Medical and Research Publications
International Open Access

Research Article **Journal of MAR Oncology (Volume 4 Issue 4)**

A Prospective Observational Comparative Study of Clinical Response in Postoperative Head and Neck Cancer Using Two Different Techniques of IMRT [Fixed Field and VMAT]

Dr. Kannan Maharajan *[1,] Dr. Amitabh Ray [2,] Dr. Sanjoy Roy [3], Dr. Sandip Sarkar [4], Dr. Dipanjan Majumder[5]

1. Registrar Department of Radiotherapy, Ruby General Hospital, Kolkata

2. Senior Consultant & Department of Radiotherapy, Chittaranjan National Cancer Institute, Newtown, Kolkata.

3. Senior Consultant & HOD Department of Radiotherapy, Ruby General Hospital, Kolkata

4. Senior Consultant, Department of Radiotherapy, Ruby General Hospital, Kolkata

5. Senior Consultant, Department of Radiotherapy, Ruby General Hospital, Kolkata

Corresponding Author: Dr. Kannan Maharajan, Registrar Department of Radiotherapy, Ruby General Hospital, Kolkata.

Copy Right: © 2022 Dr. Kannan Maharajan, This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received Date: August 10, 2022

Published Date: September 01, 2022

DOI: 10.1027/maroy.2022.0207

Abstract:

Background*:*

Intensity Modulated Radiotherapy [IMRT] in the HNSCC is the current standard of care practiced all over the world. Fixed field [FF] IMRT and Volumetric Arc Therapy [VMAT] is the most common planning technique. Our study focused to find out any difference between the two techniques in terms of clinical toxicity in postoperative HNC.

Methods*:*

This study was performed with 36 patients, 18 patients in the FF arm and 18 patients in the VMAT arm randomly allocated in each arm. The patient population included all postoperative HNC requiring Adjuvant Radiotherapy +/- Concurrent chemotherapy. Tumor delineation is done as per standard contouring guidelines ad planning is done in TPS using an anisotropic analytical algorithm [AAA]. All patients planned to receive 60-66Gy in 30-33 fractions @ 2Gy over 6 weeks along with weekly concurrent chemotherapy with Inj.Cisplatin 40mg/m2 in some patients. Patients are assessed for toxicities weekly during the treatment and 3 monthly follow-ups till 1 year. Toxicities are graded using CTCAE [V5], RTOG, and LENT SOMA. Dates are tabulated using Microsoft Excel and Statistical calculations are done using SPSS V26.0

Results*:*

In our study, there is significant weight reduction in the VMAT arm during the radiation mainly 5^{th} and 6^{th} weeks (p-Value <0.0001). Incidence of Grade 2 and Grade 3 acute toxicities are more in the Fixed Field arm at the 5^{th} and 6^{th} week of radiation though it's statistically insignificant. As such, there is no significant difference in the incidence of late toxicity between the two arms.

Conclusion:

Thus, in the end, it can be stated that both Fixed Field and VMAT techniques resulted in similar toxicities not significantly different. Our study was observational in nature and had a limited number of patients and the duration of follow-up was also limited. A prospective randomized study with a large number of patients and a long period of follow-up is needed to conclude about the superiority.

Keywords: *HNC, IMRT, VMAT, HNSCC, Intensity Modulated, Radiotherapy*

Introduction

Squamous Cell Carcinoma in the Head and Neck develop from the mucosal epithelium in the oral cavity, larynx and pharynx are the most common malignancy in head and neck regions. According to GLOBOCON 2020, the incidence and mortality of Head and Neck Squamous Cell Carcinoma [HNSCC] is 10.3% and 8.8% respectively in India. HNSCC is 2nd in Incidence following breast cancer and 3rd in Mortality as per the latest GLOBOCON 2020[1] Indian data. The burden of HNSCC varies across regions and had generally been correlated with exposure to tobacco and alcohol consumption or both. No screening examination found effective till now, only careful physical examination remains the primary approach for early detection.

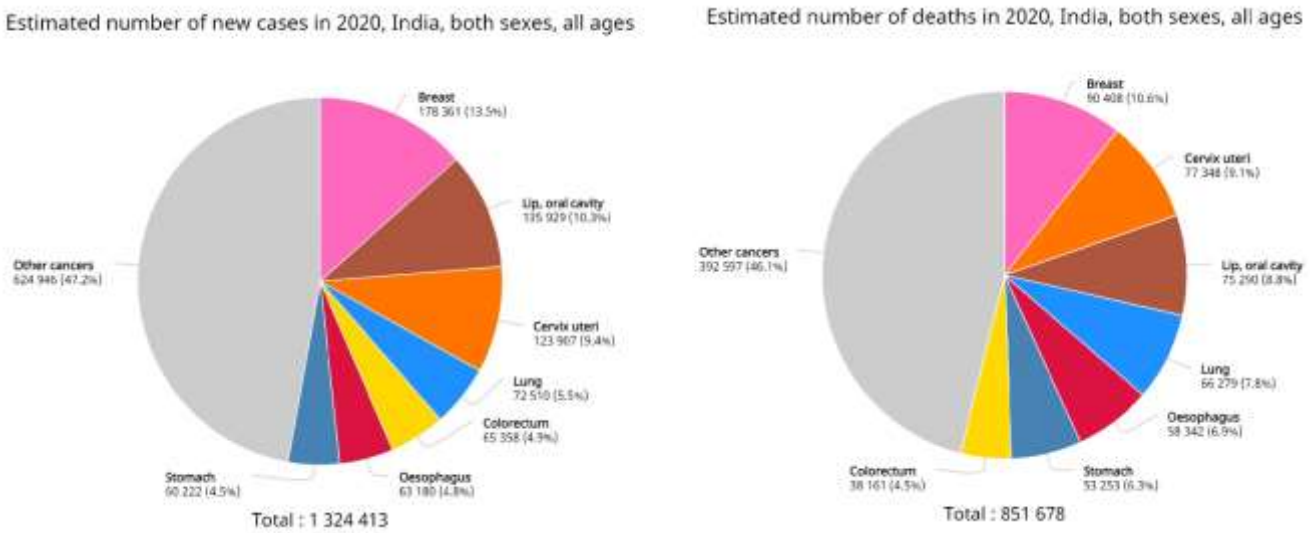

Figure 1: Head and Neck Cancer Incidence and Mortality Rate in India as per latest GLOBOCON 2020

