Google Scholar [Internet]. [cited 2017 Jul 26]. Available from: https://scholar.google.com/scholar_lookup?title=Concomitant%20radiotherapy%20and%20chemotherapy%20for%20early-stage%20nasopharyngeal%20carcinoma&author=SH%20Cheng&author=SY%20Tsai&author=KL%20Yen&publication_year=2000&journal=J%20Clin%20Oncol.&volume=18&pages=2040-2045

19. Xu C, Zhang L-H, Chen Y-P, Liu X, Zhou G-Q, Lin A-H, et al. Chemoradiotherapy Versus Radiotherapy Alone in Stage II Nasopharyngeal Carcinoma: A Systemic Review and Meta-analysis of 2138 Patients. J Cancer. 2017 Jan 15;8(2):287–97.

20. Chua DTT, Ma J, Sham JST, Mai H-Q, Choy DTK, Hong M-H, et al. Long-term survival after cisplatin-based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of two phase III trials. J Clin Oncol Off J Am Soc Clin Oncol. 2005 Feb 20;23(6):1118–24.

21. Marks JE, Bedwinek JM, Lee F, Purdy JA, Perez CA. Dose-response analysis for nasopharyngeal carcinoma. An historical perspective. Cancer. 1982 Sep 15;50(6):1042–50.

22. Vikram B, Mishra UB, Strong EW, Manolatos S. Patterns of failure in carcinoma of the nasopharynx: I. failure at the primary site. Int J Radiat Oncol • Biol • Phys. 1985 Aug 1;11(8):1455–9.

23. Moon SH, Cho KH, Lee C-G, Keum KC, Kim Y-S, Wu H-G, et al. IMRT vs. 2D-radiotherapy or 3D-conformal radiotherapy of nasopharyngeal carcinoma : Survival outcome in a Korean multi-institutional retrospective study (KROG 11-06). Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al. 2016 Jun;192(6):377–85.

24. Peng G, Wang T, Yang K-Y, Zhang S, Zhang T, Li Q, et al. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2012 Sep;104(3):286–93.

25. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol. 2002 May 1;53(1):12–22.

26. Kam MKM, Teo PML, Chau RMC, Cheung KY, Choi PHK, Kwan WH, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: The Hong Kong experience. Int J Radiat Oncol. 2004 Dec 1;60(5):1440–50.

27. Zhang B, Mo Z, Du W, Wang Y, Liu L, Wei Y. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. Oral Oncol. 2015 Nov;51(11):1041–6.

28. Zheng X-K, Chen L-H, Wang Q-S, Wu F-B. Influence of [18F] fluorodeoxyglucose positron emission tomography on salvage treatment decision making for locally persistent nasopharyngeal carcinoma. Int J Radiat Oncol. 2006 Jul 15;65(4):1020–5.

29. Low JSH, Chua E-T, Gao F, Wee JTS. Stereotactic radiosurgery plus intracavitary irradiation in the salvage of nasopharyngeal carcinoma. Head Neck. 2006 Apr 1;28(4):321–9.

30. My C, X G, Wp W, Yj H, L G, Nw L, et al. [Salvage surgical operation via endoscopic transnasal approach for local persistent or recurrent nasopharyngeal carcinoma]. Ai Zheng Aizheng Chin J Cancer. 2007 Jul;26(7):673–8.

31. Liu L-Z, Zhang G-Y, Xie C-M, Liu X-W, Cui C-Y, Li L. Magnetic resonance imaging of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma: Patterns of spread. Int J Radiat Oncol. 2006 Nov 1;66(3):721–30.

32. Y S, C Z, Cm X, Lx L, Y S, F H, et al. [Evaluation of CT, MRI and PET-CT in detecting retropharyngeal lymph node metastasis in nasopharyngeal carcinoma]. Ai Zheng Aizheng Chin J Cancer. 2006 May;25(5):521–5.

33. Chen L, Hu C-S, Chen X-Z, Hu G-Q, Cheng Z-B, Sun Y, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. Lancet Oncol. 2012 Feb;13(2):163–71.

