

**EFFECT OF ADAPTIVE REPLANNING ON  
ORGAN AT RISK DOSES AT 40 Gy IN HEAD AND  
NECK CANCERS**



A dissertation submitted to  
the Tamilnadu Dr. M.G.R. Medical University, Chennai,  
in partial fulfillment of the requirements for the award of the degree of  
**DOCTOR OF MEDICINE (M.D.) IN RADIOTHERAPY**

**APRIL 2018**

## **CERTIFICATE**

This is to certify that this dissertation titled," **Effect of adaptive replanning on ORGAN AT RISK doses at 40 Gy in head and neck cancers** " is a bonafide record of the work done by Dr.Sivakumar.G, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of his postgraduate study for the degree of M.D. (Branch IX – Radiotherapy) from 2015-2016 under my direct guidance and supervision.

Date:

Place: Chennai

Dr.G.Selvaluxmy,

Professor and Head of Department,

Division of radiation oncology,

Cancer institute, (WIA), Chennai

## **ACKNOWLEDGEMENT**

I am ever-grateful to **Late. Dr. S. Krishnamurthi, Advisor, Dr. V. Shanta, Chairman,** Cancer Institute (WIA), Adyar, for providing me all the facilities for this study

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I express my gratitude to all the patients who form the most important part of this study

I thank my wife, my parents, my friends and all my family members all of whom have been the greatest sources of motivation and support for me.



# CANCER INSTITUTE (W.I.A)

(REGIONAL CANCER CENTRE)  
INSTITUTIONAL ETHICS COMMITTEE

Reg. No. ECR/235/Inst/TN/2013  
Adyar, Chennai - 600 020.

Phone : 044-22209150 Extn : 129, Fax : 044-22354508  
E-mail : [iec@cancerinstitutewia.org](mailto:iec@cancerinstitutewia.org)



Date :

Ethics Committee Re-Registration No.ECR/235/Inst/TN/2013/RR-16

17 August 2017

To,  
Dr. Siva Kumar. G.  
Resident  
Dept. of Radiation Oncology  
Cancer Institute (W.I.A)  
38, Sardar Patel Road  
Chennai 600 036

**Subject: Ethics Committee Approval Letter**

**Reference: Study Protocol titled "Effect of adaptive re-planning on OAR doses at 40 Gy in Head and Neck Cancers".**

Dear Dr. Siva kumar,

This is with reference to the letter dated 14 July 2017 for review of the above referenced study Protocol. The ethics committee reviewed the following documents,

- 1) Study Protocol
- 2) Patient Information Sheet (English)
- 3) Patient Informed Consent Form( English)

The following members of the ethics committee were present at the ethics committee meeting held on 22.07.2017 at 2.00 pm at auditorium, 1<sup>st</sup> Floor, Bhagwan Adinath Jain Complex, Dr. Krishna Murthy Campus, Cancer Institute (W.I.A), Chennai 600 036.

<b>S. No</b>	<b>Name</b>	<b>Role/ Designation in ethics committee</b>	<b>Affiliation of the member with Institution</b>	<b>Attendance to the meeting 22.07.2017</b>
1	Dr. V.I. Mathan	Chairman	Not affiliated with Cancer Institute	Present
2	Dr. T.G. Sagar	Member Secretary	Affiliated with Cancer Institute	Present
3	Dr.G.Selva Luxmy	Clinician	Affiliated with Cancer Institute	Present
4	Dr.K.Kalai Chelvi	Clinician	Not affiliated with Cancer Institute	Present
5	Dr.V. Sridevi	Clinician	Affiliated with Cancer Institute	Present
6	Dr.V.K. Ramadesikan	Basic Medical Scientist	Not affiliated with Cancer Institute	Present
7	Mrs. Ranganayaki Kumar	Lay Person	Not affiliated with Cancer Institute	Present
8	Mr. M. Suresh	Legal Expert	Not affiliated with Cancer Institute	Present
9	Dr. S. Padma	Legal Expert	Not affiliated with Cancer Institute	Present
10	Mr. Chaganti V. K. Maitreya	Social Scientist	Not affiliated with Cancer Institute	Present
11	Dr.Niranjali Devaraj	Scientific Member	Not affiliated with Cancer Institute	Present

The Institutional Ethics Committee, Cancer Institute (W.I.A) functions in accordance with Ethical Guidelines for Bio-Medical Research on Human Participants issued by ICMR, Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 and Indian Good Clinical Practice Guidelines.



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E-mail : [iec@cancerinstitutewia.org](mailto:iec@cancerinstitutewia.org)



Date :

The above documents were reviewed and the study was approved by the ethics committee to be conducted in its presented form in accordance with applicable regulations.

Yours Sincerely,

**Dr. T.G. Sagar**  
**Member Secretary**  
**Institutional Ethics Committee**



## Urkund Analysis Result

**Analysed Document:** GSK Thesis-final.docx (D31344111)  
**Submitted:** 10/15/2017 10:45:00 PM  
**Submitted By:** gsktamil@gmail.com  
**Significance:** 6 %

Sources included in the report:

[http://www.dartmouth.edu/~humananatomy/part\\_8/chapter\\_53.html](http://www.dartmouth.edu/~humananatomy/part_8/chapter_53.html)

Instances where selected sources appear:

3

## **ABSTRACT**

### **Effect of adaptive replanning on ORGAN AT RISK doses at 40 Gy in head and neck cancers.**

#### **Aim:**

To evaluate the dose volume histogram datas in patients diagnosed as stage III/IV cancer in the Nasopharynx /Oropharynx /Hypopharynx. All patients are treated with IMRT using planning CT images and evaluated with CBCT images during the course of treatment.

#### **Materials and methods :**

This is a prospective study of DOSIMETRIC analysis done at our institute between March 2017 to August 2017. We evaluate the TCP and NTCP datas calculated based on equivalent uniform dose(EUD). Cone beam CT images are taken for patients at 40Gy and organ at risk (OAR) such as spinal cord, brainstorm, parotid gland, mandible are contoured by the same radiation oncologist on the CBCT image set and deformed to initial planning CT. DVH generated for these structures from initial clinical plan was evaluated - NTCP and TCP are calculated.

**Description :**

In this study we have evaluated that the mean average parotid volume dose received has increased by 10%. The Median dose increase by 7 %.

**Conclusion :**

In this study we observed a significant increase in NTCP if the same clinical plan continued beyond 40Gy.

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## **I.INTRODUCTION:**

The incidence of head and neck cancers are on the rise, and hence awareness is required among treating oncologists to cater different means of approach, to ensure in such a way that patients treated with concurrent chemoradiation should have better quality of life, inspite of improving overall outcome after the end of treatment. Head and neck cancers employ multidisciplinary approach, and radiation plays a major role as most of the head and neck cancers require organ preservation to ensure an adequate quality of life.

The era of Organ preservation in Head and neck cancers dates back to the Veteran Affairs Laryngeal study trial, in which patients treated with surgery led to unfortunate side effects like dependency with feeding tube, tracheostomy and the rest. This led to search of functional preservation, and with concurrent chemoradiation, the outcome was similar with that of surgery, with patients having an improved quality of life inspite of improved overall survival.

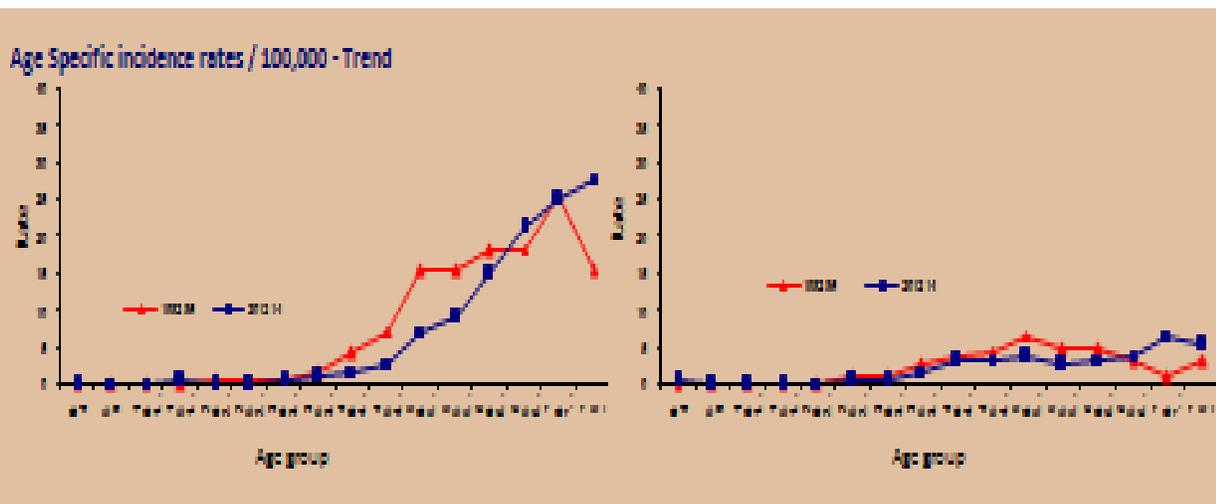
a.Incidence of head and neck cancers from 1982 to till date has been given below which clearly illustrates a rising trend over the years.

## INCIDENCE OF HYPOPHARYNGEAL CANCER:

Cancer Hypopharynx  
 ICD-10: C12-C13  
 Period: 1982-2014  
 Cases: 3,747  
 Male : 2,661  
 Female: 1086

Hypopharynx cancer	1982-1986	1987-1991	1992-1996	1997-2001	2002-2006	2007-2011	2012-2014
Annual No. of cases: Men	56	79	82	91	85	91	81
Women	23	32	28	33	38	41	37
% to total cancers	3.0	3.5	3.2	3.1	2.7	2.4	2.0
Men: CIR / 100,000	3.1	4.1	4.0	4.2	3.8	3.9	3.4
ASR / 100,000	4.4	5.7	5.2	5.1	4.3	4.2	3.5
Cumulative Risk % - One In	185	141	156	159	189	185	178
Women: CIR / 100,000	1.4	1.7	1.4	1.6	1.7	1.8	1.6
ASR / 100,000	1.7	2.2	1.8	1.9	1.9	1.8	1.4
Cumulative Risk % - One In	592	418	495	454	463	500	563

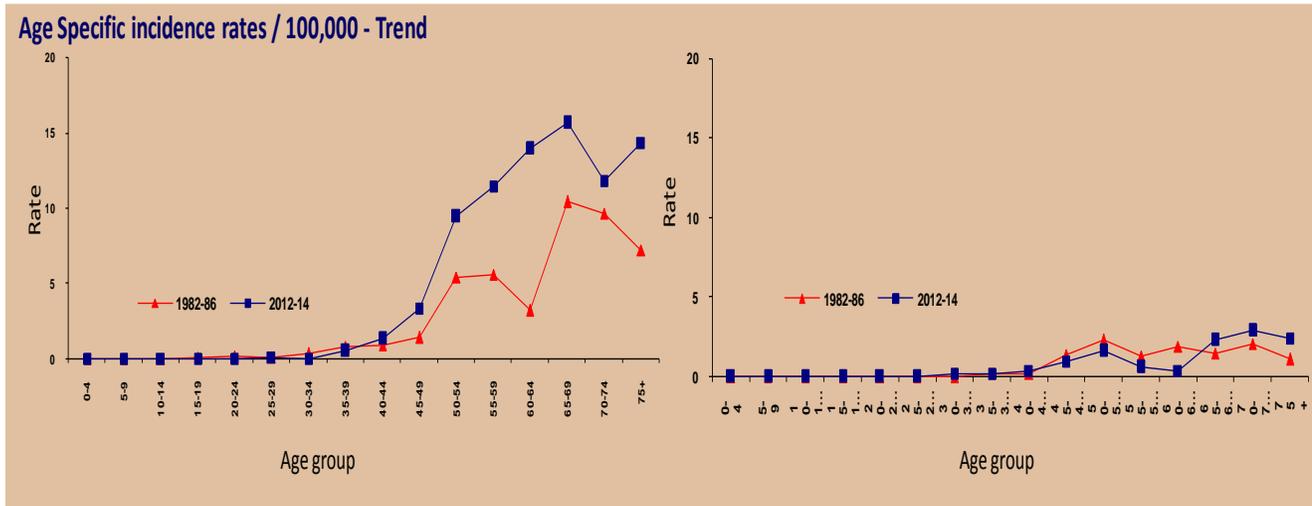
CIR: Crude incidence rate; ASR: Age Standardized Rate



## INCIDENCE OF OROPHARYNGEAL CANCER:

Cancer Oropharynx ICD-10: C09-C10	Period: 1982-2014 Cases: 1,616	Male : 1,377 Female: 239					
Oropharynx cancer	1982-1986	1987-1991	1992-1996	1997-2001	2002-2006	2007-2011	2012-2014
Annual No. of cases: Men	19	30	37	42	61	67	67
Women	5	7	5	8	7	10	10
% to total cancers	0.9	1.2	1.2	1.2	1.4	1.4	2.0
Men: CIR / 100,000	1.1	1.5	1.8	1.9	2.7	2.9	2.8
ASR / 100,000	1.5	2.2	2.4	2.4	3.0	3.0	2.8
Cumulative Risk % - One in	526	364	334	322	272	261	
Women: CIR / 100,000	0.3	0.4	0.3	0.4	0.4	0.4	0.5
ASR / 100,000	0.4	0.5	0.3	0.5	0.4	0.5	0.4
Cumulative Risk % - One in	1818	1587	2222	1923	2703	1724	1716

*CIR: Crude incidence rate; ASR: Age Standardized Rate*

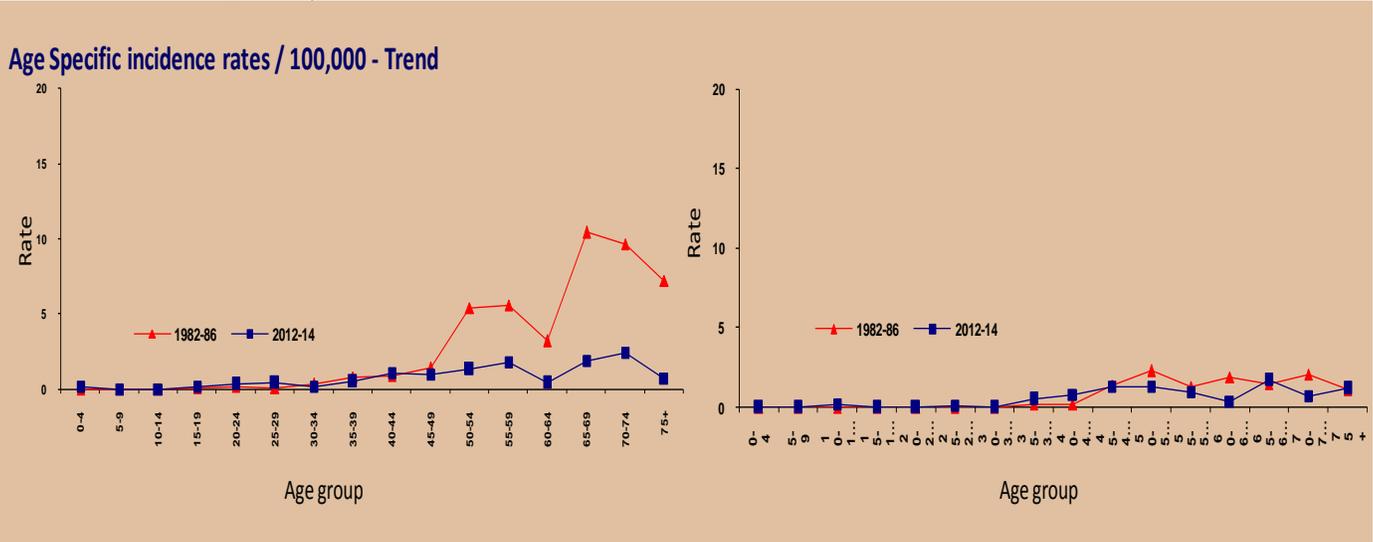


## INCIDENCE OF NASOPHARYNGEAL CANCER:

**Cancer Nsaopharynx**                      **Period: 1982-2014**                      **Male : 466**  
**ICD-10: C11**                                      **Cases: 690**                                      **Female: 224**

Oropharynx cancer	1982-1986	1987-1991	1992-1996	1997-2001	2002-2006	2007-2011	2012-2014
Annual No. of cases: Men	11	12	14	17	15	17	14
Women	16	17	19	24	22	26	10
% to total cancers	0.7	0.6	0.6	0.7	0.5	0.5	0.4
Men: CIR / 100,000	0.6	0.6	0.7	0.8	0.7	0.7	0.6
ASR / 100,000	0.7	0.7	0.8	0.8	0.7	0.7	0.4
Cumulative Risk % - One in	1538	1316	1149	1176	1316	1220	1613
Women: CIR / 100,000	0.3	0.3	0.3	0.3	0.3	0.4	0.4
ASR / 100,000	0.4	0.3	0.3	0.3	0.3	0.4	0.4
Cumulative Risk % - One in	3125	2941	3704	3226	3226	2326	2174

*CIR: Crude incidence rate; ASR: Age Standardized Rate*



## **b.EVOLUTION OF RADIATION TECHNIQUES:**

Radiation therapy started with conventional two opposing fields, unilateral wedge fields and three field technique, which led to appreciable morbidity which had a detrimental effect in quality of life post treatment. Over the years, Radiation treatment has seen a significant improvement with new techniques such as conformal therapy, intensity modulated radiation therapy, volumetric modulated arc therapy, Stereotactic therapy, etc. There was also considerable improvement in interstitial brachytherapy with switch over from low dose rate to high dose rate brachytherapy leading to significant reduction in treatment times, outpatient procedures which resulted in significant evolution of treatment techniques. Organ preservation is a significant task for radiation oncologists, because of the fact that improved treatment techniques does also have some unwanted effects such as increased integral dose, which theoretically has demerits, and also because of the fact that long term data in newer techniques are lacking to exactly pinpoint long term effects of the same. Hence there is a growing need among oncologists not only to compare overall survival and disease free survival, but also functional morbidity, which helps in assessing the quality of life that are experienced by the patients.