Radiotherapy (RT) is an extremely effective treatment for head and neck cancer, both as a primary modality and as an adjuvant treatment following surgery. RT causes significant acute (during and up to 3 months post-radiation) and late toxicities when used at doses required to sterilize the locoregional disease (radical doses). The acute toxicities of RT include mucositis, dysphagia, xerostomia, dermatitis, and pain. Radiation-induced mucositis of the upper aerodigestive tract results in significant morbidity and altered quality of life (QOL) during RT [2]. The late radiation-induced toxicities include xerostomia (60–90% incidence), grade 3 dysphagia [3,4] (15–30%), osteoradionecrosis (ORN) of the jaws [5] (5–15%), sensorineural hearing loss [6] (40–60%), skin fibrosis and laryngeal cartilage necrosis. The late radiation

toxicity is permanent and results in reduced QOL for the patient (particularly xerostomia and dysphagia) [7]

Intensity-modulated radiotherapy (IMRT) is an advanced approach to three-dimensional (3D) treatment planning and conformal therapy. It optimizes the delivery of irradiation to irregularly shaped volumes and can produce concavities in radiation treatment volumes. For head and neck cancer, the clinical target volume 1 (CTV1), which includes the primary tumor and the involved nodes, typically receives a higher radiation dose than CTV 2 [Elective regions]. The different doses to CTV1 and 2 can be delivered simultaneously while sparing the parotid salivary glands and the spinal cord [8,9]. In the head and neck region, IMRT has several potential advantages: (I) it allows for greater sparing of normal structures such as salivary glands, oesophagus, optic nerves, brain stem, and spinal cord; (ii) it allows treatment to be delivered in a single treatment phase without the requirement for matching additional fields to provide tumor boosts, and eliminates the need for electron fields to the posterior (levels II and V) neck nodes; and (iii) it offers the possibility of simultaneously delivering higher radiation doses to regions of gross disease and lower doses to areas of microscopic disease—the so-called simultaneous integrated boost (SIB) IMRT[6].

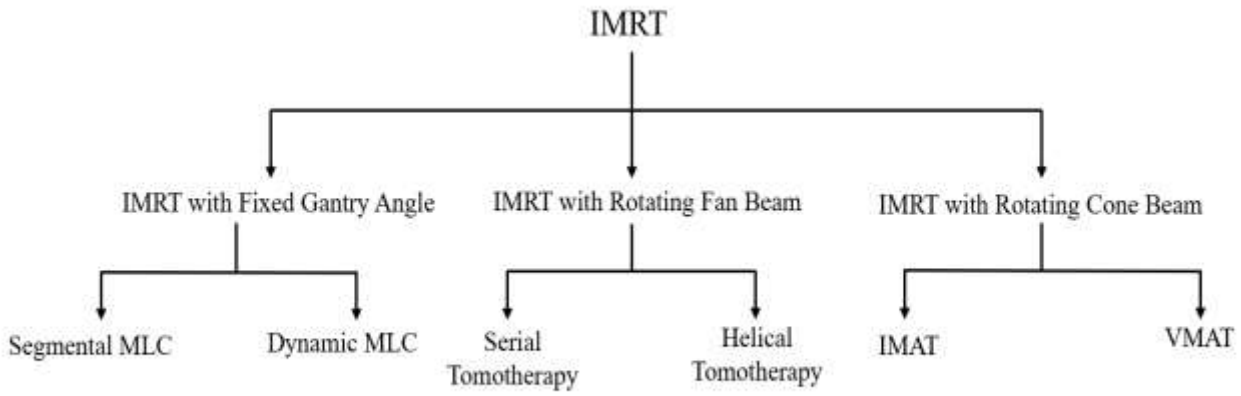

Figure 2: Different techniques of IMRT [10].

IMRT can be delivered using linear accelerators with static multileaf collimators (MLCs; step and shoot IMRT) or dynamic leaf MLCs, tomotherapy machines, or volumetric modulated arc therapy (VMAT). Tomotherapy enables the simultaneous use of image guidance and treatment delivery [11]. However, adaptive RT based on image guidance is yet to be clinically optimized in head and neck cancer. VMAT is a newer technique of delivering IMRT. VMAT delivers IMRT-like distributions in a single rotation of the

gantry, varying the gantry speed and dose rate during delivery, in contrast to standard IMRT, which uses fixed gantry beams. Planning studies using RT demonstrate shorter planning and treatment time, fewer monitor units for treatment delivery, and better dose homogeneity and normal tissue sparing [12,13].

Aims & objectives:

Aim: Our study aimed to assess compare the clinical outcomes [Acute and Late side effects] of postoperative patients treated with Fixed Field IMRT vs VMAT technique for HNSCC.

Primary Objective: The primary objective of our study was to compare the clinical response between two treatment techniques during the radiation and 3 monthly till 12 months

Material and Methods:

Study site:

The present study was conducted at the Department of Radiation Oncology, Ruby General Hospital, Kolkata, West Bengal.

Study Population:

Patients were selected consecutively for accrual in the study, Patients with histopathological proven head and neck cancer undergoing adjuvant radiotherapy.

Period of Study

- Preparation of protocol: July 2019 to August 2019
- Data collection: October 2019 to October 2020
- Analysis & writing: October 2020 to March 2021

Study Design & Sample Size:

Our study was a single institutional prospective observational study, with the intervention of providing postoperative radiation with or without concurrent chemotherapy to the HNSCC using IMRT

Our research question was "Is there any difference in the clinical outcomes between two different techniques of IMRT [FF VS VMAT]?". With the help of literature & PUBMED search most prospective comparative studies in head and neck cancer, patient selection was done from October 2019 to March 2020. Total 36 postoperative HNSCC patients were randomized based on the patient's slot's basis into Fixed Field and VMAT.

Selection of Patients:

Patients were selected consecutively for accrual in the study, those who underwent surgery in HNSCC planned for adjuvant radiation with or without chemotherapy based on following inclusion and exclusion criteria.