34. Newbold K, Castellano I, Charles-Edwards E, Mears D, Sohaib A, Leach M, et al. An exploratory study into the role of dynamic contrast-enhanced magnetic resonance imaging or perfusion computed tomography for detection of intratumoral hypoxia in head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2009 May 1;74(1):29–37.

35. Donaldson SB, Betts G, Bonington SC, Homer JJ, Slevin NJ, Kershaw LE, et al. Perfusion Estimated With Rapid Dynamic Contrast-Enhanced Magnetic Resonance Imaging Correlates Inversely With Vascular Endothelial Growth Factor Expression and Pimonidazole Staining in Head-and-Neck Cancer: A Pilot Study. Int J Radiat Oncol. 2011 Nov 15;81(4):1176–83.

36. Donaldson SB, Betts G, Bonington SC, Homer JJ, Slevin NJ, Kershaw L, et al. Perfusion estimated with rapid dynamic contrast-enhanced magnetic resonance imaging correlates inversely with vascular endothelial growth factor expression and pimonidazole staining in head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):1176–83.

37. Kim S, Loevner L, Quon H, Sherman E, Weinstein G, Kilger A, et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting early response to chemoradiation therapy of squamous cell carcinomas of the head and neck. Clin Cancer Res Off J Am Assoc Cancer Res. 2009 Feb 1;15(3):986–94.

38. Vandecaveye V, Dirix P, De Keyzer F, Op de Beeck K, Vander Poorten V, Hauben E, et al. Diffusion-weighted magnetic resonance imaging early after chemoradiotherapy to monitor treatment response in head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2012 Mar 1;82(3):1098–107.

39. Srinivasan A, Mohan S, Mukherji SK. Biologic Imaging of Head and Neck Cancer: The Present and the Future. Am J Neuroradiol. 2012 Apr 1;33(4):586–94.

40. Gaillard F. BOLD imaging | Radiology Reference Article | Radiopaedia.org [Internet]. Radiopaedia. [cited 2017 Sep 22]. Available from: https://radiopaedia.org/articles/bold-imaging

41. Comoretto M, Balestreri L, Borsatti E, Cimitan M, Franchin G, Lise M. Detection and Restaging of Residual and/or Recurrent Nasopharyngeal Carcinoma after Chemotherapy and Radiation Therapy: Comparison of MR Imaging and FDG PET/CT. Radiology. 2008 Oct 1;249(1):203–11.

42. Greven KM, Williams DW, McGuirt WF, Harkness BA, D'Agostino RB, Keyes JW, et al. Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer. Head Neck. 2001 Nov 1;23(11):942–6.

43. MacManus MP, Hicks RJ. Where do we draw the line? Contouring tumors on positron emission tomography/computed tomography. Elsevier; 2008.

44. Thoeny HC. Diffusion-weighted MRI in head and neck radiology: applications in oncology. Cancer Imaging. 2011 Feb 10;10(1):209–14.

45. Hamstra DA, Lee KC, Moffat BA, Chenevert TL, Rehemtulla A, Ross BD. Diffusion magnetic resonance imaging: an imaging treatment response biomarker to chemoradiotherapy in a mouse model of squamous cell cancer of the head and neck. Transl Oncol. 2008 Dec;1(4):187–94.

46. Schmainda KM. Diffusion-weighted MRI as a biomarker for treatment response in glioma. CNS Oncol. 2012 Nov;1(2):169–80.

47. King AD, Chow K-K, Yu K-H, Mo FKF, Yeung DKW, Yuan J, et al. Head and Neck Squamous Cell Carcinoma: Diagnostic Performance of Diffusion-weighted MR Imaging for the Prediction of Treatment Response. Radiology. 2013 Feb 1;266(2):531–8.