One of the most important factors that is usually overlooked is patient's nutrition. The common complaint among head and neck cancer patients is

dysphagia, which in turn leads to poor nutrition, thereby leading to loss of weight and altered body mass ratio, thereby causing major impact on treatment delivery. Numerous studies have emphasized the fact that Intensity modulated radiotherapy can minimize dose to organs at risk, especially the parotid glands, which was the major component of PARSPORT trial, without compromising tumour dose. Non randomized trials also suggests that xerostomia, was less common among patients treated with newer techniques compared to that of conventional and conformal radiotherapy.

In the past, head and neck cancers have lower percentage of local control, due to various factors. Also, conventional treatment led to increased dose to the organs at risk. One of the studies showed that 5 year local control was 84% with increase in radiation dose to the tumour area, but also noticed the fact that such patients, had increased toxicity profile due to irradiation of normal structures with higher dosage. Hence newer techniques were developed to offset and curb the problem.

Radiotherapy has its roots in the discipline of radiology from which branch of cancer treatment –radiation oncology developed. From time Roentgen discovered xrays 2 dimensional images of human body provided unprecedented images of bony land marks allowing the radiologist to locate the internal organs. This helped the radiation oncologist that with the advent of planar radiograph they planned the

cancer treatments by collimating the rectangular fields encompassing the tumor location<sup>2</sup>. Human anatomy however is three dimensional ,by treating a large volume of normal tissue the dose achieved by the structure is very high that the treating physicians themselves have limited by the dose received by the normal tissues.

### **C.EVOLUTION OF IMRT:**

Evolution of radiotherapy from 2D planning to 3D conformal treating plan came after the development of computed tomography techniques.

In three dimensional (3D CRT ) conformal technique a target volume is defined by the xray beams positioned in a two dimensional (2D ) beams eye view of the target. During the planning the patients are positioned with immobilization devices and images are taken in their treatment palnning positions.

These images are reconstructed ,data sets acquired, using the spiral CT scanners which are capable of acquiring 50-100 transverse image planes which can be spaced from 2mm to 5mm cuts according to the desire of the treating physician .

The data transmission sets are equipped to reconstruct the images to 3 dimensional data consisting of Hounsfield numbers associated with Voxels.

DICOM-Digital imaging and communication in medicine software is being used for exchange of data sets from one vendor to the other .This allows the radiation oncologist to plan and treat the patient in another vendor<sup>1</sup>.

The 3 D planning treatment has evolved into Intensity modulated radiotherapy (IMRT) which evolved in clinical practice in the early 1980's. But the widespread usage of the IMRT happened only in the early 1990's in the United States with commercially available peacock IMRT planning system and MIMiC fan beam delivery device (NOMOS RADIATION Oncology Division ,Cranberry Township ,PA)<sup>2,3</sup>. Basically the common feature of IMRT is that they try to have the control over the three dimensional dose distribution by having a large number of independent fields either fixed or from multiple arcs in different positions. With time there came MLC-Multi leaf collimator based IMRT . MLC's allows the adjustment of the treatment aperture which is best suited for dynamic radiation beam.

IMRT techniques are broadly classified into :

- 1.Fixed gantry IMRT

- 2.Arc based IMRT

Fixed gantry IMRT treatment can be either a MLC based delivery and Compensator based delivery .

MLC based delivery technique has two types of treatment delivery technique step and shoot delivery & Dynamic delivery.

Arc based IMRT can be either FAN beam IMRT and cone beam IMRT . Fan beam therapy encompasses MIMiC slice by slice delivery and helical tomotherapy. CONE beam IMRT can be aperture modulated arc therapy (single arc) and intensity modulated arc therapy (multiple arcs).<sup>1</sup>

Intensity modulated radiotherapy IMRT adds a degree of freedom to the treating physicians in RT planning thereby provides an effective means to produce tightly conformal dose distributions in complex treatment situations.

### **Advantages of IMRT:**

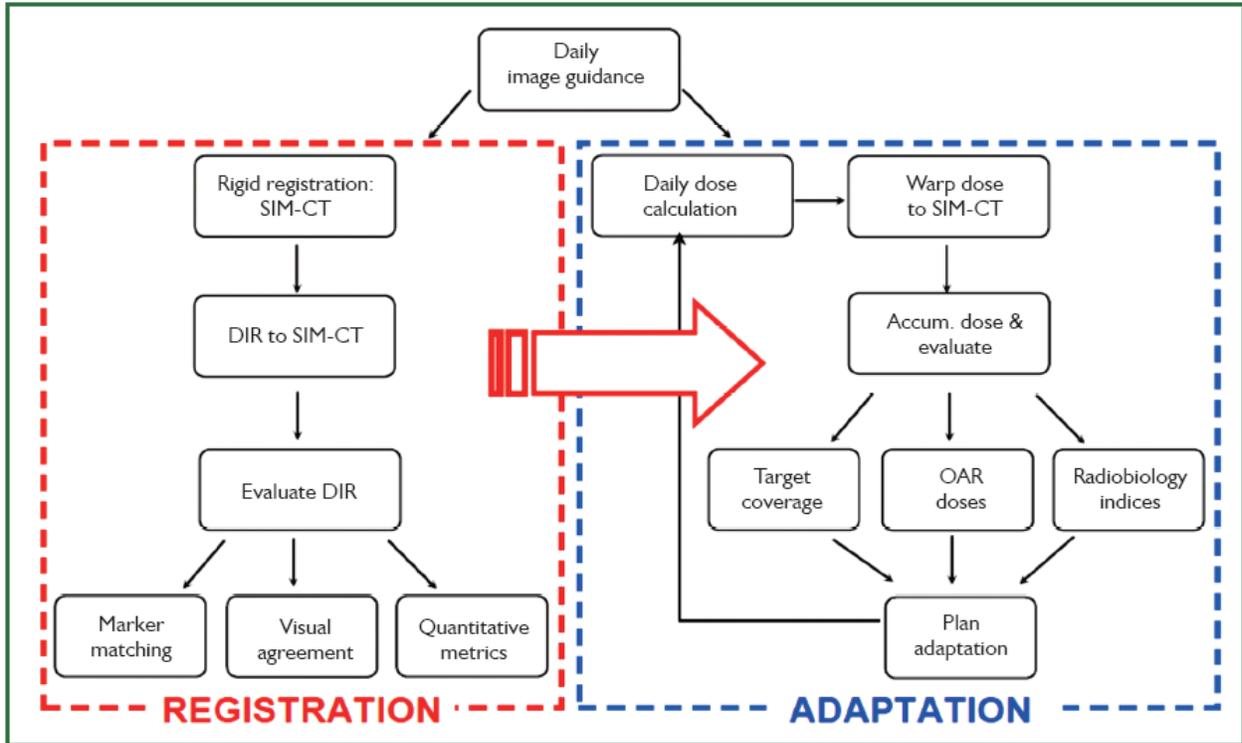
IMRT has the ability to produce high conformal dose distributions which are concave shaped isodose distributions which closely follow the shapes ,boundaries of target tissues . But the conformal technique has convex shaped dose distributions. Because of these highly concave dose distributions we can achieve high tumor control rate and less of normal tissue complications. IMRT also has advantage over the conformal in terms of choice of planning parameters such as beam direction. Further large fields and boosts can be integrated into the single treatment plan and also electrons can be dispensed with permitting the use of same integrated boost plan for entire course of treatment<sup>4,5</sup>. The IMRT also offer added advantage like reducing the dose received by the normal tissue and at the same time higher dose per fraction can be delivered to the TARGET TISSUES.

There is also a clear cut advantage of delivering high dose per fraction to the target tissues thereby it can reduce the total number of fractions received by the patient thereby reducing the overall treatment time , it also reduces the cost and burden of the treatment on the patient.

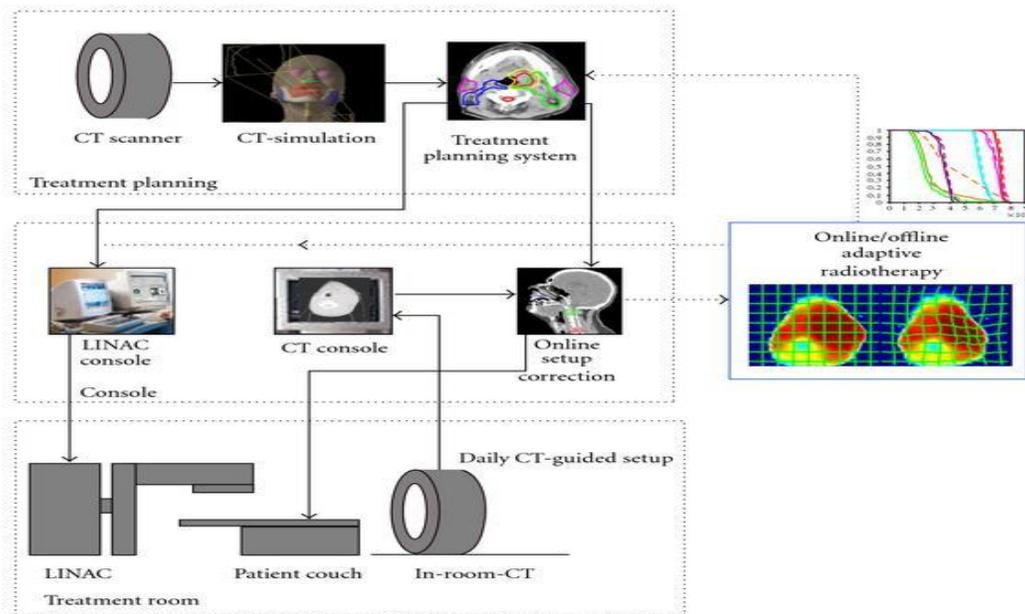
IMRT also has a lot to offer from ART-adaptive radiotherapy .ART adaptive radiotherapy which means revision of the treatment plan by assessing the organ response and tumor response ,organ movement during the course of radiotherapy<sup>6</sup>.

**There are many trials which evaluated the feasibility and advantages of the adaptive radiotherapy which included replan during the treatment course ,taking cone beam CT images to assess the response of the nodal mass and also the target<sup>7,8</sup> .**

**Sequence of registration and adaptation:**



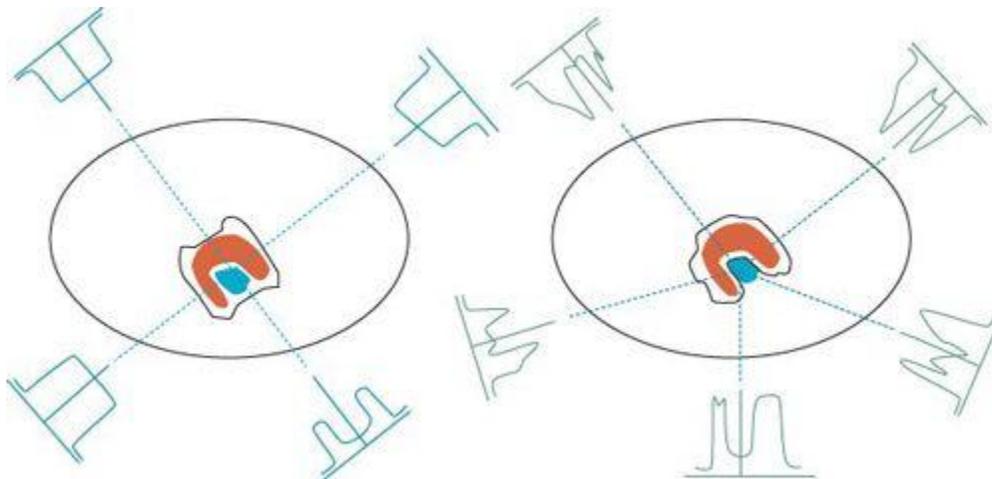
**Steps involved in treatment planning :**



## Limits and risks of IMRT:

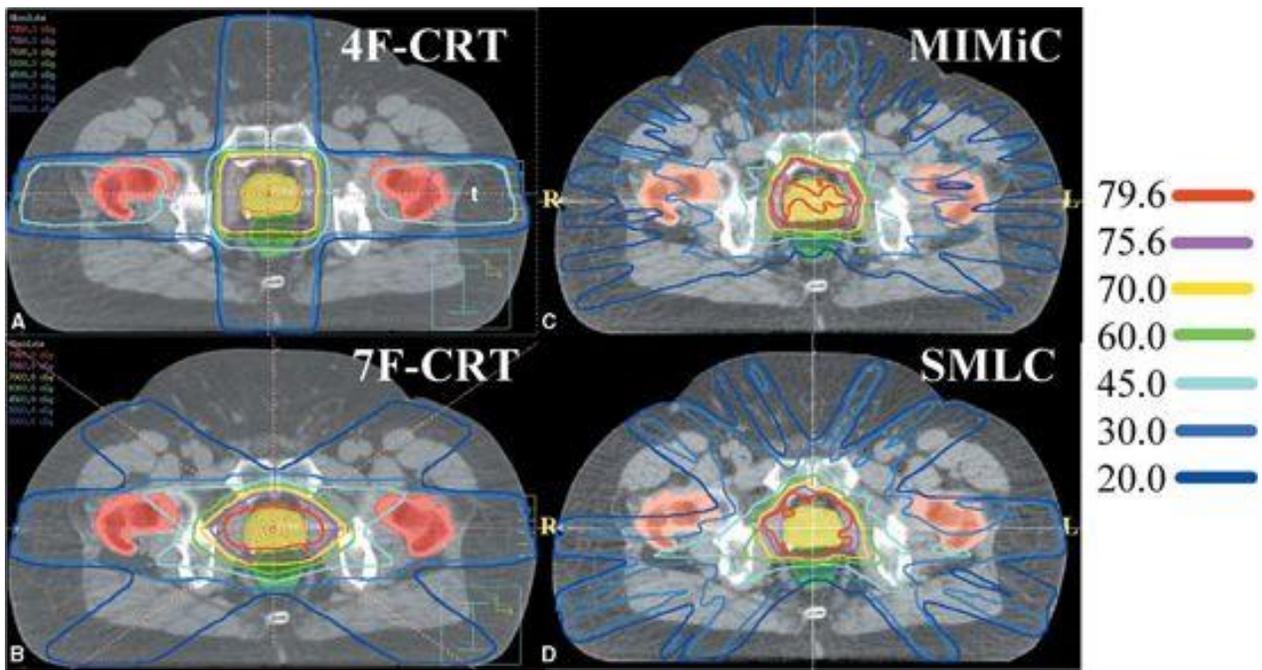
Efficacy and the applicability of the IMRT is also limited to in terms of dosimetric characteristics of dose delivery such as radiation scattering and also the transmission through the MLC leaves .

In addition ; limited temporal and spatial coverage and overall accuracy of the IMRT dose verification systems will diminish the confidence in the delivered dose.



Comparison of Conformal 3D CRTI (left) and IMRT (right). The ability of the 3D CRT to alter isodose lines was limited to shaping of field boundaries with MLCs or blocks, and the use of wedges or compensators for missing tissues and central blocks for shielding critical structures. The IMRT beams can have highly non-uniform beam intensities (fluences) and are capable of producing a more concave-shaped absorbed-dose distribution. With neither conformal therapy nor IMRT can the PRV be always completely avoided, but with IMRT the concave isodose curve that includes the PTV better avoids the PRV. The black region indicates the PTV; the gray region indicates a PRV, and the line surrounding the PTV is a typical isodose contour.<sup>9</sup>

To illustrate the dosimetric advantage of IMRT over 3DCRT techniques, Figure below shows the isodose curves for 4 different RT modalities: 2 plans of 3DCRT (with four and seven fields, respectively) and two IMRT plans, one using serial tomography and the second with a ten-field step-and-shoot MLC.



Typical isodose distributions for treating prostate cancer from (A) a four-field three-dimensional conformal radiation therapy (3DCRT) plan (4F-CRT), (B) a seven-field 3DCRT plan (7F-CRT), (C) an intensity-modulated radiation therapy plan delivered by serial tomotherapy using MIMiC (NOMOS Corp., Sewickley, PA), and (D) a ten-field step-and-shoot segmental multileaf collimator (SMLC) plan.

### **Fixed gantry IMRT:**

There are two steps involved .First a set of intensity profiles one for each incident beam is generated using the dose optimization engine. Depending on the treatment planning , beam profile is modified such that it may be continuous or discretised in space and intensity. One has to take into consideration that incident beam is already divided into grid of beamlets , each beamlet has its own intensity levels.

Fixed gantry IMRT can be either MLC based delivery or a compensator based delivery. Most frequently used IMRT is the MLC based computer controlled one.