Inclusion Criteria

1. Age: >18yrs. - <70yrs.

2. Sex: Male & Female

3. ECOG Performance Status = 0-2

4. Histopathological proven Squamous cell carcinoma of Head and Neck

5. Tumor stage: II to IVA

6. Primary site: Oral cavity, Oropharynx, and Larynx

Exclusion Criteria

1. Age: <18 yrs. &>70 yrs.

2. ECOG: > 2

3. Past History of Radiotherapy

Pre-Treatment Evaluation And Investigations

A complete Case history with the physical examination was done for every patient.

Other investigations which formed part of the pretreatment investigations were:

a) Complete blood count (Hb in gm%, TLC, DLC, Platelet count)

b) Blood biochemistry (Serum urea, Serum creatinine, LFT)

c) Histopathological confirmation of the disease

d) Pretreatment Dental Checkup

e) Pretreatment ENT Checkup

f) Nutritional Assessment

Methodology

After obtaining written informed consent, depending on their date of registration at our institute, the patients were reviewed weekly during the treatment duration and after the treatment period at 3 monthly intervals up to 1 year.

Acute toxicities were recorded during the treatment at weekly follow-ups till the end of the radiation therapy and 3 months, Late toxicities from 6 months till 1 year using CTCAE [versions 5.0] [14] RTOG [15], and LENT SOMA [16] grading system.

Treatment Planning and Contouring

The planning Computed Tomography (CT) scan (3 mm slice thickness) was generated using the Siemens 128 Slice CT Scan machine and then transferred to our Varian Eclipse Treatment Planning System. Scans from vertex to mid-thorax with the patient immobilized with thermoplastic mask in treatment position.

Contouring: [17]

According to the ICRU definition, Clinical Target Volume [CTV] includes Gross Tumor Volume [GTV] plus a volume of normal tissue at risk of microscopic tumor infiltration. In the postoperative setting, the CTV should include the primary and nodal tumor bed with suitable margin to account for microscopic spread, all pathologically involved nodal levels.

Delineation of the primary tumor and involved nodal CTV:

- CTV-P1: Preoperative GTV primary + isotropic 5mm margin
- CTV-P: CTVP1 + 1-1.5 cm wider margins are generally recommended in the postoperative setting because of the uncertainties inherent in defining the tumor bed following resection. CTV-P should be edited for anatomical barriers such as bone, fascia, and air.
- CTV-N1: Preoperative GTV nodal level plus 1 cm margins generally. When a pathologically involved node is a boundary node, located between two contiguous nodal levels both nodal levels should be included in the CTV. If a pathological lymph node abuts or invades a muscle not removed in the neck dissection, this muscle may be included in the CTV, at least for the entire invaded levels.
- Prophylactic Clinical Target Volume CTV-N2: Prophylactic or Elective CTV [CTV-N2] includes all at-risk uninvolved nodal levels, which will vary according to the sites and laterality of the primary tumor as well as the extent of neck dissection.

Classification	Node status	CTV2
Unilateral Treatment for Lateralised[a] Tumours	Node negative	• Ipsilateral level II-IVa • Ipsilateral level Ib in case of extension of an oropharyngeal tumour into anterior pillar of tonsil or into the oral cavity • Ipsilateral level Ia and Ib for oral cavity tumour
	Node positive	• Uninvolved Ipsilateral levels Ib-IVa, V (a,b) • Ipsilateral lateral retropharyngeal nodes (level VIIa) at the level of oropharynx for oropharyngeal tumours* • Ipsilateral retrostyloid space (level VIIb) when level II is involved • Ipsilateral supraclavicular fossa [SCF] (level IVb & level Vc) when level IVa or V involved • Ipsilateral level Ia for oral cavity tumours
Bilateral Treatment for Non-Lateralised[b] Tumours	Node negative	• Bilateral level II-IVa • Ipsilateral level Ib in case of extension of an oropharyngeal tumour into anterior pillar of tonsil or into the oral cavity • Bilateral level Ia and Ib for oral cavity tumours
	Node positive	• Uninvolved Ipsilateral levels Ib-IVa, V(a,b) (except laryngeal cancers where level Ib can be omitted if level II is not involved) and contralateral levels II-IVa • Bilateral lateral retropharyngeal nodes (level VIIa) for oropharyngeal and hypopharyngeal tumours • Ipsilateral retrostyloid space (level VIIb) when level II is involved • Ipsilateral SCF (level IVb & level Vc) when level IVa or V involved • Bilateral level Ia for oral cavity tumours

[a] Lateralised tumours include tonsillar cancers with < 1 cm soft palate or tongue base invasion as well as oral cavity cancers involving the buccal mucosa, retromolar trigone and superficial aspect of the mobile tongue.

[b] Non-lateralised or midline tumours include most other oropharyngeal, laryngeal, hypopharyngeal and oral cavity tumours.

* The cranial border of the retropharyngeal nodal level (level VIIa) is defined as the upper edge of the body of C1, or the upper extent of the hard palate, whichever is more cranial.

Table 1: Elective nodal delineation in lateralized and non-lateralized tumors.

- Planning Target Volume [PTV]: Isotropic Margin 5 mm added to CTV's.
- The organ at Risks: Eyes, Lens, Optic Nerves, Brainstem, Spinal Cord, Mandible, Larynx, Parotids

Dose Prescription: Post Operative Radiation Dose to CTVP and CTVN1 □ should receive at least 60Gy in 30 fractions @ 2Gy per fraction over 6 weeks. In patients with high risk for recurrence [specifically those with positive margins and or Extracapsular Extension (ECE)] dose increased up to 66Gy in 30 fractions @ 2.2Gy per fraction over 6 weeks.The prophylactic or elective dose CTV2 received 54Gy in 30 fractions @ 1.8Gy per fraction over 6 weeks.