48. Predictive value of diffusion-weighted magnetic resonance imaging during chemoradiotherapy for head and neck squamous cell carcinoma | SpringerLink [Internet]. [cited 2017 Sep 23]. Available from: https://link.springer.com/article/10.1007/s00330-010-1734-6

49. Diffusion Weighted Imaging in Predicting Progression Free Survival in Patients with Squamous Cell Carcinomas of the Head and Neck Treated with Induction Chemotherapy [Internet]. [cited 2017 Sep 23]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3168957/

50. Hong J, Yao Y, Zhang Y, Tang T, Zhang H, Bao D, et al. Value of Magnetic Resonance Diffusion-Weighted Imaging for the Prediction of Radiosensitivity in Nasopharyngeal Carcinoma. Otolaryngol--Head Neck Surg [Internet]. 2013 Jul 24 [cited 2017 Sep 23]; Available from: http://journals.sagepub.com/doi/abs/10.1177/0194599813496537

51. Chen Y, Liu X, Zheng D, Xu L, Hong L, Xu Y, et al. Diffusion-weighted magnetic resonance imaging for early response assessment of chemoradiotherapy in patients with nasopharyngeal carcinoma. Magn Reson Imaging. 2014 Jul;32(6):630–7.

52. Zhang G-Y, Wang Y-J, Liu J-P, Zhou X-H, Xu Z-F, Chen X-P, et al. Pretreatment Diffusion-Weighted MRI Can Predict the Response to Neoadjuvant Chemotherapy in Patients with Nasopharyngeal Carcinoma [Internet]. BioMed Research International. 2015 [cited 2017 Sep 23]. Available from: https://www.hindawi.com/journals/bmri/2015/307943/

53. Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia N Y N. 2009 Feb;11(2):102–25.

54. King AD, Chow K-K, Yu K-H, Mo FKF, Yeung DKW, Yuan J, et al. Head and Neck Squamous Cell Carcinoma: Diagnostic Performance of Diffusion-weighted MR Imaging for the Prediction of Treatment Response. Radiology. 2013 Feb 1;266(2):531–8.

55. Chua DTT, Ma J, Sham JST, Mai H-Q, Choy DTK, Hong M-H, et al. Long-term survival after cisplatin-based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of two phase III trials. J Clin Oncol Off J Am Soc Clin Oncol. 2005 Feb 20;23(6):1118–24.

56. Zheng D, Chen Y, Chen Y, Xu L, Lin F, Lin J, et al. Early assessment of induction chemotherapy response of nasopharyngeal carcinoma by pretreatment diffusion-weighted magnetic resonance imaging. J Comput Assist Tomogr. 2013 Oct;37(5):673–80.

ANNEXURES

Annexure 1 : Patient Information

Department of Radiotherapy
CMC Hospital Vellore, Tamil Nadu Informed Consent Sheet No.....

Title of Research –`` To study the role of diffusion weighted MRI in predicting response to concurrent chemoradiotherapy / neoadjuvant chemotherapy in nasopharyngeal malignancies ``

Person carrying out the research: Dr ----------

Part I: - Information sheet

Introduction- I am Koti Krishna Amulya, post graduate student in the department of Radiotherapy. I am doing a research on predicting response to preoperative chemoradiotherapy in patients diagnosed with non metastatic nasopharyngeal cancer with the help of the special MRI imaging during the course of your treatment. I am going to give you the information regarding my study and invite you to be a part it. At any point of time if there is any doubt or you are not clear with the study protocol please feel free to ask.
Purpose of the research: All patients with nasopharyngeal cancers similar to your type of cancer, are treated with radical chemoradiation/ neoadjuvant chemotherapy followed by chemoradiation - which is the standard treatment option. Shortly after initiation of the treatment, there is breakdown of tumour cells, which is detectable on the special MRI imaging. However the non responders to chemoradiotherapy will have less cellular breakdown as a result of the poor response to the treatment with chemoradiotherapy. Thus in my study with the help of repeated special MRI imaging at baseline ,1 week and at completion of chemoradiation patients and by correlating with the postop sample are categorized as responders(those patients responding to chemoradiotherapy) and non responders(patients not responding to chemoradiotherapy). This valuable outcome can be utilized for tailoring the treatment care for the select group of patients in future.

Participant Selection: You have been invited to participate in this study because **y**ou have been diagnosed to have nasopharyngeal cancer and through this study we will be able to predict your treatment response to the preoperative chemoradiotherapy with the help of the series of special MRI imaging.