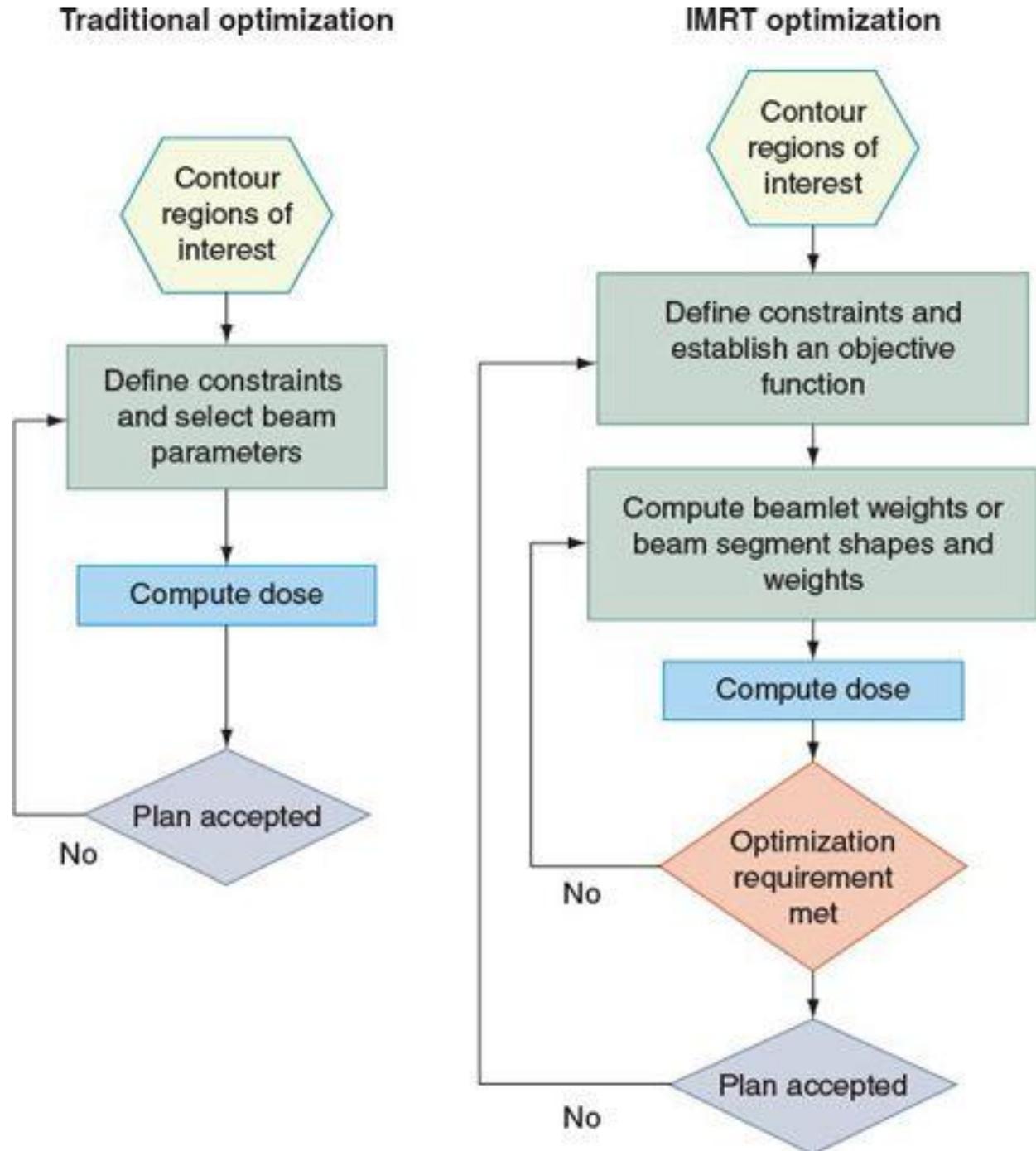
Thus after the planning is done ; an intensity map is generated with a set of apertures using the MLC formed apertures by using an algorithm of leaf sequencing. These are recorded in the treatment planning systems , based on the movement of the MLC treatment is delivered. The treatment delivery can be either a step and shoot method or it can be a dynamic mode. In step and shoot method the MLC remains static and treatment is delivered i.e., dose only , motion only .In dynamic modes MLC moves along as the radiation beam moves i.e.,leaf movement and dose delivery occurs simultaneously. <sup>6</sup>

### **TERMINOLOGY USED IN IMRT:**

**Monitor units:**It is the dose which is delivered at the central axis of the treatment beam. In a linear accelerator the machines are calibrated such that their 1 MU is equivalent to 1 cGy.

**Beamlets:** In view of intensity distribution optimization a IMRT beam is divided into a small intensity element which subdivide the intensity modulated beam. These are called bixels or rays or pencil beams. It can be expressed in terms of

energy fluence or particle fluence based on dose calculation algorithm.



Comparison between traditional (**left**) and IMRT (**right**) optimization processes. (Reprinted from J ICRU 2010: 10(1).

**Dynamic multileaf collimator:** In this mode leaves move continuously which in turn shapes the incident beam when the radiation is turned on. In this way the treatment time can be shortened and also ensures high spatial resolution.<sup>10,11</sup>

**Static multileaf collimator:** SMLC: In this mode the leaves move only when the radiation beam is turned off. They remain in their pre-determined positions and the radiation dose is delivered. This is step and shoot technique.<sup>12,13</sup>

**Segment:** A basic unit of SMLC delivery which is a shaped aperture with a beam intensity which is uniform.

**Objective function:** It is a clinical requirement of a mathematical formalism. It is of three types a) Dose based b) Dose volume based c) Dose response based.

A. Dose based—it is the minimum /maximum dose of a critical structure.

B. Dose-Volume based—it is the fraction of the volume which can receive a certain dose.

C. Dose-response based—it uses a clinical data to a dose requirement which is limited into a clinical outcome. Normal tissue complication probability, tissue complication probability and equivalent uniform doses which are certain clinical indicators.

**Score:** The key parameter for a IMRT optimization is SCORE. It's a figure of merit –a objective function of indicating the quality of treatment plan can be expressed in a numeric value.

**Forward planning:** This is type of planning which is most commonly used in conformal treatment 3D CRT. This planning can be a trial and error process such that the direction of the beams and also the beam weights are modified according to the desired acceptable clinical solution. The forward planning system is also employed in planning the field in field technique. These field in field techniques are most commonly employed in breast, prostate, head and neck cancers. But still these approaches are still inferior to inverse planning techniques.<sup>14,15,16,17</sup>

**Inverse planning:** In this process the clinical requirements calculated from mathematic formalism is transferred into intensity patterns which are deliverable. Ehrgott et al has reviewed an article based on this mathematic formalism.

**Leaf sequencing and deliverable optimization:** This consist of two steps . In the first step, there is generation of ideal fluence pattern which can satisfy the optimum solution for objective function. In the second step, fluence patterns which are ideal are delivered into the leaf sequences. A good optimization takes into account the constraints of the dose delivered and also the leaves characteristics so that it can reoptimize the leaf sequences in such a manner that it fulfills the

fluence distributions which are deliverable and also objective function is fulfilled.<sup>18,19</sup>

**Aperture based IMRT:** In this the treatment portals are divided into a subset of predefined apertures/segments. Then the optimization process becomes a standard beam weight optimization. But this technique is inferior to the inverse planning algorithm.<sup>20,21,22</sup>

**Multimodality image fusion:** IMRT is very important in terms of target organ delineation , so using two or more imaging techniques and fusing them provides additional information about the treatment targets. In simple terms it can be explained that the two or more image sets of the the same subject are combined or fused into a single data set for better understanding of the structures involved.

**Image registration:** The process by which the images are registered in correspondence with other image .

**DICOM:** The most widely used image management and transmission protocol.

**DICOM RT:** It is an extension protocol of DICOM. It has

RT structure set: Contours of the organs in the image set .

RT image: DRR images-Digitally reconstructed radiographs.

**RT plan:** Collimator settings, Gantry angle , MU's , MLC leaf position and other treatment parameters.

**RT dose :** Calculated dose .

## **IMRT TREATMENT PLANNING:**

**Delineation of Target volumes:** In ICRU 83 they have given certain guidelines for the treating volumes which forms the treatment plan. The contoured organs can be malignant tumor , normal tissue near the tumor, distant structures can be contoured. Based on the above structures the volumes are described below<sup>23</sup>.

### 1.Gross tumor volume GTV:

It is the macroscopic tumor volume which is demonstrable.

GTV-T: Primary tumor. GTV-N: Metastatic regional node . GTV-M: Metastatic .

### 2.Clinical target volume:CTV:

It is the volume which encompasses the GTV along with microscopic disease around it or subclinical malignant tissues .Usually it is given as GTV plus 1cm Or 2 cm margin is given.

3.Planning target volume: PTV:It is the volume in which margin was given to the CTV so that the absorbed dose is delivered to all the CTV parts with acceptable probability inspite of differences in the setup variations and organ motion .

## **Organ at risk:OAR:**

These are the normal tissues /organs which are at the risk of exposure to radiation while treating the tumor . Organ at risk if they receive a certain amount of radiation it results in a significant morbidity. This emphasizes the importance of contouring the CTV and PTV with utmost care since the OARs can be exposed to the PTV /CTV doses which lead to morbidity of the patient. There are two types of OARs serial organ and parallel organ. Serial organ are those in which point dose is calculated beyond which it may lead to unacceptable damage .e.g.,spinalcord.

Parallel organs are those in which the dose is calculated according to the volume of tissue exposed -they suffer a loss of portion without loss of function.

## **Planning organ at risk volume:PRV:**

In view of the differences in the organ motion and setup variations a margin has to be given to the organ at risk to avoid significant morbidity.

Remaining volume at risk :RVR :Its the difference between volume enclosed by CTV's and OAR's and external contour of the patient. RVR is very much important with respect to IMRT atleast in dose constraints. Without these volumes being contoured the dose optimization software can produce an excellent dose distribution but with significant morbidity to the patient.

### **Treated volume:TV:**

The absorbed dose for the volume of tissue which comes under the isodose envelope which is prescribed by the radiation oncologist. The ICRU 83 proposes that the TV defined as the 98% of the PTV receiving the prescribed dose. So it can be  $D_{\text{NEAR MINIMUM}}$  and  $D_{\text{NEAR MAXIMUM}}$  .

It should be taken into consideration that the PTV ,GTV,CTV are the volumes which are independent of particular radiation protocol employed. In IMRT treatment planning supplementary margins are given accordingly such that the variations in the organ motion and setup uncertainties are also to be taken into account. So the number of normal structure to be drawn also increases. The dose is escalated to unprecedented levels in IMRT the dose is at unprecedented levels ,distribution of the dose is also highly non-uniform and the plans are generated ,evaluated by computer optimization processs ,basically all the structures to which the dose needs to be constrained has to be contoured.

### **IMRT TREATMENT PLANNING AND OPTIMIZATION:**

The main part of IMRT is the planning and optimization process. In this process the amount of dose to be administered and also the distribution of dose can be monitored. By changing the direction of the beams and also the fluence-by

changing the leaf position . By these processes the treatment is delivered according to the specific clinical problem into a machine deliverable beams.

### **A.Fractionation and treatment schedule:**

IMRT plans are designed in line with conventional fractionation schedules. The doses can be delivered using 3D conformal methods followed by IMRT boost .

IMRT plans are also done from the initial treatment in which larger fields are treated and also the boost fields are planned initially.<sup>24</sup>

When target volumes in an IMRT plan are treated simultaneously it is the most conformal form of treatment. It can be thus said as SIB IMRT(Simultaneous integrated boost).SIB IMRT produces superior dose distribution, more efficient,less error prone in delivering the treatment because the same initial plan was followed till the end of treatment .<sup>24,4,5.</sup> During the course of treatment there arise problem of matching the fields can be minimized.<sup>25</sup>In SIB IMRT the nominal dose and also the size of fraction are corrected according to the number of IMRT fractions.

The effect of acute and late toxicity of the organ at risk /normal tissues should also be considered in case of modified fractionation schedule. Because of the increased conformality of the IMRT plan the dose received by the organ at risk are also very low when compared with the conventional plans.

In the radiotherapy oncology group H-0022 study has evaluated the dosage fractions such as 2.2 Gy per fraction for 5 days x 6 weeks TD:66 Gy to the PTV, 2 Gy per fraction to high risk subclinical disease(nodal regions) TD:60 Gy , 1.8 Gy per fraction to the subclinical disease TD:54 Gy given .All these corresponds to the biologically equivalent dose of 70,60 and 50 Gy. Also the dose constraints for the organ at risk are brain stem -54 Gy , Spinalcord-45 Gy , Mandible-70 Gy. The mean dose of the parotid glands should also be kept below 26 Gy or 50 % of one parotids should be well kept below 30 Gy. When compared with the conventional 2 D ,3 D planning techniques the dose received by the parotids in IMRT is very less which in turn significantly affects the post treatment morbidity in patients . Treatment associated development of xerostomia reduced significantly with improved treatment techniques.<sup>26</sup>

The SIB strategy at Virginia Commonwealth University study the dose-escalation protocol ,the primary nominal dose are 68.1, 70.8, and 73.8 Gy, in 30 fractions which are biologically equivalent to 74, 79, and 85 Gy , if given in 2 Gy per fraction are used.<sup>27</sup> Also the subclinical disease (nodes ) prescribed are 60 and 54 Gy, respectively which are biologically equivalent to 60Gy and 50 Gy, respectively, given in 2 Gy fractions. Spinal cord-45 Gy and brainstem-55 Gy respectively .

In Mallinckrodt institute of radiology , Simultaneous integrated boost strategy for definitive IMRT TD:70 Gy in 35 Fractions in 2 Gy per fraction to the gross disease The soft tissue at risk and nodal areas at high risk received TD:63 Gy in 1.8 Gy per fraction ,the elective nodal regions received TD:56 Gy in 1.6 Gy per fraction .<sup>28</sup>

In a study by Mendenhall et al. altered dosage fractionations are described<sup>29</sup>.

### **B.Beam configuration:**

Optimisation of a beam angle is very much important in IMRT plan so that there is a greater control of beam on dose distributions .However greater control of beam angles may find path which is least obstructed by critical structures. The number of beams used and number of combinations which are compared are some of the advances in the mathematical research . For eg., for a three beam combination atleast 60,000 beam combinations are compared, for a five beam nearly 14 million combinations are tested,for seven beam nearly 1.5 billion combinations are tested.<sup>30-33</sup> In general if there is an increase in the number of beams there is an opportunity to get a desired dose distribution very easily. But in practical ,in case of fixed gantry beam IMRT , it is always advisable to reduce the number of beams to reduce the treatment time and also the effort required to put in the dosimetric verification, delivery of treatment, Quality assurance, planning. In his study Webb et al. has emphasized that 7 to 9 treatment beams are itself necessary to produce highly conformal and adequate dose distribution.<sup>34</sup> The most advantage of placing

the beams is in the directions such that they are not opposing each other . most often beams are constrained to lie in the transverse plane. In general the beam configurations used for 3 D conformal are not optimal for IMRT.<sup>35</sup>

C. Systems using rotating slit approach:

1. Tomotherapy delivery<sup>36</sup>

2. Peacock system<sup>37</sup>

### **PLANNING OBJECTIVES:**

Optimization engines help in optimization of ray intensities by several methods with its own strengths and weakness depending on the nature of objective function and individual preference. The basic principle is that each ray of each beam that pass through the target volume is traced from the source of radiation through the patient<sup>70</sup>. Each patients 3D image is divided into VOXELS. Every voxel has a dose in the patients body which is calculated for the initial set of rays. The score of the treatment plan is calculated from this resulting dose distribution. The ray tracing process identifies the tumor and also traces it down to the normal tissues that along the path of the ray. By changing the weight of the ray , score is calculated. If the weight of the score is increased which leads to favourable consequences for that patient then the weight is increased and vice versa. With each and every change in the weight of the beam the treatment optimization improves . Only a few changes in ray weight is is permitted at a time.

## Objective functions:

### Dose based :

It can be explained as sum of the squares of differences in dose and computed dose in each point within an each volume of interest. This is called as quadratic or variance objective function. The main function of the optimization process is to bring down the value of  $S$ .

$$S = \sum_i (D_{T,0} - D_{T,i})^2 + \sum_n p_n \times \sum_j H(D_{n,0} - D_{n,j}) \times (D_{n,0} - D_{n,j})^2$$

(Eq. 1.1)

$D_{T,0}$ - Target volume receiving the desired dose.

$D_{n,0}$ -n th normal structures tolerance dose.

$D_{T,i}$ -I th voxel of the targets computed dose.

$D_{n,j}$ -j th voxel of the n th normal structures computed dose.

$P_n$ - the relative penalty for exceeding the tolerance dose.

The voxel does not contribute to the score function if the dose in normal tissue not exceeding the tolerance limit.