Treatment Planning:

Static Field IMRT planning: 7 fields equidistantly spaced were taken [0°, 51°, 102°, 153°, 209°,255°, 306°] on the treating planning system. Beam energy of 6 MV X rays was used most commonly. After sufficient numbers of iteration desired fluence map were created using Multileaf Collimator [MLC] motion while the gantry is static with the sliding window technique

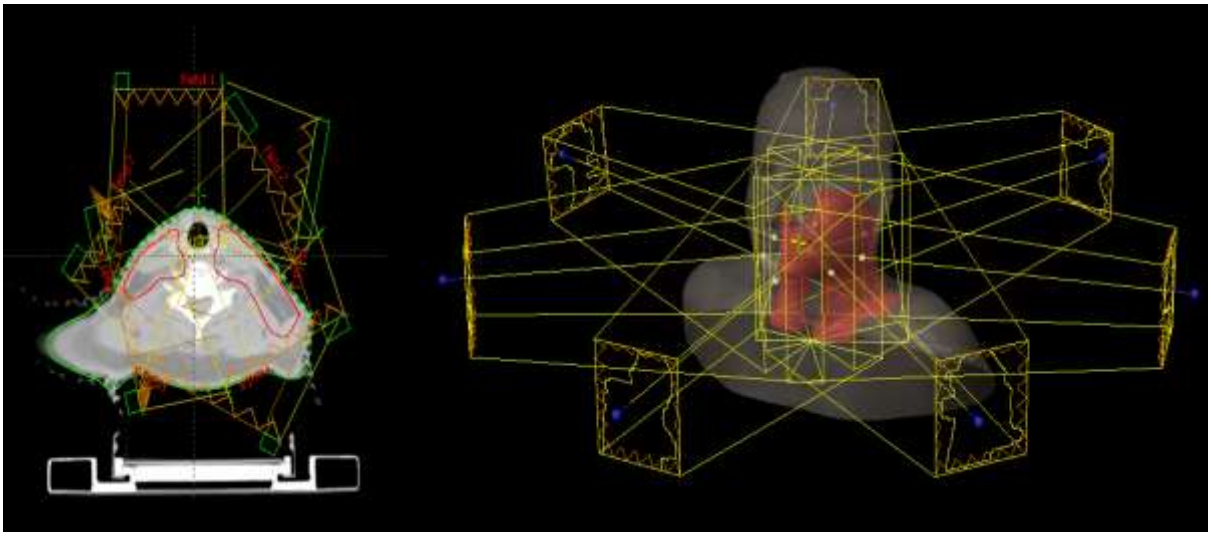

Figure 3: Fixed Field Beam placement in Bilateral Neck Treatment

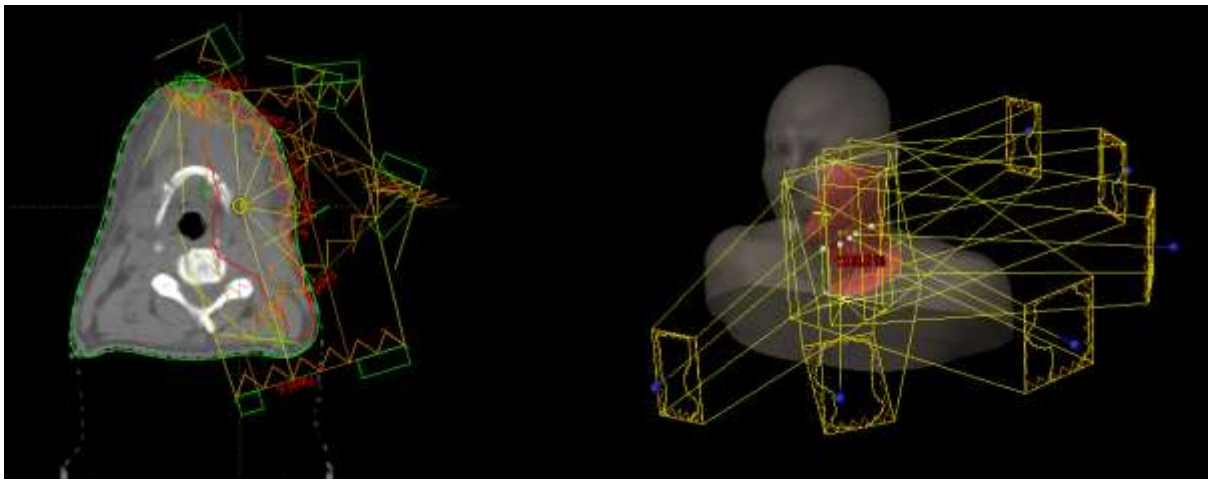

Figure 4: Fixed Field Beam placement in Unilateral Neck Treatment

VMAT planning: Plans were generated using double full arc in a co-planner, one in clockwise and another in anticlockwise direction [gantry angles from 181° to 179° and 179° to 181° respectively]. Similar to IMRT plans, beam energy of 6 MV photon beams was used. Optimization and calculation were done on the TPS [Eclipse Planning System version using the anisotropic analytical algorithm [AAA]. The collimator angle was typically set to a value of 30°, 330° for CW & CCW beams respectively to avoid tongue and groove effects.

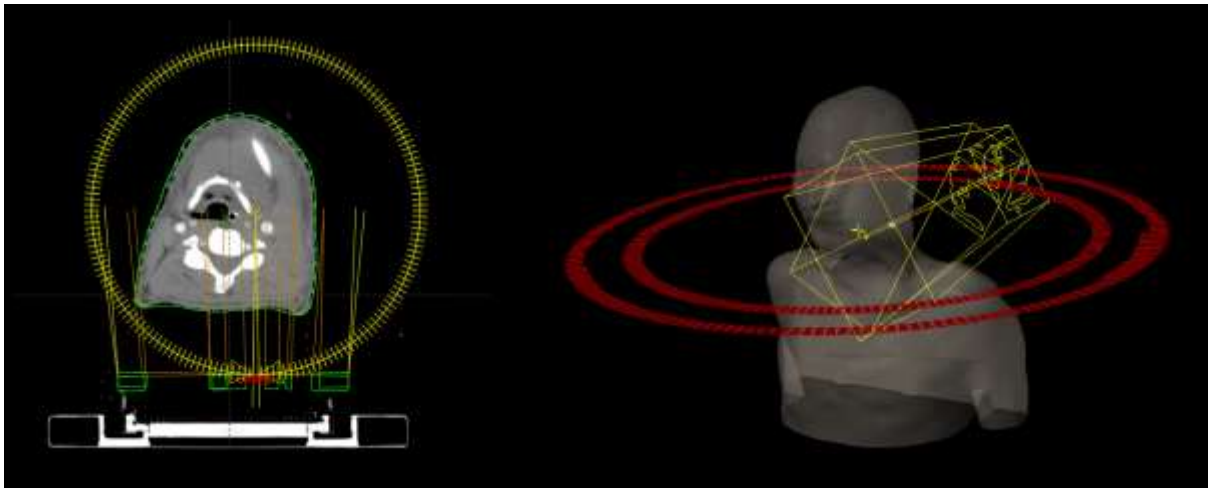

Figure 5: VMAT planning with Double Arc

Plan optimization was restarted typically four to five times after the initial run without prior resetting the earlier optimization results including segments and the earlier optimization results including segments and dose rate along the arcs [this is called Intermediate Dose Calculation]

We have a single Linear Accelerator installed in our department- Varian Clinic IX with flattening-filter-free (FFF) beam technology. All the radiation treatment plans were executed using this machine.