Voluntary participation: Your participation in this research is entirely voluntary. It is your choice to participate or not. Whether you choose to participate or not, your management does not change at all. You may even change your mind and withdraw even if you had agreed earlier.
Information on the Research study: All patients who have been selected for the study –ie the patients diagnosed with nasopharyngeal cancer planned for preoperative chemoradiotherapy. A series of special MRI imaging at baseline, 1st week, and completion of chemoradiotherapy would be done. The imaging study would just take 6 minutes in all and would be well coordinated with the Department of Radiology for your

convenience without much waiting time. With this study we will be able to categorize you as responders and non responders to the current treatment of choice of radical chemoradiotherapy. This valuable information would be useful as a practise changing trend in tailoring the treatment patients diagnosed with locally advanced carcinoma esophagus. The series of special imaging would be provided free of cost for you.

Side effects: This is an observational study posing no harm to the patients. This special form of imaging is a non invasive procedure with absolutely no side effects.

Risks: Being an observational study it poses no risks to the patients.

Benefits: Categorizing the patients as responders and non responders does not warrant any change in the management of the select group of patients. However the results of this study would help in the validation of the role of diffusion weighted MRI study in predicting the treatment response in a similar group of patients in the future and to tailor their treatments based on their ADC values.

Confidentiality: Your name will not be mentioned anywhere in the data sheet or the final published study. Your data will bear a study number and the same number will be used till analysis**.**

Sharing of the result: The result of research is the property of Christian Medical College and I am entitled to publish it in a journal or at a conference.

Right to refuse or withdraw: You do not have to participate in this research if you do not wish to. It is your choice and all your rights will be respected. This study has been reviewed by [IRB, Christian Medical College], which is a committee whose task is to make sure that research participants are protected from harm. If you wish to find more about the IRB

Contact
Institutional Review Board,
Christian Medical College
Office of Research, I st Floor, Carman Block, Bagayam, Vellore 632 002 India.
E-mail: research@cmcvellore.ac.in.
Tel: 0416 -2284294, 2284202 Fax: 0416 – 2262788, 2284481.
It has also been reviewed by the Ethics Review Committee CMC Vellore, which is supporting the study.

Annexure 2: Certificate of Consent

Title of Research –`` To study the role of diffusion weighted MRI in predicting response to concurrent chemoradiotherapy / neoadjuvant chemotherapy in nasopharyngeal malignancies"

Study Title:_____
Study Number: _____
Subject's Initials: _____
Subject's Name: _____
Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.
(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
(v) I agree to take part in the above study.
(vi)I agree to give my blood sample for EBV DNA titres which would be done at a later date.

Signature (or Thumb impression) of the Subject/Legally Acceptable
Date: _____/_____/_____
Signatory's Name: _____
Representative: _____
Date: _____/_____/_____
Signatory's Name: _____
Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: _____
Signature (or thumb impression) of the Witness: _____
Date: _____/_____/_____
Name & Address of the Witness: _____

Annexure 3: Clinical Research Form

PROFORMA SHEET
DWI-MRI in Nasopharyngeal cancer study

Name:
Age:
Sex:
Diagnosis:
Radiotherapy dose:
Chemotherapy agent:
No. of Cycles:

Pretreatment Signal Intensity:
Pretreatment Size:
Pretreatment ADC1:
Pretreatment ADC2:
Pretreatment ADC3:
Pretreatment ADC4:

1 st Week Signal Intensity:
1 st Week Size:
1 st Week ADC1:
1 st Week ADC2:
1 st Week ADC3:
1 st Week ADC4:

At completion Signal Intensity:
At completion Size:
At completion ADC1:
At completion ADC2:
At completion ADC3:
At completion ADC4:

Annexure 4: Raw data

NODE	ADCn1avg (	ADCn2avg (	ADCn3avg	ADCn1min (	ADCn2min (	ADCn3min (	VRn1	VRn2	VRn3	sizen1	sizen2	sizen3
1	0.60	0.836	1.07	0.483	0.707	0.832	PRESENT	PRESENT	PRESENT	3.3 x 2.1	1.1 X 1.2	1.2 x 0.7
2	0.648	1.443	2.45	0.445	1.327	1.689	PRESENT	PRESENT	ABSENT	2.8 X 2.7	1.9 X 2.3	NO DISEASE
3	0.703	1.128	2.489	0.494	0.904	2.286	PRESENT	PRESENT	ABSENT	1.1 X 1.4		NO DISEASE
4	1.271	1.387	1.713	1.065	1.288	1.565	ABSENT	ABSENT	ABSENT	1.3 X 1	1 X 0.6	NO DISEASE
5	1.352	2.255	2.504	1.135	2.155	2.438	PRESENT	ABSENT	ABSENT	0.6 X 0.7	0.5 X 0.5	NO DISEASE
6	1.125	1.174	1.041	0.574	0.88	0.481	PRESENT	PRESENT	PRESENT	1.2 X 1.2	0.7 X 1.1	0.9 x 1.4
7	0.811	0.983	1.303	0.601	0.576	1.164	PRESENT	PRESENT	PRESENT	0.7 x 1.4	0.6 X 1.3	0.5 X 0.8
8	0.815		7.4	0.667		0.624	PRESENT		PRESENT	1 X 1.9		0.6 X 1.1
9	0.732		8.87	0.437		0.623	PRESENT	ABSENT	PRESENT	1.3 X 1.2	1.5 X 1	0.7 X 0.5
10	1.826	2.027		1.611	1.663		ABSENT	PRESENT		1 X 0.8	1 X .8	
11	1.323	1.486	1.489	0.85	1.104	1.323	PRESENT	ABSENT	ABSENT	0.9 X 0.7	NO DISEASE	NO DISEASE
12	0.874			0.818			PRESENT			2.4 X 3.8		
13	1.92	1.622		1.502	1.515		ABSENT	ABSENT		0.7 X 1.2	0.4 X 0.7	

PRIMA	ADC1a	ADC2av	ADC3avg	ADC1min	ADC2min	ADC3min (	VR1	VR2	VR3	size1	size2	size3
1	0.764	1.452	1.978	0.395	0.977	1.491	PRESENT	ABSENT	ABSENT	3.6 x 3.4	2.2 x 3	2.4 x 3.3
2	0.807	0.995	1.728	0.601	0.77	1.6	PRESENT	PRESENT	ABSENT	3.6 X 3.5	3.0 X 3.3	NO DISEASE
3	0.842	1.03	2.902	0.524	0.61	1.771	PRESENT	ABSENT	ABSENT	2.8 X 4		NO DISEASE
4	1.285	1.706	1.842	0.827	1.542	1.73	ABSENT	ABSENT	ABSENT	1.2 X 1.4	1.1 X 0.8	NO DISEASE
5	0.954	1.509	1.561	0.608	1.27	1.482	PRESENT	ABSENT	ABSENT	2.1 X 1.4	1.1 X 0.9	NO DISEASE
6	0.823	1.368	2.03	0.579	0.51	1.642	PRESENT	PRESENT	ABSENT	0.6 X 1.2	0.9 X 0.9	NO DISEASE
7	1.181	2.064	2.126	0.958	1.563	1.845	ABSENT	ABSENT	ABSENT	1.1 X 1.1	NO DISEAS	NO DISEASE
8	0.836		1.565	0.394		1.205	PRESENT		ABSENT	1.2 X 1.2		0.7 X 0.7
9	0.848		1.495	0.558		0.969	PRESENT	PRESENT	PRESENT	0.6 X 1.2	0.8 X 0.7	0.7 X 1.2
10	1.323	1.947		0.897	1.792		ABSENT	ABSENT		1.5 X 0.9	1 X 0.8	
11	1.235	1.959	2.783	1.146	1.886	2.426	ABSENT	ABSENT	ABSENT	0.6 X 0.5	NO TUMOR	NO TUMOR
12	1.049	1.276		0.682			PRESENT	PRESENT		2.9 X 3		
13	1.122	1.2		0.7	0.934		PRESENT	PRESENT		1.5 X 1.9	1 X 1.6	