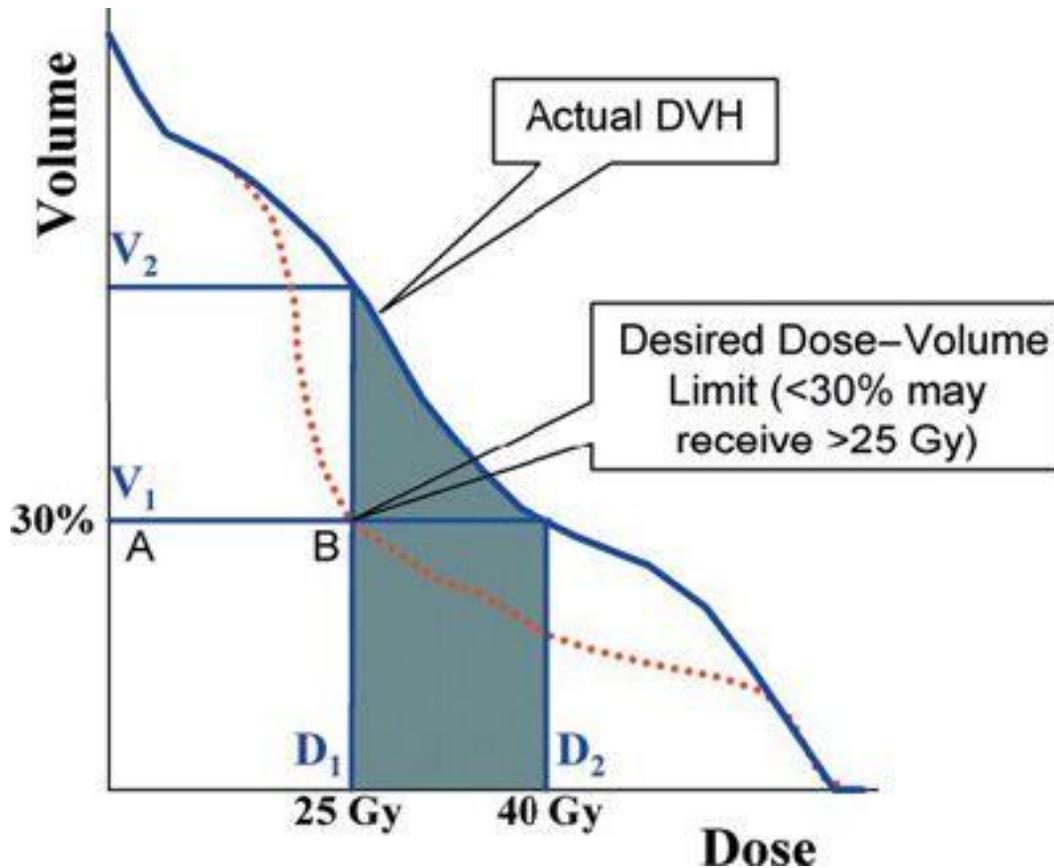
For the normal organs,  $H(D_{n,j} - D_{n,0})$  is a step function defined as follows:

$$\begin{aligned}
H(D_{n,j} - D_{n,0}) &= 0 \text{ for } D_{n,j} \leq D_{n,0} \text{ and} \\
&= 1 \text{ for } D_{n,j} > D_{n,0}.
\end{aligned}
\tag{Eq. 1.2}$$

### **Dose--volume based : Advantages:**

Both the normal tissue and the tumor mass responds to the radiation which can be explained by the amount of radiation each of it has received which is most commonly expressed in volume. The dose volume based objective function is most widely used and it also explains the volume of the structure which can receive a particular limit of dose. It is mandatory as explained in ICRU-83 that the doses received by the structures should always be expressed in terms of DVH dose volume histograms and dose volume criteria. In his study Bortfeld et al.<sup>110</sup> the objective are laid for dose volume histograms. Two points are taken into consideration D1 & D2. The volume receiving more than D1 has a volume which is less than V1. So it is necessary that this constraint needs to be implemented depend on the another dose value D2. So that in the current DVH data  $V(D2) = V1$ . The objective function of the organ at risk can be given as :

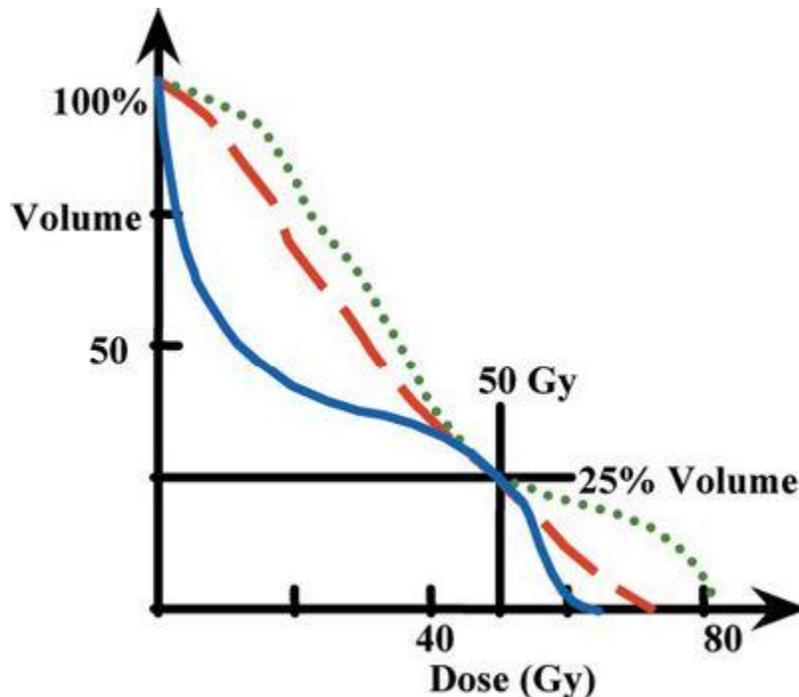
$$p_n \cdot \sum_j H(D_2 - D_j) \cdot H(D_j - D_1) \cdot (D_j - D_1)^2 \tag{Eq. 1.3}$$



A method of incorporating dose–volume constraints in IMRT optimization. (Adapted from Wu Q, Mohan R. Algorithms and functionality of an intensity modulated radiation therapy optimization system. Med Phys 2002;27:701–711.

So to limit the hot and cold spots, there should be two dose volume criteria needs to be specified. So while prescribing the data for desired dose of 80 Gy. We specify that volume receiving >85 Gy should be less than 5% and volume receiving >79 Gy should be >95%. So thus for objective optimization of the technique a dose volume criteria is more flexible and have a greater control over the dose distributions.

## Limitations of Dose volume histogram:



One limitation of the dose–volume histogram (DVH) prescription: one DVH control point (at 50 Gy and 25% of the volume) can have multiple DVH lines of inequitable clinical implications.

To illustrate one such limitation, consider the example of a normal structure the constraint has been not more than 25% of the volume to receive 50 Gy or higher. All the above dose–volume histograms meet this criteria. However, the DVH represented by the solid curve clearly causes the least damage. In order to overcome this limitation by specifying multiple dose–volume constraints or even the entire DVH it would be too limiting. Multiple DVHs could lead to similar

levels of injury to a particular organ, but each DVH may produce a different effect on other organs and the tumor. When this happens, DVHs usually cross each other, as shown. Only one of them is optimum so far as the tumor and other organs are concerned. So the ICRU has come up with the terms such as

NTCP-Normal tissue complication probability.

TCP- Tumor control probability.

EUD-Equivalent uniform dose.

#### **D.RATIONALE BEHIND THIS STUDY:**

Concurrent chemoradiation is an essential component of treatment in locally advanced head and neck cancers .The treatment in unresectable head and neck cancers is concurrent chemoradiation. Techniques of RT varies from conventional to that of IMRT . Some of the most common side-effects are Mucositis ,dysphagia and late side effect xerostomia in patients with head and neck cancers. Among them Xerostomia which is late complication of RT causes difficulty in speech, difficulty in swallowing leading to impairment of QOL .In the treatment for head and neck cancers there are instances in which there is incidental high dose radiation to the Organ at risk (OAR) such as parotid glands,resulting in long term xerostomia is a well-recognized problem after radiation therapy for head and neck cancers. These affect the quality of life of a patient during his post treatment follow

up.QOL after RT is largely related to xerostomia in survivors. Recent technological advances have led to the successful clinical use of **intensity-modulated RT (IMRT)**.IMRT helps in decreasing the number of patients who develop xerostomia , at the same time by sparing organ at risk , without compromising tumor control in head and neck patients. However, large variations can be observed during the course of IMRT treatment, such as body weight loss and primary tumor shrinking . Due to these anatomical variations and to the tight IMRT dose gradient, the actual administered dose may therefore not correspond to the planned dose, with a risk of radiation overdose to the parotid gland. This dose difference clearly reduces the expected clinical benefits of IMRT, increasing the risk of xerostomia.So there is a need to determine the indications for adaptive radiotherapy. To evaluate the predictors of xerostomia in patients with head and neck cancers treated with IMRT, we compared dosimetric parameters of the parotid glands with the grade of xerostomia.

As many studies indicated that in patients with locally advanced head and neck cancers treated with IMRT, there is erroneous distribution of dose to the Organ at risk (OAR) such as parotid, pharyngeal constrictors, submandibular glands. **ART (adaptive radiotherapy) replanning (remould and repeat CT planning) during the course of radiation treatment aims to decrease the radiation**

**overdosage to the organ at risk significantly.** In this study we aim to calculate the dose received by the ipsilateral parotid and also the contralateral parotid .

In our study the mean dose received by the parotid gland , during the start of treatment and later at 40 Gy (20<sup>th</sup> fraction) were compared. However we need some prospective studies which aim to assess the dose received by the OAR. Main aim was to detect the differences in planned dose delivered to the organ and the actual dose received by the organ. Thus it also helps in finding out dose differences with replanning at 40 Gy and without replanning at 40 Gy. This finds out the advantage of adaptive radiotherapy. In this study we planned to take a CBCT image of the patient at 40 Gy in the varian system –treatment delivering room. The physicist has calibrated the CBCT images in such a way that the images are comparable to the CT planning images taken before the start of the treatment. Thus the CBCT image taken is transferred to the TPS planning system using the DICOM server . The images are imported and are superimposed onto the initial CT plan . The organ at risk and the GTV, CTV and PTV are contoured. These images are then superimposed on the initial planning CT . The dose to the PTV and organ at risk are calculated. **We do this study to estimate/quantify the level of errors that would be introduced if we don't do adaptive replanning based on patient's morphological changes .**

## **CONE BEAM CT:**

Cone beam CT images are different from that of the normal routine CT images. The cone beam CT images are volumetric images . The cone beam CT incorporated into the VARIAN has a quality which can match that of the normal routine CT images . The volumetric images are then reconstructed into 2 D images. These 2D images have lesser resolution quality and also the image quality is relatively less . Thus also takes lesser time to acquire the 3D volume information. It carries on board imaging advantage. It is also very much cost effective when compared with replanning CT . The quality of the Cone beam CT images are to be calibrated by the physics team in such a way they are equivalent to the CT images. The physics team makes sure that the Electron density curve of the CBCT (calibrated) to near match with the electron density curve of the CT

## **E.ANATOMY :**

The word throat is used for the parts of the neck anterior to the vertebral column, especially the pharynx and the larynx.

The pharynx is the part of the digestive system situated posterior to the nasal and oral cavities and posterior to the larynx.

It is therefore divisible into nasal, oral, and laryngeal parts:

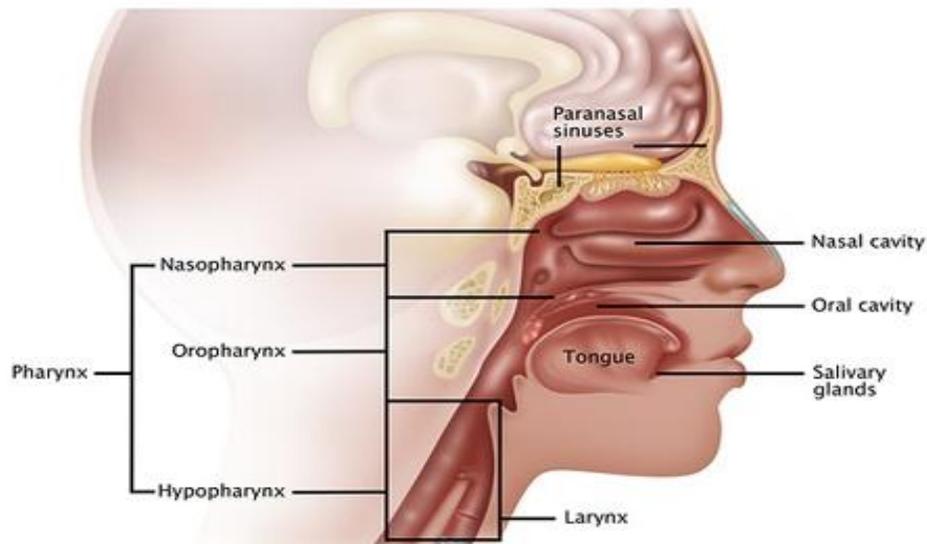
(1) nasopharynx, (2) oropharynx, and (3) laryngopharynx.

The extension of the pharynx is from the base of the skull to the inferior border of the cricoid cartilage (around the C6 vertebral level), below which it is continuous with the esophagus.

Superiorly there is the sphenoid and occipital bones, whereas the prevertebral fascia and muscles as well as the upper six cervical vertebrae, posteriorly.

The pharynx is a fibromuscular tube and is lined by mucous membrane.

The pharynx is the common channel for both deglutition (swallowing) and respiration, where the food and air pathways cross each other. During anesthesia, the extension of the neck facilitates the passage of air through the pharynx.



**Subdivisions:****Nasopharynx:**

The nasopharynx in its small anterior portion, continues as the posterior portion of the nasal cavity and functions as part of the respiratory system.

The nasopharynx communicates with the oropharynx through the pharyngeal isthmus, which is bounded by the soft palate, the palatopharyngeal arches, and the posterior wall of the pharynx.

The isthmus is closed by muscular action during swallowing.

The junction between nasopharynx and the nasal cavity proper is the choanae.

The (naso)pharyngeal tonsil is a mass of lymphoid tissue embedded in the mucous membrane of the posterior wall of the nasopharynx.

Enlarged (naso)pharyngeal tonsils are termed 'adenoids' and may cause respiratory obstruction. A minute pharyngeal hypophysis (resembling the adenohypophysis) is present high up.

Each lateral wall of the nasopharynx has the pharyngeal opening of the auditory tube, located about 1 to 1.5 cm

- (1) inferior to the roof of the pharynx,
- (2) anterior to the posterior wall of the pharynx
- (3) superior to the level of the palate
- (4) posterior to the inferior nasal concha and the nasal septum .

An opening like a nostril is present on the auditory tube .

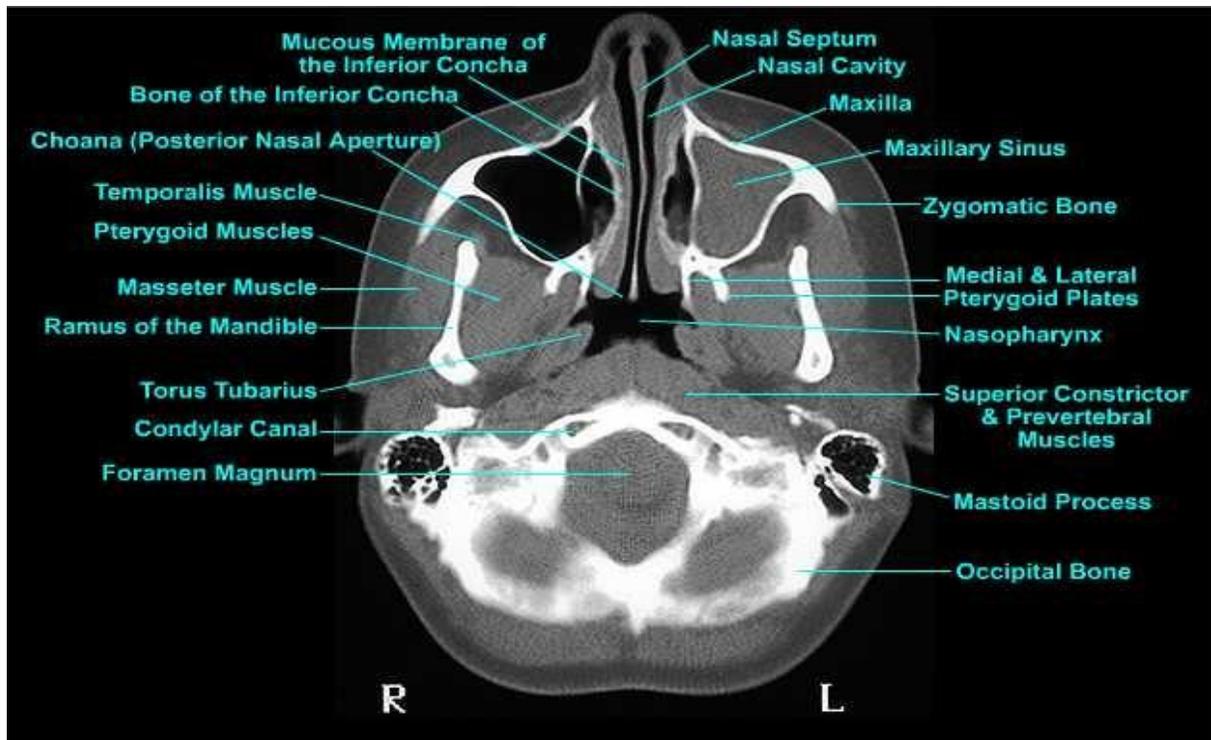
Superiorly by a tubal elevation(tubal torus),through which the auditory tube can be catherised.

Mucosal folds extend from this area of the auditory tube to the palate and the side walls of the pharynx.

The pharyngeal recess is the part posterior to this tubal elevation and the lymphoid tissue near it is reffered to as the tubal tonsil.

Infections can easily spread from the pharynx to the auditory tube as it is 'pharyngotympanic'.