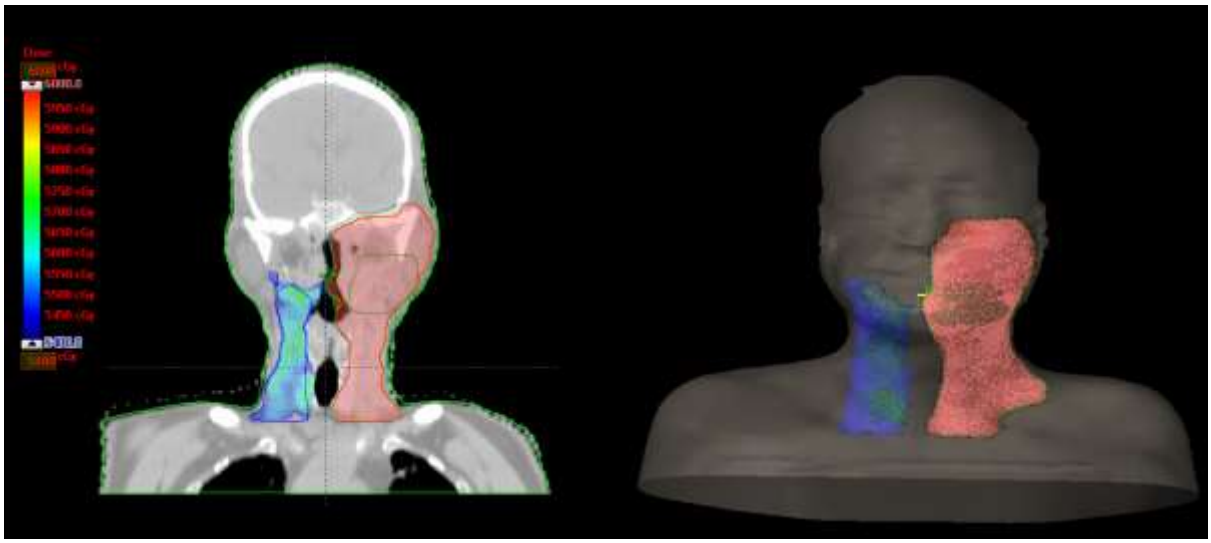

Figure 6: Isodose distribution in Fixed Field IMRT planning.

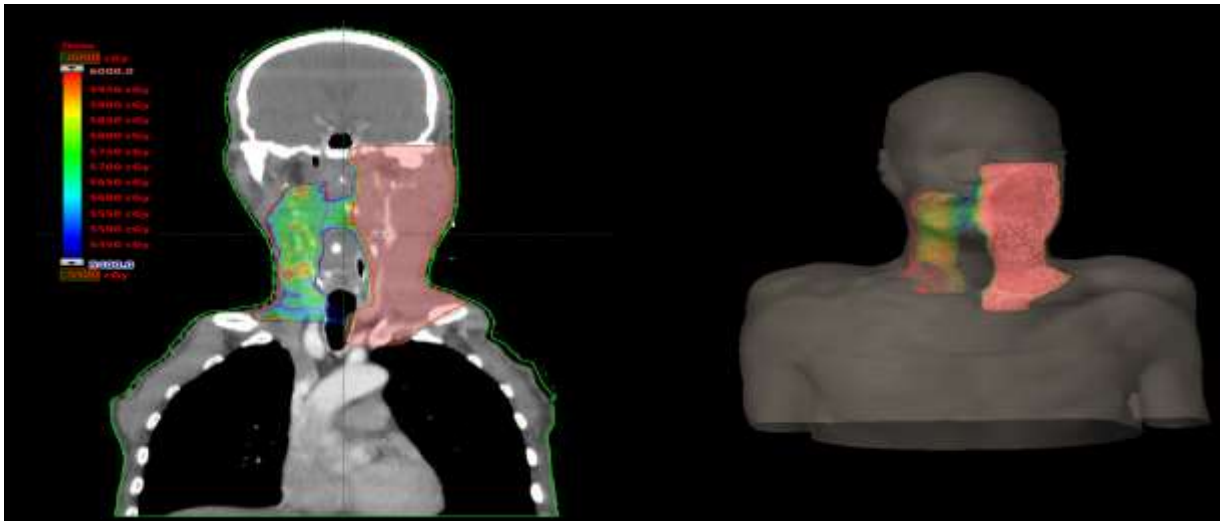

Figure 7 : Isodose distrubition in VMAT planning.

Statistical Analysis

For statistical analysis, all data were entered into a Microsoft Excel spreadsheet, and then the data was analyzed using the IBM SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA). To compare the efficacy over the two methods FF and VMT applied on the various parameters, this study unveiled the statistical significance with the application of two sample proportional Z tests for the change of the grades (grade 0, grade 1, grade 2, and grade 3) over the periods from 1st week to 3months of randomly selected 18 patients in each group.

Follow Up

History and physical examination along with physician associated objective assessment of acute skin toxicity every week during radiotherapy till its completion, and till 3rd month. Similarly, for late toxicity every 3 monthly for 1 year for this study.

Observation and Results:

Descriptive Statistics

We have accrued 36 consecutive patients who were diagnosed with HNSCC who underwent surgery that required Adjuvant Radiotherapy with or without concurrent chemotherapy were randomized into Fixed Field (FF) and VMAT arm.