This tube equalizes the pressure of the external air and that in the tympanic cavity.



## Oropharynx:

The oropharynx extends inferiorly from the soft palate to the superior border of the epiglottis. It communicates

Anteriorly: faucial (oropharyngeal) isthmus,

Superiorly : soft palate .

Laterally: palatoglossal arches

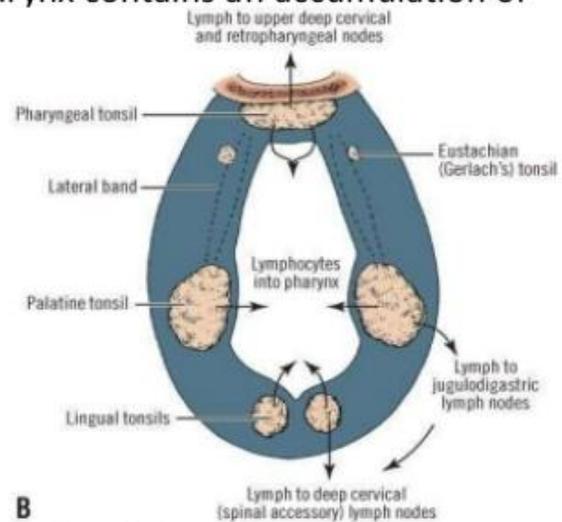
Inferiorly: tongue.

This area is characterized by a lymphatic ring composed of the nasopharyngeal, tubal, palatine, and lingual tonsils.

## Waldeyer's Lymphatic Ring

- Posterior part of mouth and pharynx contains an accumulation of lymphatic tissues-

- Pharyngeal tonsil
- Palatine tonsil
- Lingual tonsil
- Tubal tonsil

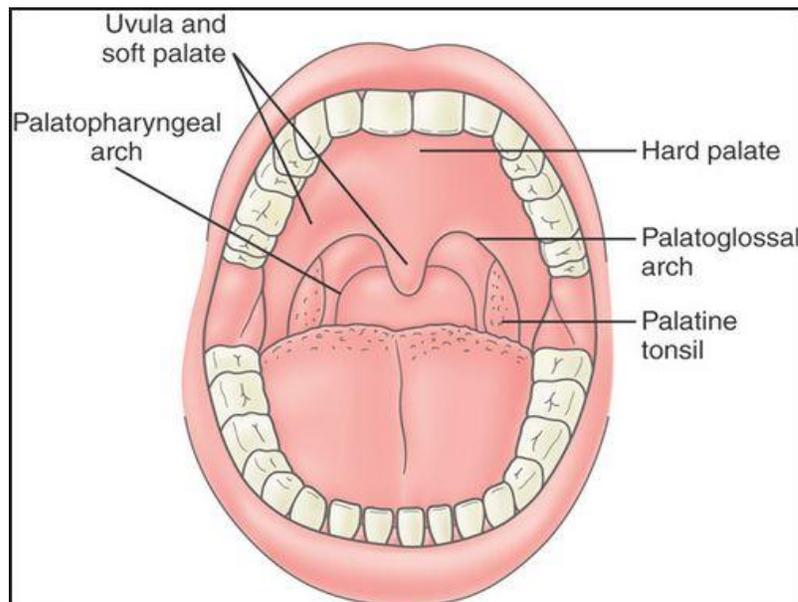


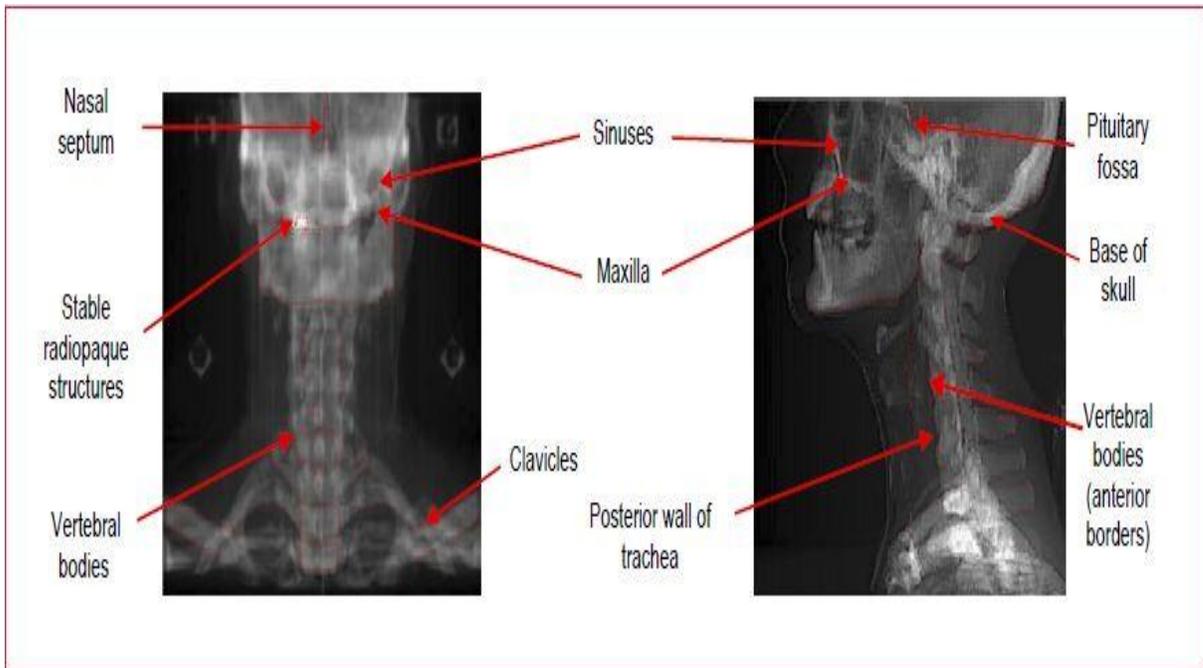
- The ring collects lymphatics and drains into retropharyngeal nodes → jugulo-digastric lymph nodes.

The mucous membrane of the epiglottis is reflected onto the base of the tongue and onto the lateral wall of the pharynx. The space on each side of the median glosso-epiglottic fold is termed the epiglottic vallecula.

Each lateral wall of the oropharynx has the diverging palatoglossal and palatopharyngeal arches, which are produced by the similarly named muscles and are often called the anterior and posterior pillars of the fauces, respectively. The

triangular recess (tonsillar fossa) between the two arches lodges the palatine tonsil, which is often referred to as merely 'the tonsil'. (A tonsil is a mass of lymphoid tissue containing reaction or germinal centers and related to an epithelial surface in the pharynx.) The medial surface of the tonsil usually has an intratonsillar cleft (commonly but inaccurately called the "supratonsillar fossa") and a number of crypts. The lateral surface is covered by a fibrous capsule and is related to fascia, the paratonsillar vein (the chief source of hemorrhage after tonsillectomy), and pharyngeal musculature. The tonsil is supplied by the tonsillar branch of the facial artery, and it drains into the facial vein. Involution of the tonsil begins at puberty





## Hypopharynx:

**Hypopharynx** projects laterally on each side of the larynx.

The three main parts of hypopharynx are

- 1) Postcricoid region
- 2) Posterior Pharyngeal wall
- 3) Two Pyriform sinus.

It lies at the level of 3<sup>rd</sup> to 6<sup>th</sup> cervical vertebra.

Superiorly: Tip of epiglottis

Inferiorly: lower border of cricoid cartilage.

### 1)PYRIFORM SINUS:

It is an inverted shaped pyramid.

Extent: -Superiorly: epiglottis .

Lateral: thyroid cartilage

Medial: arytenoid cartilage; aryepiglottic fold.

Posteriorly: open & continuous with posterior pharyngeal wall.

Apex: meeting of anterior, lateral &medial wall inferiorly

### 2)POST CRICOID REGION

Pharynx continues with the esophagus at the post cricoid region.

Extent :

Superiorly:Arytenoids and inferiorly by the esophagus.

### **3)POSTERIOR PHARYNGEAL WALL**

covers the middle and inferior constrictor muscle

separated from pre vertebral fascia by the retropharyngeal space.

Extent: Superiorly: upper border of epiglottis

Inferiorly: lower border of cricoid

Sideways: apex of one pyriform sinus to other.

## **Nerve supply of hypopharynx**

Internal branch of superior Laryngeal nerve :vagus(X)

Glossopharyngeal nerve :(IX)

sensory: External branch of superior Laryngeal nerve (X) Recurrent laryngeal nerve (X) Pharyngeal plexus (IX) motor

## **LYMPHATIC DRAINAGE**

Deep cervical lymph node : level 2,3& 4

Prelaryngeal&paratracheal lymph nodes: level 6.

Retropharyngeal node -Node of rouviere at base of skull.

## **CARCINOMA HYPOPHARYNX**

Constitute 5.2% of upper aerodigestive tract cancer.

Mostly squamous cell carcinoma.

Mean age of presentation 65 years

Common stage of presentation : stage III& IV -POOR PROGNOSIS

## **INCIDENCE OF HYPOPHARYNX CARCINOMA.**

65-75%-pyriform sinus carcinoma

5-15% - post cricoid carcinoma.

10-20% -posterior pharyngeal carcinoma.

## **RISK FACTORS IN CARCINOMAHYPOPHARYNX**

Age & Sex: carcinoma pyriform fossa- male > 40 years

Carcinoma postcricoid region: females 20 to 40 years

Carcinoma posterior pharyngeal wall : males above 50 years

Personal history -Tobacco ,Alcohol

Exposure :polyaromatic compounds ; asbestos & welding fumes

Nutritional deficiency. Vitamin A& E. iron, Carotenoids and flavenoids.

### **RISK FACTORS OF CARCINOMA HYPOPHARYNX :**

Infections; HPV (20–25% only positive for HPV DNA&Ab against HPV 16 E6 & E7)

Associated diseases: PLUMMER VINSON SYNDROME

GENETIC: P53 & EGFR mutation -Synchronous &metachronous malignancy.

### **FIELD CANCERIZATION :**

Hypopharyngeal carcinoma occur within the field of diseased mucosa.Carcinogens induce dysplastic changes in mucosa of the upper aero digestive tract which increases the risk of malignancy.

### **CARCINOMA OF PYRIFORM SINUS :**

Age:40 years

presentation: late; Metastatic neck nodes

Local Spread:Upwards- base of tongue – Downwards: post cricoid region-

Medially:AE fold and ventricles- Laterally: thyroid cartilage

Lymphatic spread: upper and middle group of jugular cervical nodes –

Distant metastasis: occur late and may be seen in lung, liver, bone

### **CARCINOMA OF POST CRICOID REGION :**

Plummer-Vinson syndrome age group of 20-40; female Progressive dysphagia

Voice change Weight loss

Spread: local spread - cervical oesophagus, arytenoids

Lymphatic spread - paratracheal nodes, may be bilateral due to midline nature of lesion

### **CARCINOMA OF POSTERIOR PHARYNGEAL WALL :**

Mostly seen in males above 50 years of age

Clinical features: dysphagia, metastatic neck node

Spread: local - prevertebral fascia, muscles and vertebrae

Lymphatic: usually bilateral, retropharyngeal and deep cervical nodes involved

### **CLINICAL PRESENTATION :**

Hoarseness of voice: vocal cord fixation

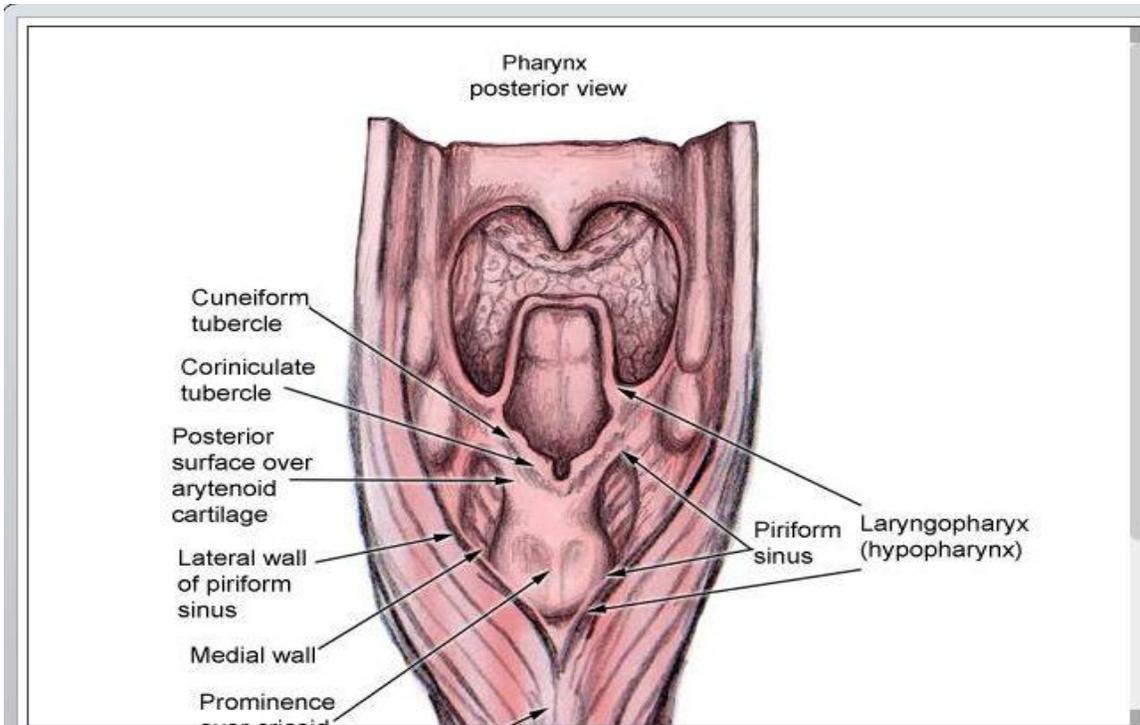
Stridor: mass effect on trachea

Weight loss, Anemia, malnutrition, Throat pain, Sore throat, dysphagia

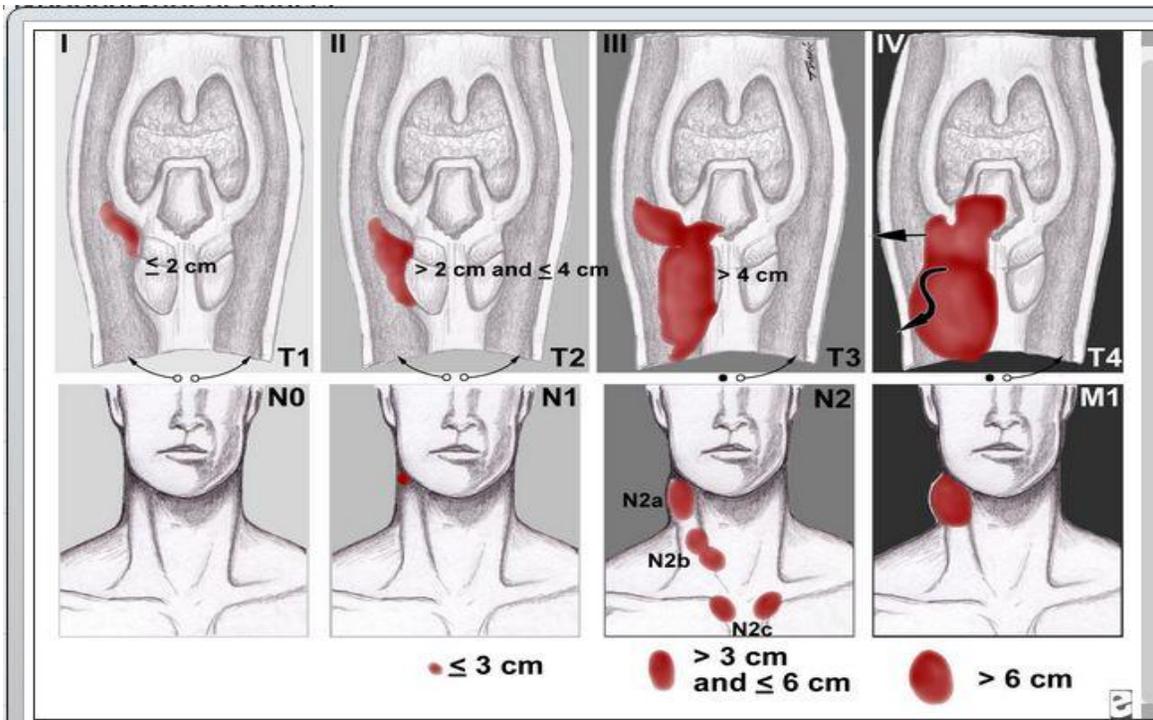
Odynophagia ,pooling of saliva

Referred otalgia: cause int. laryngeal nerve (X) Neck mass: metastatic neck node

Direct extension :most frequent presenting symptoms include a neck mass (either representing the tumour or nodal metastases .



ANATOMY OF HYPHOPHARYNX



STAGING OF HYPOPHARYNGEAL CANCER

## **Anatomy of PAROTID GLAND:**

The parotid gland is the largest of the three salivary glands.

Weighs around 14 to 28 gm.

It lies upon the side of the face, immediately below and in front of the external ear.

The main portion of the gland is superficial, somewhat flattened and quadrilateral in form.

It is placed between the ramus of the mandible in front and the mastoid process and Sternocleidomastoideus behind, overlapping, however, both boundaries.

Above, it is broad and reaches nearly to the zygomatic arch;

Below, it tapers somewhat to about the level of a line joining the tip of the mastoid process to the angle of the mandible.

The remainder of the gland is irregularly wedge-shaped, and extends deeply inward toward the pharyngeal wall.

The gland is enclosed within a capsule continuous with the deep cervical fascia; the layer covering the superficial surface is dense and closely adherent to the gland; a portion of the fascia, attached to the styloid process and the angle of the

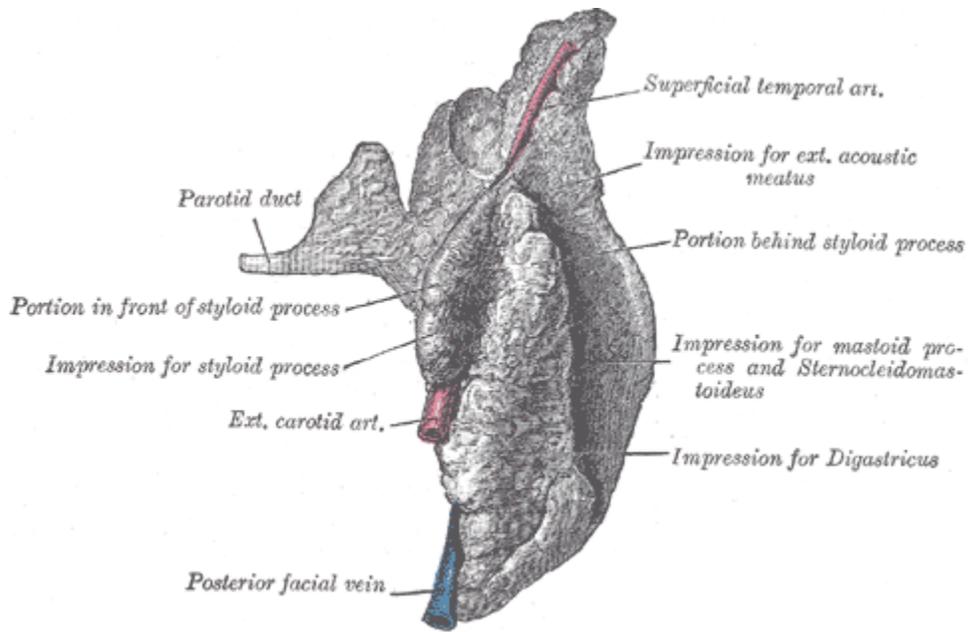
mandible, is thickened to form the stylomandibular ligament which intervenes between the parotid and submaxillary glands.

The **parotid duct** (*ductus parotideus; Stensen's duct*) is about 7 cm. long.

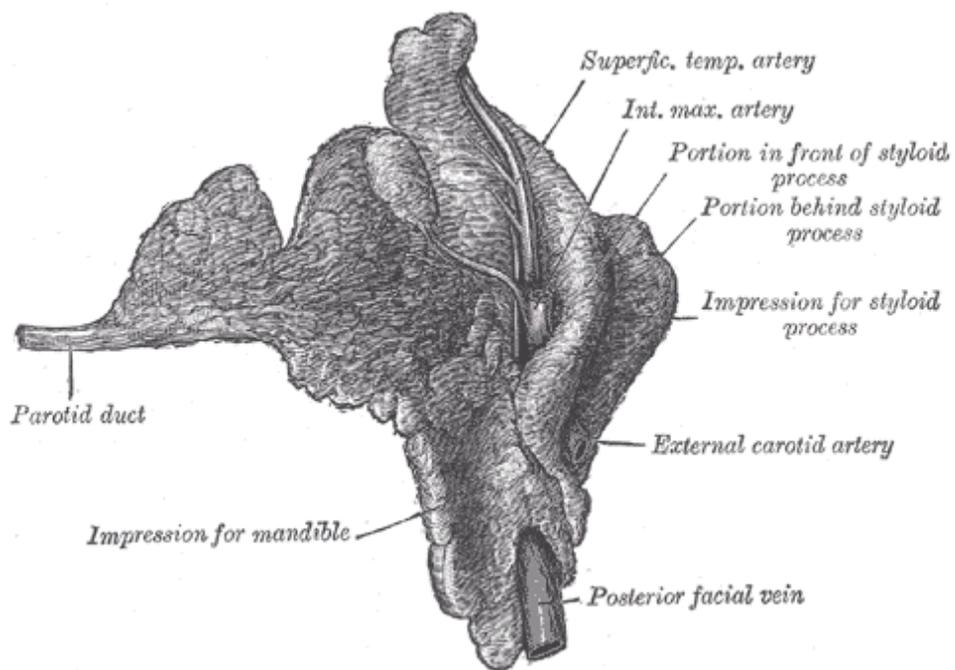
It begins by numerous branches from the anterior part of the gland, crosses the Masseter, and at the anterior border of this muscle turns inward nearly at a right angle, passes through the corpus adiposum of the cheek and pierces the Buccinator; it then runs for a short distance obliquely forward between the Buccinator and mucous membrane of the mouth, and opens upon the oral surface of the cheek by a small orifice, opposite the second upper molar tooth. While crossing the Masseter, it receives the duct of the accessory portion; in this position it lies between the branches of the facial nerve; the accessory part of the gland and the transverse facial artery are above it

**Structure.**—The parotid duct is dense, its wall being of considerable thickness; its canal is about the size of a crow-quill, but at its orifice on the oral surface of the cheek its lumen is greatly reduced in size. It consists of a thick external fibrous coat which contains contractile fibers, and of an internal or mucous coat lined with short columnar epithelium

Right parotid-Posterior and deep aspects



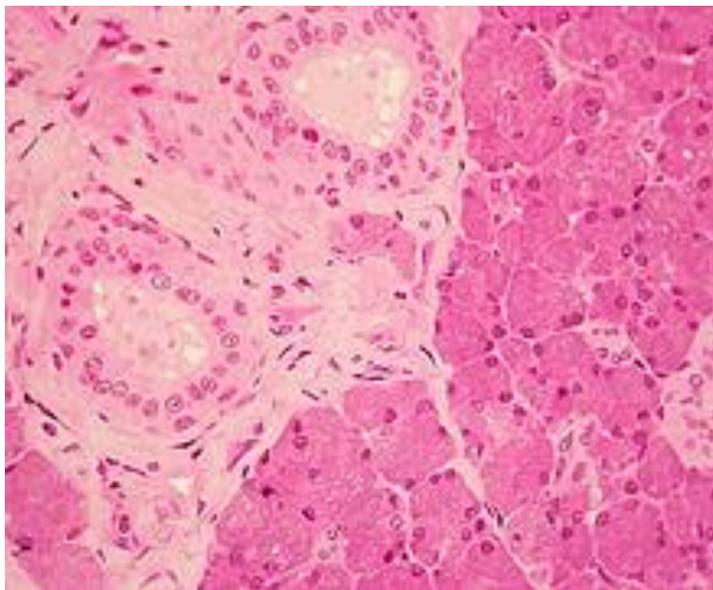
Right parotid gland. Deep and anterior aspects



## **HISTOLOGY:**

The gland has a capsule of its own of dense connective tissue, but is also provided with a false capsule by investing layer of deep cervical fascia.

Parotid gland is the largest, it provides 25% of the total salivary volume. The serous cell predominates in the parotid, making the gland secrete a mainly serous secretory product.



The parotid gland also secretes salivary alpha-amylase (sAA), which is the first step in the decomposition of starches during mastication. It is the main exocrine gland to secrete this. It breaks down amylose (straight chain starch) and amylopectin (branched starch) by hydrolyzing alpha 1,4 bonds. Additionally, the alpha amylase has been suggested to prevent bacterial attachment to oral surfaces and to enable bacterial clearance from the mouth.

## **CLINICAL EVALUATION**

History of illness

General examination

Oral hygiene and dentition

Airways

History of voice change & difficulty.

Examination of oral cavity , oropharynx.

Examination of neck nodes.

Indirect laryngoscopy

Direct laryngoscopy

## **EXAMINATION OF NECK NODES**

Location ,Size,number ,Mobility ,Tenderness ,Relationship with adjacent structure.

Examination of neck nodes: sub mental(Ia) ,submandibular(Ib),upper.,middle& lower deep cervical (ii; iii. iv)

**INDIRECT LARYNGOSCOPY** –mirror is warmed; -Hold tongue with gauze - Introduce mirror into the oral cavity facing downward - mirror brought to rest against the uvula -do not touch the posterior pharyngeal wall - laryngeal inlet is visualized.

Structures seen on indirect laryngoscopy (in order):

Base of the tongue ,Vallecula,Median and lateral glossoepiglottic folds  
Epiglottis ,Vestibular fold ,True vocal cords ,Trachea ,Laryngeal cartilage

### **PRE TREATMENT EVALUATION:**

- a.To assess extent of tumor Relation with other structure
- b.Mobility of vocal cords
- c.Direct laryngoscopy
- d.Oesophagoscopy
- e.Chest xray :infection; malignancy;metastasis
- f.HRCT : thickness, invasion, L.N metastasis
- g.MRI :soft tissue details, tissue edema
- h.PET :residual or recurrent tumor after RT.

### **f.REVIEW OF LITERATURE:**

Several studies have investigated setup uncertainty in HNC patients which could change the dose distribution to the target volume and OARs.<sup>38</sup> An inappropriate definition of the CTV ,PTV margin, accounting for organ motion and setup errors,may yield an under dose to the CTV.

ART(adaptive radiotherapy) planning can be initiated to minimize uncertainties for patients with a great reduction of the circumference or thickness at the level of

mastoid tip at the 20<sup>th</sup> fraction of RT. Generally most of the patients had a reduction in body mass factors (BMF'S) with time.<sup>39</sup>

All patients were positioned supine in an individualized thermoplastic head and neck mask for CT simulation and treatment. This leads to target underdosing and overdosing of nearby OARs (organ at risk), whereas overcompensation for uncertainties leads to unnecessary irradiation of normal tissue and constraints in treatment planning.

So the ratio between tumor control probability (TCP) and normal tissue complication probability (NTCP) emphasizes the role of minimizing uncertainties to enhance the therapeutic ratio of radiation.

Daily online image guidance helps in correcting these setup uncertainties. For patients with anatomic changes due to tumor shrinkage or weight loss adaptive radiotherapy is considered. But increased costs, higher staff workload, and radiation doses to OAR (organ at risk) of the patients should also be considered. So is the need to evaluate suitable indications for adaptive radiotherapy in head and neck cancers. CBCT (cone beam CT) images are taken at 20 Gy and 40 Gy. Organ at risk (OAR) like spinal cord, brainstem, parotid gland, submandibular gland, mandible are contoured by the same radiation oncologist on the CBCT (cone beam CT) images and deformed to the initial planning CT. DVH

generated for these structures from the initial clinical plan was evaluated, NTCP and TCP were calculated.

One plausible factor is that the shrinkage of soft tissue after RT leads to errors in immobilization.<sup>48</sup> So as a result there will be erroneous distribution of dose to the OARs. In order to overcome this, CBCT images are taken at 20 Gy and 40 Gy, during which the differences are maximum. OARs are contoured in CBCT images and registered on planning CT, to evaluate the NTCP for OARs mainly parotids. Thus the consistency between setup errors for the bony structure and the target could be established. CBCT images were calibrated and the electron density curve is matched close to the fan beam CT (Planning CT's electron density curve) to ensure minimal deviation in dose calculation. Replans were calculated on the acquired CBCT images. There was a significant reduction in gross tumor volume at the 20<sup>th</sup> fraction of radiation/40 Gy, this in turn reflects in the volume of the planning target. In our study, organ at risk especially the parotids are significantly away from the planning target i.e., away from the planning target volume.

If the same initial plan is continued till 40 Gy, the parotids which are well away from the planning target volume tend to move into the treatment field thereby it receives dose more than that which is planned leading to xerostomia which significantly causes dryness of mouth, dysphagia. This in turn reflects the morbidity of the patient.

## **II.OBJECTIVE OF STUDY:**

### **a)AIM OF THE STUDY:**

- To analyse the impact of adaptive radiotherapy on organ at risk at 40 Gy before radiotherapy and changes occurring during radiation leading to erroneous dose distribution to normal tissues ,organ at risk in patient with head and neck cancers and need of replanning at 40 Gy. To evaluate the dose volume histogram datas in patients diagnosed as stage III/IV cancer in the Nasopharynx/Oropharynx/Hypopharynx.
- All patients are treated with IMRT using planning CT images and evaluated with CBCT images during the course of treatment.

### **b.Primary objective:**

This is a prospective study done in our institute between March 2017 to August 2017. To evaluate whether organ at risk OAR receive higher doses compared to that of planned dosage due to anatomical variation. .

### **Secondary objective:**

- 1.TCP/NTCP ratio calculation .
- 2.Change in Body mass factors and need for replanning.
- 3.Impact of replanning .

So in this study we have to do treatment planning and delineate target and normal structures. Then we have to do Image guidance and treatment verification using electronic portal imaging device which corrects using matching of bony anatomy and reference markers. At 40 Gy replanning is done in CBCT, OAR, GTV, CTV, PTV are contoured and superimposed on initial planning CT images to calculate the TCP/NTCP of OAR.

Methodology:

STUDY DESIGN: PROSPECTIVE STUDY.

STUDY PERIOD: MARCH 2017- AUGUST 2017

No. of patients : 30.

ELIGIBILITY CRITERIA:

Inclusion criteria:

All patients with

1. Age >30 years.
2. Both sexes
3. Sites included- Nasopharynx, oropharynx, hypopharynx. (stage II/III)
4. Patients planned for definitive Chemoradiation/definitive radiation.

5. ECOG performance status-0/1

Exclusion criteria:

1. Poor performance status. (PS 2 or above)
2. Previously treated or treated outside initially.
3. Upfront surgery.
4. Palliative intent treatment/Metastatic disease .

### **c.Methods and Materials:**

Methods of Planning:

1. Patients are immobilised with thermoplastic mask.
2. CT for RT planning done from Orbit to shoulder with 3mm cuts
3. Marks like leadshot are placed at 3 places in same line over patients surface using laser to facilitate accurate daily position.
4. For patients receiving definitive radiation CTV was defined as GTV+1-1.5cm margin. Guidelines for delineation of elective nodal CTV were followed. PTV was extended 3mm around CTV.
5. IMRT plans are generated.

6.Prescription dose will be 54 Gy to CTV and boost to high risk regions primary and involved lymph nodes upto a Total dose of 66 Gy.

Method of Treatment verification:

1.Patients are positioned on the couch according to reference marks already kept during planning.

2.Online On board imaging (2D KVCT daily and 3D CBCT at 10 th and 20 th fraction were taken and registered with Digitally reconstructed radiographs from the treatment planning images.

3.Images are compared by correlation of bony anatomy and differences are corrected by shifting couch translationally before treatment.

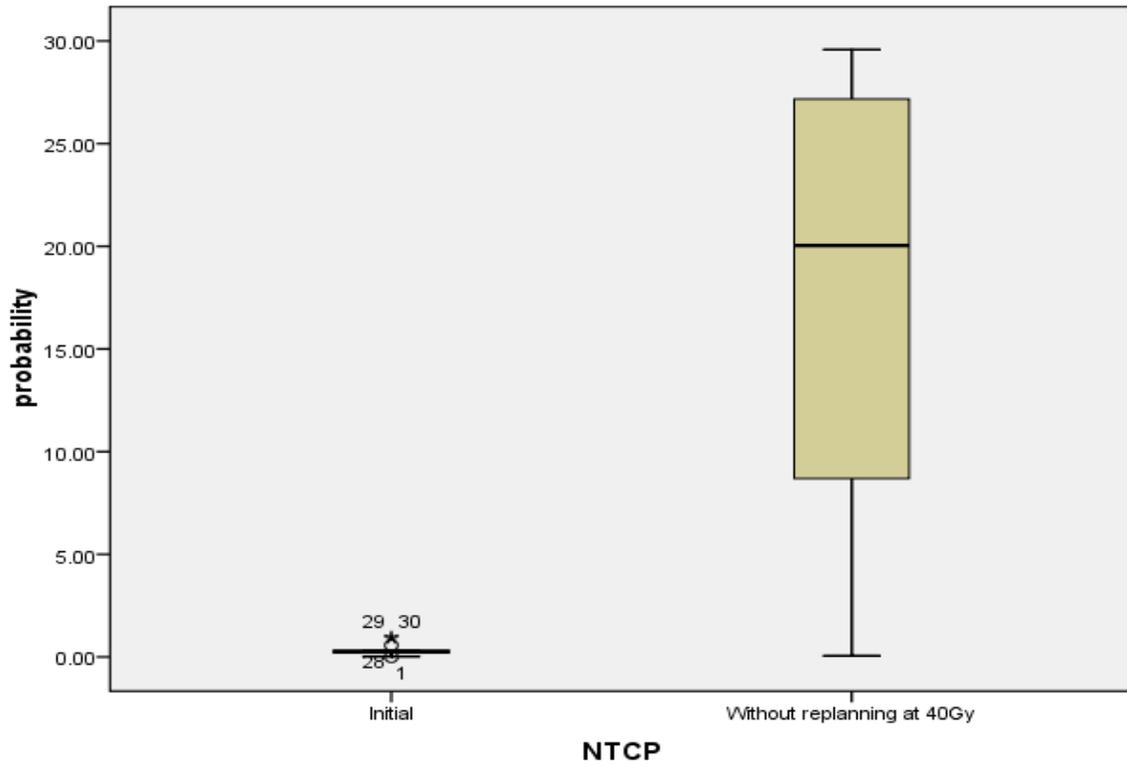
4.Atleast 3 reference landmarks included-3 visible bony landmarks:

1.Vertebra of Cervical Spine.2.Nasal septum.3.Mandible profile.