The most common primary cancer site in FF arm is Oral Cavity {Buccal Mucosa (44.44%), Retromolar Trigone (22.22%), Alveolus (16.66%), Gingivobuccal sulcus (11.11%), Tongue (5.55%)}. The most common primary cancer site in the VMAT arm is Oral Cavity {Tongue (44.44%), Buccal Mucosa (27.77%), Gingivobuccal sulcus (5.55%), Maxilla (5.55%)}

Patient and tumor characteristics have been summarized in Table 6.

Characteristics	***Total Patients***	
	FIXED FIELD	*VMAT*
Total No	18	18
Mean Age [Range]	51 Yrs. [31-70]	51 Yrs. [33-70]
Performance Status 0 1 2	 8 [44.44%] 10 [55.55%] 0 [0%]	 9 [50%] 7 [38.88%] 2 [11.11%]
Primary Site	(I) Oral Cavity: 1.Buccal Mucosa: 8 [44.44%] 2.Retromolar Trigon: 4 [22.22%] 3.Alveolus: 3 [16.66%] 4. Gingivobuccal sulcus: 2 [11.11%] 5.Tongue: 1 [5.55%]	(I) Oral Cavity: 1.Tongue: 8 [44.44%] 2.Buccal Mucosa: 5 [27.77%] 3.Gingivobuccal Sulcus: 1 [5.55%] 4.Maxilla: 1 [5.55%] (II) Laryngeal: 2 [11.11%] (III) Oropharynx: 1[5.55%]
Tumor Staging pT1 pT2 pT3 pT4	 1 [5.55%] 8 [44.44%] 6 [33.33%] 3 [16.66%	 0 [0%] 6 [33.33%] 6 [33.33%] 6 [33.33%]
pN0 pN1	7 [38.88%] 2 [11.11%]	7 [38.88%] 0 [0%]

pN2 pN3	6 [33.33%] 3[16.66%]	4[22.22%] 7[38.88%]
Concurrent Chemotherapy Yes No	 8 [44.44%] 10 [55.55%]	 10 [55.55%] 8 [44.44%]

Table 2: Patient and Tumor Characteristics:

Acute toxicity:

Evaluation of Overall Weight Reduction: [Figure 8]

During RT: 1st week and 2nd week no significant weight reduction in both arms. 3rd week - Grade 1: 2 [11.11%] in FF arm and Grade 1: 1 [5.56%] in VMAT arm. Comparison between the two-arms p-value was Grade 1 [p value=0.00001].4th week- Grade 1 :3 [16.67%] in FF arm and Grade 1: 3[16.67%] in VMAT arm. Comparison between the two arms of p-value was Grade 1[p=1].5th week – Grade 1: 3[16.67%] in FF arm and Grade 1: 1[5.56%] and Grade 2: 2[11.11%] in VMAT arm. Comparison between the two arms of p-value Grade 1 [p=0.00001] and Grade 2 [p=0.00001].6th week-Grade 1: 2 [11.11%] in FF arm and Grade 1: 1[5.56%] and Grade 2: 2 [11.11%] in VMAT arm. Comparison between the two arm p values were Grade 1[p=<0.00001] and Grade 2 [p = < 0.00001].

At 3rd Month: Grade 1: 0, Grade 2: 1 [5.56%] in FF arm and Grade 1: 1[5.56%], Grade 2: 1 [5.56%] IN VMAT arm. Comparison between the two-arms p value of Grade 1 [p =<0.00001] and Grade 2 [p = 1]

Overall, there is significant Grade 1 weight reduction seen in the FF arm compared to VMAT arm in respect to acute toxicities but in week-wise assessment incidence of Grade 2 weight reduction is more significant in 5th and 6th week in VMAT arm with p-value < 0.00001.

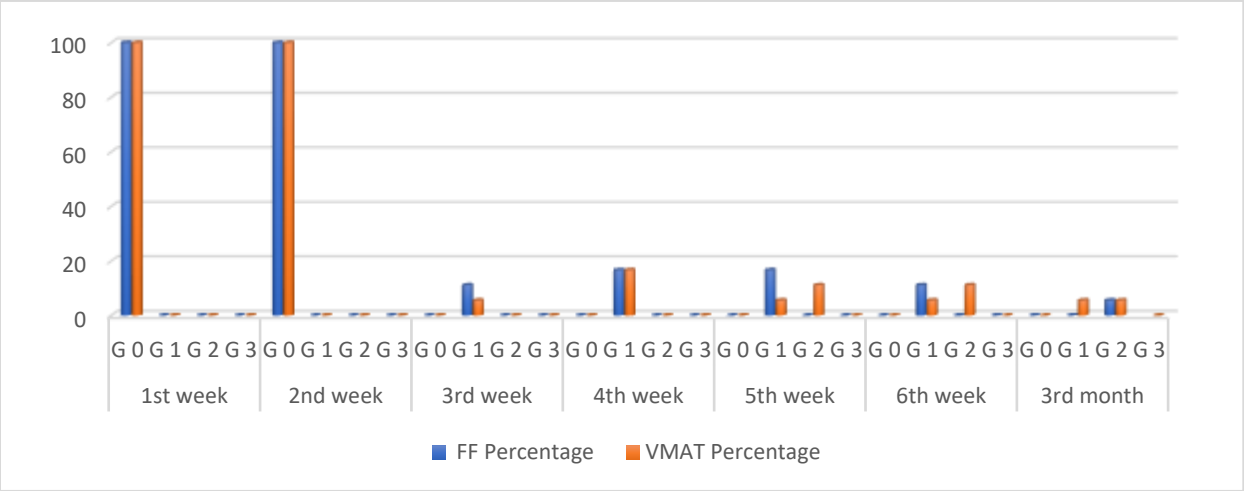

Figure 8: Overall Weight Reduction

Evaluation of Overall Dermatitis [Figure 9]:

During RT:

1st week there is no significant incidence of dermatitis in both arms.2nd week – no significant incidence of dermatitis in FF arm and Grade 1: 2 [11.11%] in VMAT arm. Comparison between the two-arm p value Grade 1[p = 0.1443].3rd week- Grade 1: 4 [22.22%] and Grade 3: 1[5.56%] in FF arm and Grade 1: 9[50%] in VMAT arm. Comparison between the two-arm p value with Grade 1 [p=0.08363] and Grade 3[p=0.3125]. 4th week – Grade 1: 12 [66.67%], Grade 2: 1 [5.56%], Grade 3: 1 [5.56%] in FF arm and Grade 1: 15 [83.33%], Grade 2: 2 [11.11%], Grade 3: 0 in VMAT arm. Comparison between the two-arm p value with Grade 1 [p=0.25014], Grade 2 [p=0.5483] and Grade 3 [p=0.3125].5th week – Grade 1: 10 [55.56%], Grade 2: 4 [22.22%], Grade 3: 4 [22.22%]in FF arm and Grade 1: 12[66.67%], Grade 2: 6 [33.33%] and Grade 3:0. Comparison between the two-arm p value with Grade 1 [p=0.4965], Grade 2 [p=0.4593] and Grade 3 [p=0.0314]. 6th week – Grade 1: 9[50%], Grade 2: 4 [22.22%] and Grade 3:5 [27.78%] in FF arm and Grade 1: 8 [44.44%], Grade 2: 8 [44.44%] and Grade 3: 1 [5.56%] in VMAT arm. Comparison the between two arm p value with Grade 1 [p=0.7414], Grade 2[p=0.15943] and Grade 3 [p=0.0314].

At 3rd Month:

Grade 1: 4 [22.22%], Grade 2: 1[5.56%] in FF arm and Grade 1 :5[27.78%], Grade 2: 1 [5.56%] in VMAT. Comparison between the two-arm p value with Grade 1[p=0.70394] and Grade 2 [p=1].

Overall, there was no statistically significant difference between the two arms in respect to acute toxicities but in weekly assessment incidence of grade 3 toxicity in the 5th week in the FF, the arm is more significant than the VMAT arm with Z = 2.1213 and a p-value = 0.014.

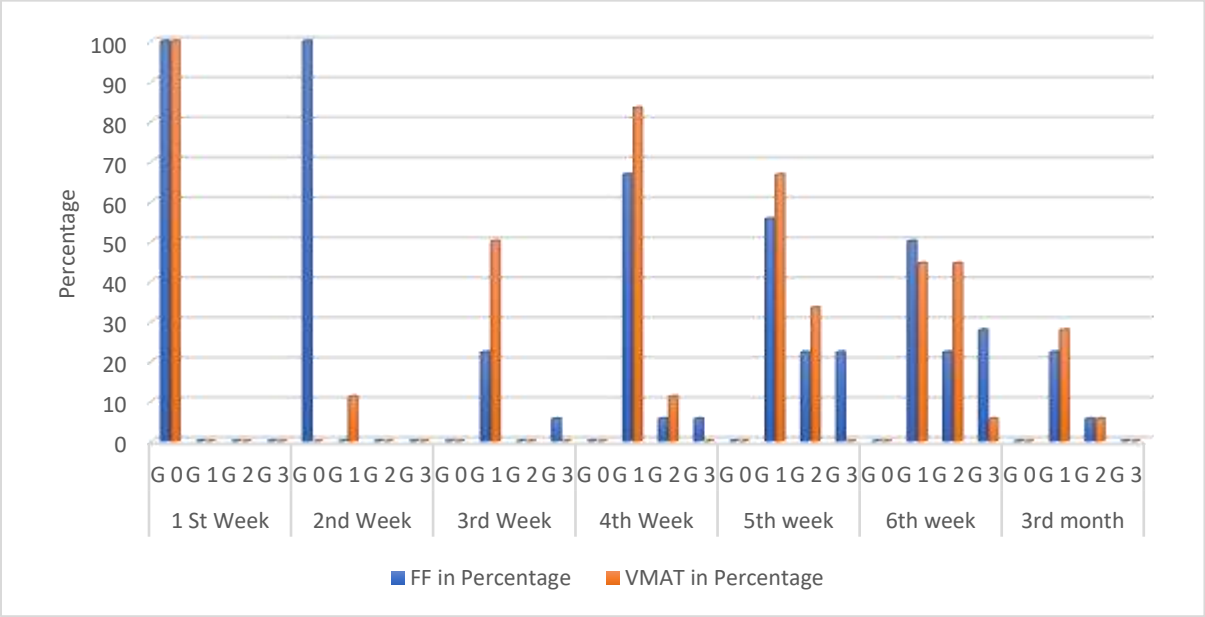

Figure 9: Overall Dermatitis.

Evaluation of Overall Mucositis [Figure 10]:

During RT:

1st week – Grade 1: 3[16.66%], Grade 2: 1 [5.55%] in FF arm and Grade 1: 4 [22.22%] in VMAT arm. Comparison between the two-arm p value with Grade 1 [p=0.3125] and Grade 2 [p=0.3125].2nd week – Grade 1: 4 [22.22%], Grade 2: 5 [27.77%] in FF arm and Grade 1 :7[38.88%], Grade 2: 1 [5.55%] in VMAT arm. Comparison between two arm p value with Grade 1 [p=0.27572] and Grade 2 [p=0.7346]. 3rd week – Grade 1: 9 [50%], Grade 2: 7 [38.88%] in FF arm and Grade 1: 9 [50%], Grade 2: 5 [27.77%] and Grade 3: 1 [5.55%] in VMAT arm. Comparison between the two-arm p value with Grade 1 [p=1], Grade 2 [p=0.4775] and Grade 3 [p=0.3125].4th week – Grade 1: 6 [33.33%], Grade 2: 12 [66.66%] in

FF arm and Grade 1: 6 [33.33%], Grade 2: 7 [38.88%] and Grade 3: 3[16.66%] in VMAT arm. Comparison between the two-arm p value with Grade 1 [p=1], Grade 2[p=0.09492] and Grade 3 [p=0.0703].5th week – Grade 1: 3 [16.66%], Grade 2: 10 [55.55%], Grade 3: 5 [27.77%] in FF arm and Grade 1: 4 [22.22%], Grade 2: 9 [50%], Grade 3: 5 [27.77%] in VMAT arm. Comparison between the two-arm p value with Grade 1 [p=0.3125], Grade 2 [p=0.7414] and Grade 3 [p=1]. 6th week – Grade 1: 1 [5.55%], Grade 2: 10 [55.55%], Grade 3: 7[38.88%] in FF arm and Grade 1: 2 [11.11%], Grade 2: 10 [55.55%], Grade 3: 5 [27.77%] in VMAT arm. Comparison between the two-arm p value with Grade 1 [p=0.5483], Grade 2 [p=1] and Grade 2 [p= 0.4775].