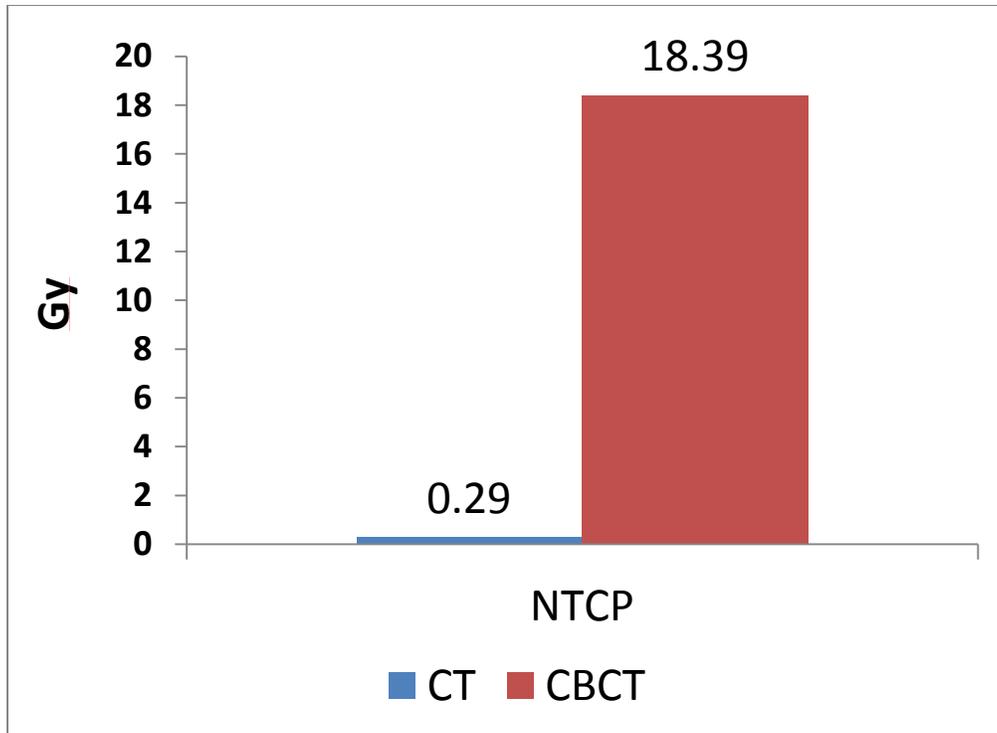
5.In CBCT OAR image structures are outlined and registered with the planning CT.Registered structures are evaluated for dose delivered by clinical plan.

### III.RESULTS AND ANALYSIS:

#### 1.NTCP of parotids:



The box plot analysis explains the probability of the normal tissue complication probability of parotids without replanning at 40 Gy. There was an apparent increase in the dose received by the parotids if the same initial plan is continued till 60 Gy. The p value in our study is about  $<.0001$ , which is statistically significant. These statistically significant values also transformed to give us practically significant results.

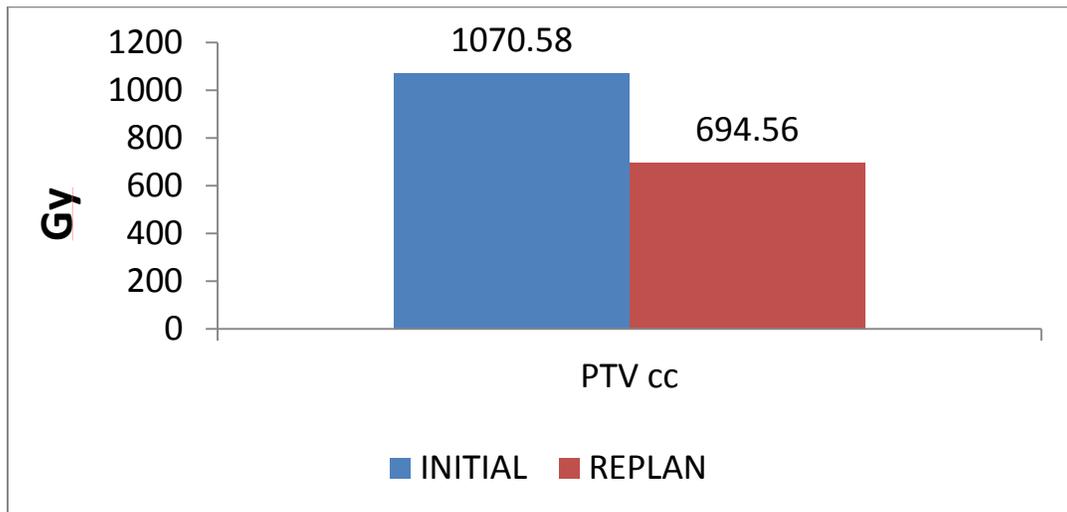


So from this we can infer that replanning at 40 Gy will reduce the dose received by the parotids and thereby reducing the normal tissue complication probability. This means that the mean parotid dose received is only around 28-30 Gy for both the parotids. So this is very much in favor of the study which aims to reduce the morbidity and also the longterm complication such as xerostomia which can be prevented in our patients by adaptive replanning at 40 Gy .

### **B.Planning target volume:**

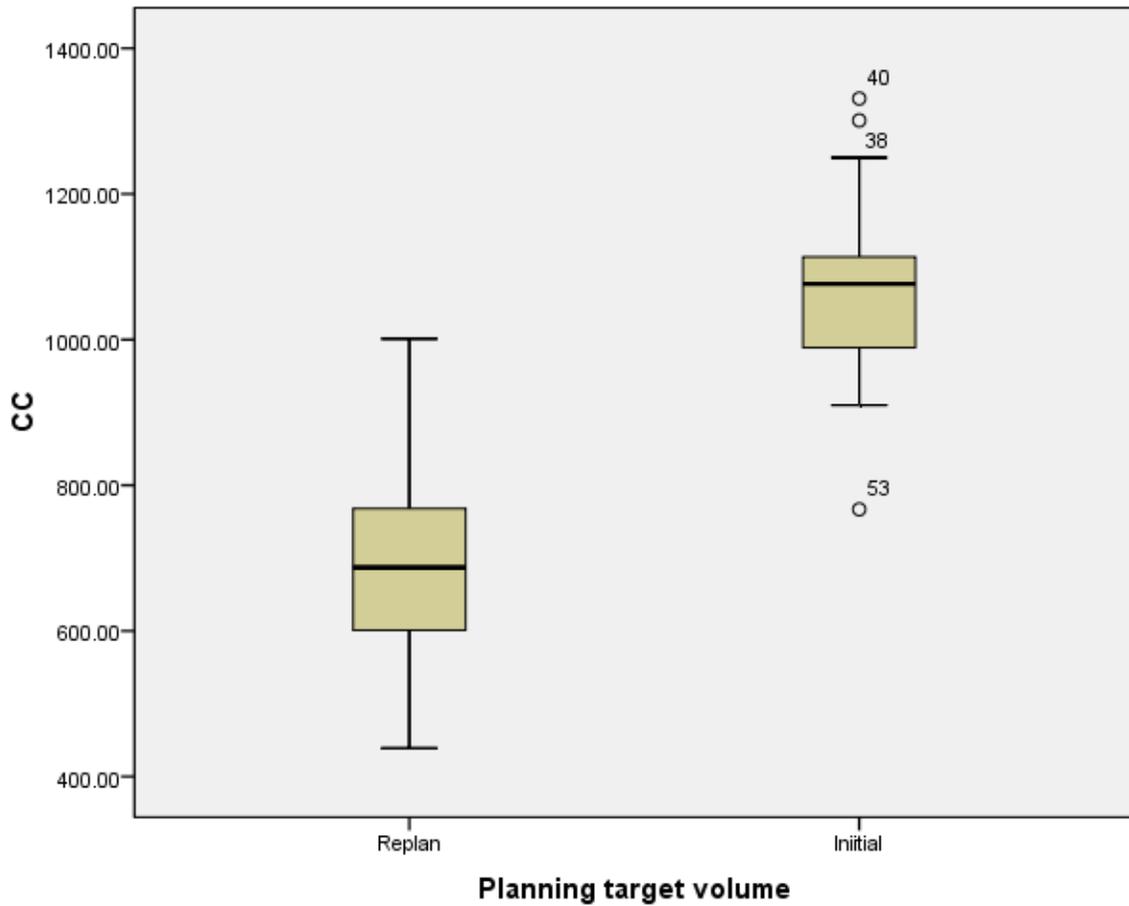
The planned target volume comparison between the initial planning and the replanning CBCT(cone beam CT ) structure sets also showed that there was a significant reduction in the volume of the gross tumor volume. From this we can

infer that at 20 th fraction of the radiation regimen there was a significant reduction in the planning target volume which if taken into consideration during replanning can reduce the normal tissue complication . The box plot curve of the planning target volume (PTV) shows a significant reduction in the volume of the planned target which is prescribed to get a V95% dose.



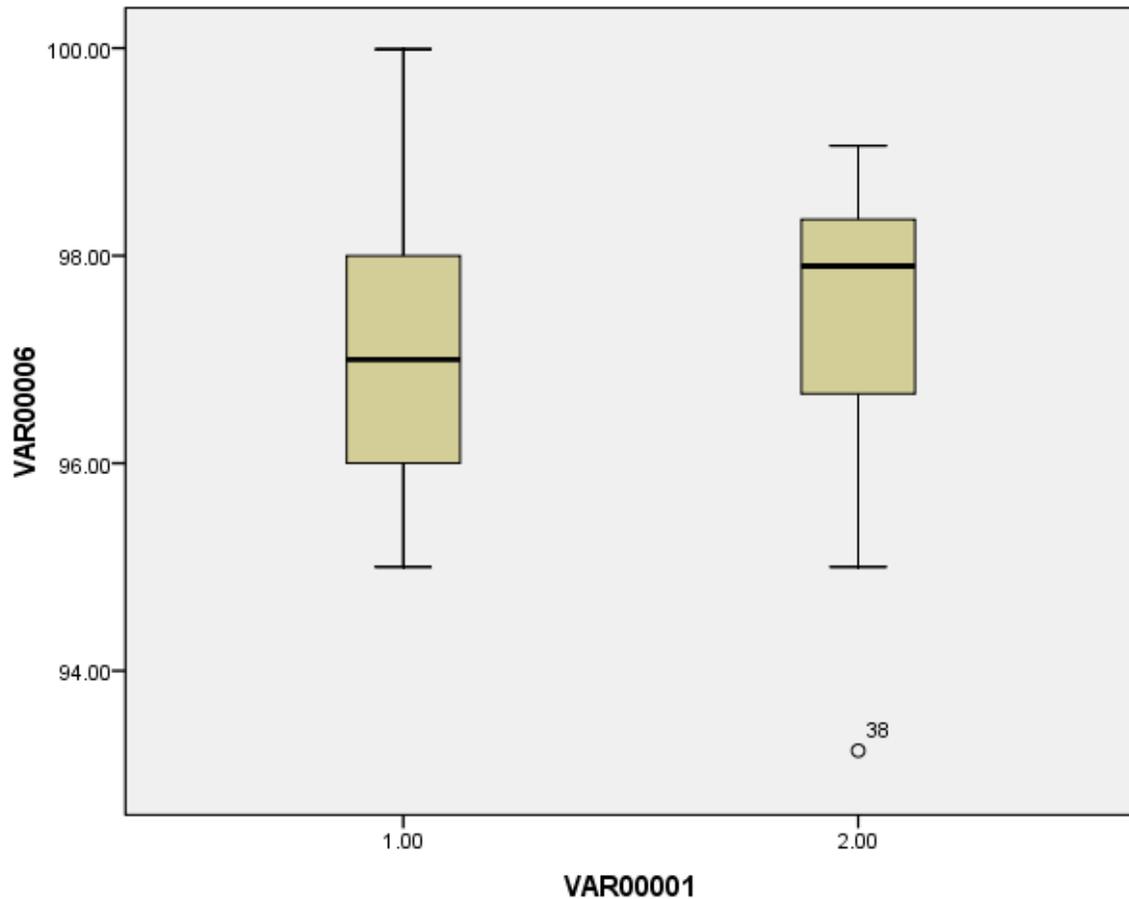
When the initial planning target volume was compared with the replanning target volume the values are statistically significant with the p value of  $>.0001$ . This variable also supports this study whereby the effect of replanning at 40 Gy can bring about significant change/reduction in the morbidity of the patient.

Paired Samples Correlations				
		N	Correlation	Sig.
Pair 1	PTV2 VOL CC & PTV1 VOL CC	30	.752	.000



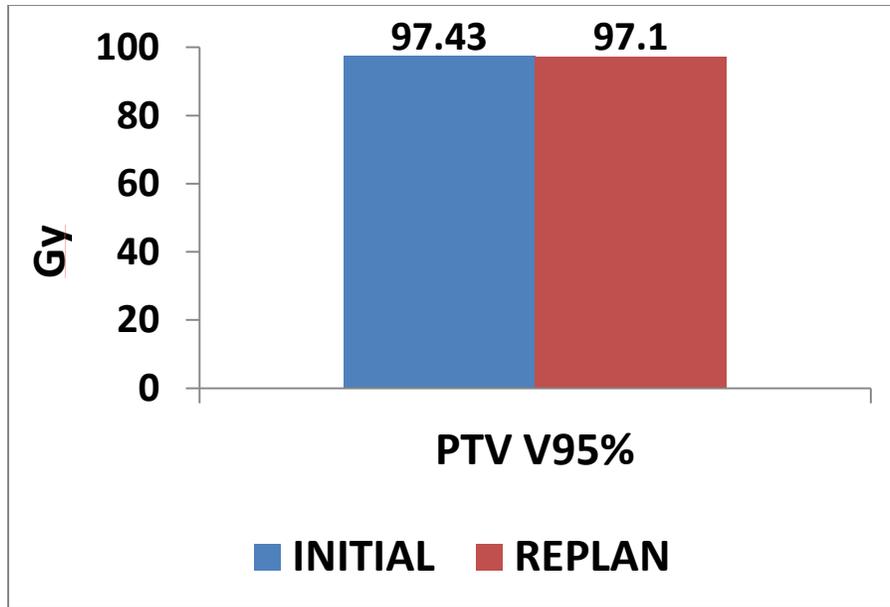
C.PTV V95% dosage:

The V95% is that volume of the planned target volume receiving 95% of the dose prescribed. There was no significant difference in the paired T test compared with the initial PTV V95%.



So this analysis shows that eventhough there is a change in the gross tumor volume , the dose which has to be received by the planned target volume is not compromised , which in turn reflects the study in a positive way.

The above bar diagram also indicates that the PTV V95 % for the initial planning CT was 97.43 % . The PTV V95% for the replanning CT is about 97.1 % . Thus there is not much of a difference in the dose received by the target.



Thus from this we infer that without compromising the dose received by the planned target volume we are able to spare the parotid glands thereby reducing the normal tissue complication probability.

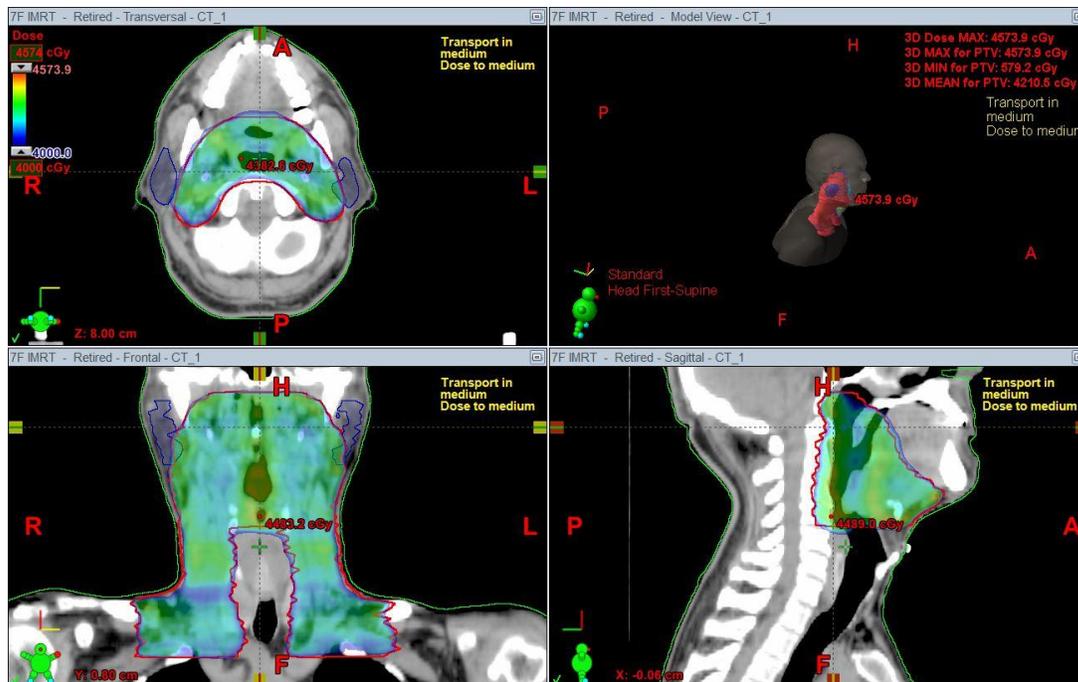
	Mean	Std. Deviation	N
PTV2 V95	97.0980	1.46420	30
PTV1 V95	97.4317	1.33127	30

#### D.Dose distribution at 40 Gy:

The below picture clearly depicts that during replanning at 40 Gy the dose distribution to the parotids show a significant change when compared with initial planning target volume. Also the volume of the gross tumor also shows a significant decrease in the volume so the shrinkage of the tumor and also other

body mass factors related with it shows that if the same initial plan is followed the parotids will also get the target /prescribed dose leading to increase in the dose received by the normal tissues leading to unplanned normal tissue complication.

Dose distribution at 40 Gy

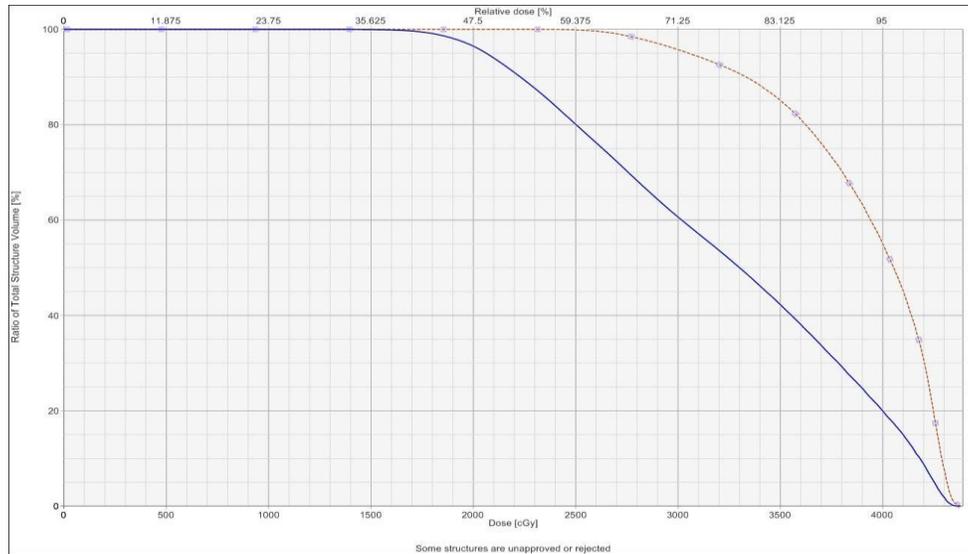


#### E. Dose volume histogram of parotids:

The below dose volume histogram of the parotids shows the DVH of the initial parotids with that of the DVH of the replanning CBCT image taken at 40 Gy. So from this graph it is evident that there is a significant increase in the dose received by the parotids if the same initial clinical plan is continued till 60 Gy. The blue line

denotes the initial planning CT with DVH of parotid ,the red dotted line denotes the DVH of parotids for replanning CBCT images at 40 Gy.

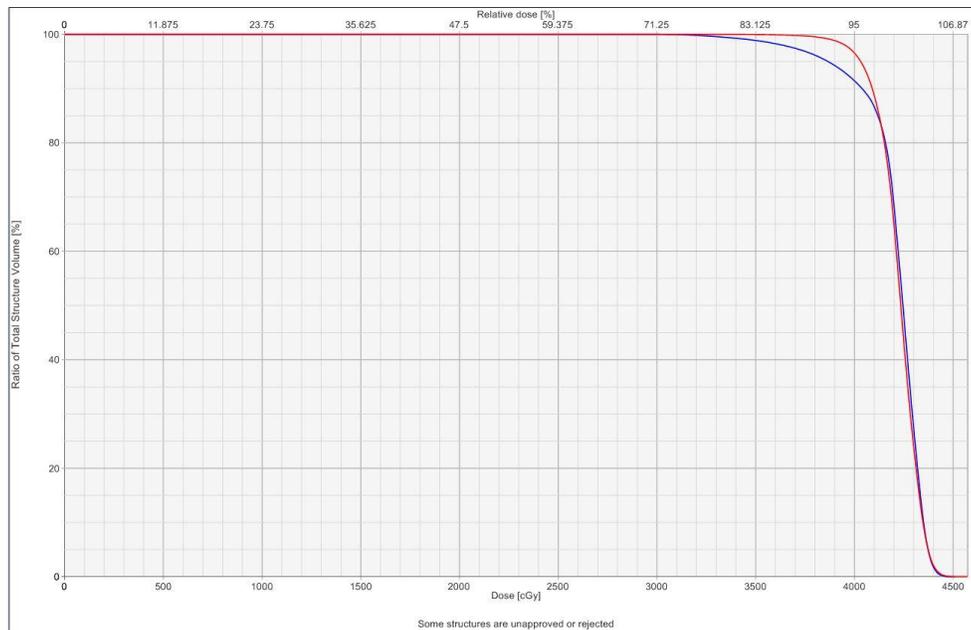
## DVH of Parotid



Thus the dose volume histogram depicts a clear advantage in favour of replanning CT at 40 Gy .

F.Dose volume histogram of PTV:

## DVH of PTV

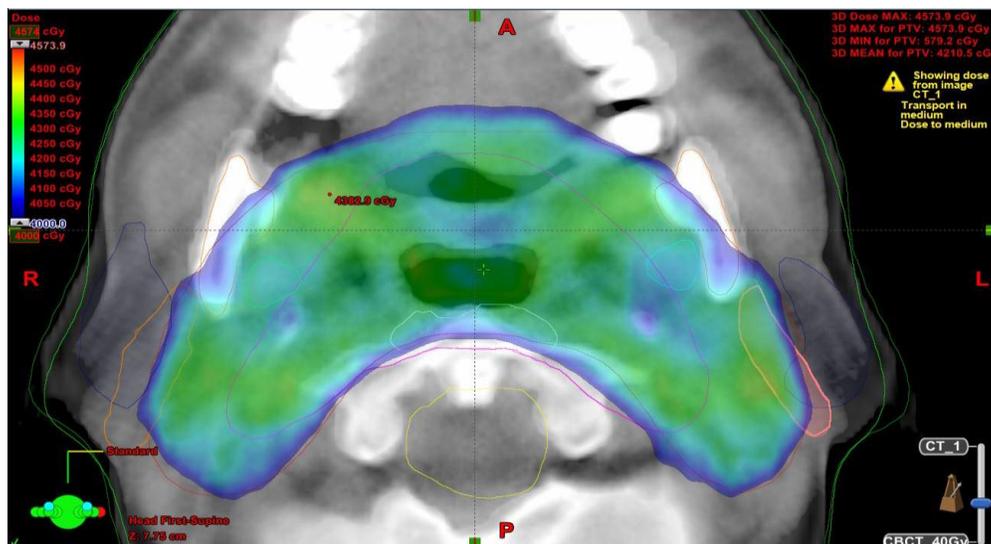


The dose volume histogram of the PTV – initial dose compared with the replanning PTV dose . From the above we infer that the dose received by the planned target volume always receives the maximum prescribed dose , so thereby it helps in achieving the planned dose and also at the same time helps in reducing the dose received by the parotids. Parotids being the major salivary gland ,sparing it will help reducing the late complications such as xerostomia , difficulty in swallowing.

## G.Fusion of CT with CBCT image:

The above image shows the initial planning CT images are fused with the Cone beam CT images (CBCT) so that we can evaluate the percentage of normal tissue receiving the dose higher than the initial plan. The parotids which are away from the planning target volume in the initial CT have very well moved into the treatment field thereby receiving the planned target dose which in turn increases the mean volume of the parotids .

## Image showing parotid sinking into field



The sinking of the parotids into the PTV results in increased dose to the parotids leading to xerostomia.

The following table is data analysis obtained from this study:

S NO	PAROTID REPLAN	PAROTID INITIAL	PTV2 V95	PTV2 VOL CC	PTV1 V95	PTV1 VOL CC	CORD GY INITIAL	CORD GY REPLAN	NTCP CT	NTCP CBCT
1	1.75	18.55	99.5	768	97.55	1099	33.55	10.99	0.0000015	0.062
2	4.5	28.46	96.6	687	98	1078	30.75	13.4	0.019	5.67
3	4.63	18.24	98.64	687	97.8	1008	27.56	15.28	0.11	27.17
4	5.65	19.9	97	599	98	1126	35.9	8.83	0.13	28.03
5	5.66	17.55	98	611	97.5	910	30.65	10.35	0.14	13.58
6	6.5	27.2	95	650	96.5	989	28.65	12.5	0.17	20.21
7	6.86	27.66	99.99	650.2	99.06	1113.4	35.99	9	0.19	29.58
8	7	20.65	95	1001	93.23	1301	34.82	10.5	0.2	16.24
9	10.05	26.8	95.56	650	98.06	1075	33.06	9.86	0.21	19.86
10	10.41	24.48	95	991	95.56	1331	32.82	12.5	0.22	16.86
11	10.45	18.8	95	550	97.5	995	29.56	11.02	0.22	27.87
12	10.5	22.38	96	698	96	1086	27.65	10.92	0.23	24.45
13	10.52	25.06	96	439	98.5	977	29.08	14.54	0.23	28.88
14	10.55	17.66	97	596	98.5	1176	38.22	8.98	0.23	28.15
15	10.96	15.9	97.55	550	99.01	979	34.32	7.55	0.24	25
16	11.55	23.56	98	750	97	1100	35.8	9.1	0.25	26.69
17	12.09	25.6	97.6	855	98	1195	30.06	12.22	0.27	27.77
18	12.55	33.57	98.9	756	96.67	989	35.6	8.56	0.28	8.69
19	13.01	26.2	96.8	585	98.7	927	29.86	10.96	0.29	16.62
20	13.21	30.32	97.87	610	98.86	1111	35	8.1	0.3	28
21	13.23	31	97.33	707	96	1100	28.46	13.9	0.3	23.84
22	15	30.03	96	727	97.5	1068	33.08	9	0.32	24.31
23	15.45	30.55	97.42	505.5	97.54	767	32.65	12.66	0.33	6.75
24	15.55	16.62	95	672	95	1051	37.7	8.15	0.33	15.52
25	15.56	28.86	99	690	98.5	938	30.5	11.6	0.33	5.55
26	15.58	31.58	95.68	601	98.26	983	31.66	9.87	0.34	23.43
27	16.21	32.42	98.5	800	98	1250	32	9.66	0.35	12.21
28	16.51	15.6	97	823	98	1216	36.58	12.29	0.57	8.27
29	17.28	34.31	97	859	95.8	1112	30.12	11.56	0.9	5.89
30	17.65	31.41	99	769	98.35	1067	31.27	11	0.98	6.58

## **IV.DISCUSSION:**

Effect of adaptive radiotherapy in head and neck cancers is long been considered as a means to produce accurate dose delivery to the planned target volume variations in the anatomy due to shrinkage of the tumor volume and positional error all have an overall impact in the treatment of head and neck cancers. The effect of radiation on gross tumor volume happens at about 20<sup>th</sup> fraction of radiation /40 Gy tumor dose . Most of our patients showed a gross reduction in the tumor volume.

### **A.Planning target volume initial vs replan:**

From our study involving 30 patients,we observed that the mean PTV value of initial planning CT was around 1070.58cc.The median PTV for initial plan was 1076.50 cc . The minimum PTV for initial plan is around 767 cc . The maximum PTV for initial plan is 1331 cc. After the completion of 40 Gy in 20 # fractions,we observed a gross reduction in the volume of the GTV from our weekly CBCT images by assessing other morphological changes.The mean volume of the PTV in the replan CT(CBCT) was measured to be 694.55cc.The median volume of the PTV in CBCT images is 687.0 , the minimum target volume in CBCT image is around 439.0 , the maximum target volume in CBCT image is 1001.0cc.

From this observation ,we found that most of the patients exhibited significant reduction in the PTV after the completion of 40Gy.Thus ,this study helped us to investigate the effect of dose distribution on the PTV and the close lying OARs namely parotids in our study.

As the parotids are located peripherally to the tumours,any shrinkage in the tumour volume resulted in the parotids,sinking into the treatment field.

In IMRT treatment we always happen to limit the dose to the OARs(parotids) just at the tolerance limits,due to its anatomical location.The ability of IMRT to sculpt the dose and take shapes avoiding parotids,can be appreciated very much in the treatment plans.After approving the plan,which has already met the dose volume objectives of the OARs and PTV,we assume mostly that the same has been delivered but due to tumour regression and other factors,including morphological changes,we end up in blindfolding ourselves from retrieving and correcting for the dosimetric impact of the structures.

Considering the effect of parotids sinking into the treatment fields at 40 Gy due to various factors listed above ,we studied volume regression and dose distortion based on CBCT data acquired at 40 Gy.

We analysed the PTV volumes in CBCT data sets and the effect of it in OARs dose increase. We calculated the normal tissue complication probability for

parotids based on a MAT LAB programme which,calculated the parotids' NTCP based on the EUD obtained from the DVH data.

The following results were observed in NTCP (normal tissue complication probability) increase,in case of replan as been initiated for the dodse deposition on the parotids.The NTCP of parotids,for the initial planning CT plans are as follows,

<b>Statistics</b>			
		<b>PTV2 V95</b>	<b>PTV2 VOL CC</b>
<b>N</b>	<b>Valid</b>	30	30
	<b>Missing</b>	0	0
<b>Mean</b>		97.0980	694.556667
<b>Median</b>		97.0000	687.000000
<b>Minimum</b>		95.00	439.0000
<b>Maximum</b>		99.99	1001.0000

<b>Statistics</b>			
		<b>PTV1 V95</b>	<b>PTV1 VOL CC</b>
<b>N</b>	<b>Valid</b>	30	30
	<b>Missing</b>	0	0
<b>Mean</b>		97.4317	1070.580000
<b>Median</b>		97.9000	1076.500000
<b>Minimum</b>		93.23	767.0000
<b>Maximum</b>		99.06	1331.0000

All the above values on paired T test was found to have a significant p value of  $<.0001$  which is statistically significant in our study.

**B.NTCP for CT Vs CBCT :**

The mean NTCP of parotids for the initial planning CT plan for parotid is about 0.289% ,the median NTCP of parotids for initial planning CT plan was 0.245% , maximum NTCP of parotids received by the initial plan for the parotid is about 0.980% .

Statistics			
		NTCP CT	NTCP CBCT
N	Valid	30	30
	Missing	0	0
Mean		.289300	18.391067
Median		.245000	20.035000
Minimum		.0000	.0620
Maximum		.9800	29.5800

When the same initial plan is continued till 40 Gy the dose recived by the parotids show a significant difference , i.e., the mean dose received by the parotids in CBCT image contoured sets is 18.39 Gy , median dose received by the parotids in CBCT is 20.03 Gy , the maximum dose received by the parotids if the same initial plan is continued can go high upto 29.58 Gy.

These values are then calculated for the p value which is very much significant  $P < 0.0001$ .

### **C. Planning target volume V95% :**

V95% is defined as the 95 % of the planned target volume receiving equal or more than 95 % of the prescribed dose .

The mean PTV V95% for initial plan and V 95% for the plan done in the replanning CBCT image is 97.43% and 97.09% respectively. The median volume of PTV receiving equal or greater than 95% of the prescribed dose when compared between the initial plan and also the replanning CBCT image is 97.90% and 97.00% respectively. The maximum PTV V95% for initial plan is around 99.06 and 99.99 for replanning CBCT image set .

When these variables are calculated for the p value using the paired t test it did not turn out with significant p values . Thus from this we infer that although there were changes with respect to the volume of the planned target and the parotid moving into the field the planning target volume V 95% dose received by the initial plan and the replanning CBCT does not show much of a difference. Thus the p value is not statistically significant in this case which means that even though replanning is done at 40 Gy the dose to be received by the planned target will not be significantly reduced or affected . This means that the effect of adaptive

radiotherapy has much significant role to play when it comes to reducing the normal tissue complication and especially, the dose received by the parotids (which reciprocates in terms of reduction of xerostomia in patients who had adaptive radiotherapy).

**D.Spinal cord:**

<b>Statistics</b>			
		<b>CORD GY INITIAL</b>	<b>CORD GY REPLAN</b>
<b>N</b>	<b>Valid</b>	30	30
	<b>Missing</b>	0	0
<b>Mean</b>		32.430667	10.828333
<b>Median</b>		32.325000	10.940000
<b>Minimum</b>		27.5600	7.5500
<b>Maximum</b>		38.2200	15.2800

The initial plan for the spinal cord had a mean dose of 32.32 Gy and the mean dose for the spinal cord in replanning cone beam CT image is around 10.94 Gy. Thus the total point dose of the parotid was not more than 45 Gy in all the patients included in this study.

## **V. Conclusion:**

Adaptive replanning is must for head and neck cancers at 40 Gy to evaluate the dose that is received by the tumour area in contrast to the dose received by the organs at risk. Continuing radiotherapy without replanning leads to dosimetrical errors in dose distribution to the planning target volume, which in turn leads to inappropriate high doses to the normal structures, and leads to increase in morbidity of the same. Also, in high volume centres, cone beam computed tomography provides an efficient option in assessing the tumour response along with dose comparison to both tumour area and organs at risk. Replanning at 40 Gy takes into account the tumor regression , nutritional status of the patient and body mass index and hence helps in replanning dose to the planning target volume thereby improving the treatment response and also reducing treatment related morbidity, thereby resulting in improved quality of life.

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