At 3rd Month:

Grade 1:7[38.88%], Grade 2:1[5.55%], Grade 3: 1[5.55%] in FF arm and Grade 1: 5 [27.77%], Grade 2: 2 [11.11%], Grade 3: 1 [5.55%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.4775], Grade 2 [p=0.5483] and Grade 3 [p=1].

Overall, there was no statistically significant difference between the two arms in respect to acute toxicities but in weekly assessment, the incidence of Grade 3 toxicity in the 6th week of the FF arm is numerically higher than the VMAT arm though it's not statistically significant with Z value = 0.7071 and p-value = 0.4775.

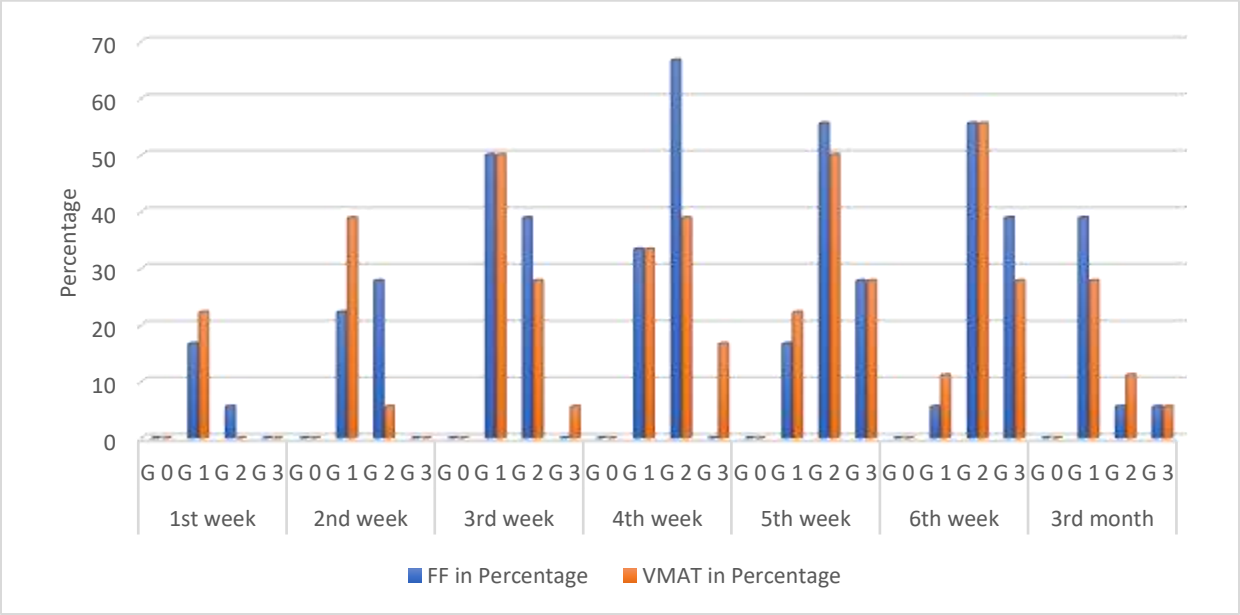

Figure 10: Overall Mucositis.

Evaluation Of Overall Dysphagia Toxicity [Figure 11]:

During RT:

1st week -Grade 1: 3 [16.67%] in FF arm and Grade 1: 3 [16.67%] in VMAT arm. Comparison between two arms p Value were in grade 1 [p = 1] .2nd week - Grade 1: 8 [44.44%], Grade 2: 1 [5.56%] in FF arm and Grade 1: 9[50%], Grade 2: 1[5.56%], Grade 3: 1 [5.56%] in VMAT arm. Comparison between two arms p value were Grade 1 [p=0.7414], Grade 2 [p = 1], Grade 3 [p = 0.03125]. 3rd week - Grade 1: 7 [38.89%], Grade 2: 7 [38.89%] in FF arm and Grade 1: 9 [50%], Grade 2: 3[16.67%], Grade 3: 1[5.56%]. Comparison between two arms p values were in Grade 1 [p=0.50286] , Grade 2 [p=0.13622] , Grade 3 [p=0.3125].4th week – Grade 1 : 6[33.33%] , Grade 2 : 7 [38.89%] ,Grade 3 : 3[16.67%] in FF arm and Grade 1 : 8 [44.44%] , Grade 2 : 7 [38.89%] , Grade 3: 3[16.67%].Comparison between two arm p value were in Grade 1 [p=0.4965], Grade 2 [p=1] , Grade 3[p=1].5th week – Grade 1 : 4 [22.22%] , Grade 2 : 10[55.56%] , Grade 3 : 4 [22.22%] in FF arm and Grade 1 : 4 [22.22%] , Grade 2 : 10 [55.56%] , Grade 3 : 4 [22.22%] in VMAT. Comparison between two arm p value were in Grade 1 [p = 1], Grade 2 [p = 1], Grade 3 [p = 1].6th week: Grade 2: 12 [66.66%], Grade 3: 6 [33.33%] in FF arm and Grade 1: 3 [16.67%], Grade 2: 11 [61.11%], Grade 3: 3 [16.67%] in VMAT. Comparison between two arms p value in Grade 1 [p = 0.0703], Grade 2 [p=0.0394], Grade 3 [p = 0.7278].

At 3rd month – Grade 1: 4 [22.22%], Grade 2: 7 [38.89%] in FF and Grade 1: 4 [22.22%], Grade 2: 3 [16.67%] in VMAT arm. Comparison between two p value in Grade 1 [p =1] and Grade 2 [p =0.52218].

Overall, there was no statistically significant difference between the two arms in respect to acute toxicities but in week-wise assessment incidence of grade 2 toxicity in 6th week in FF arm is more significant than VMAT arm with Z = 2.0599 and p-value = 0.039.

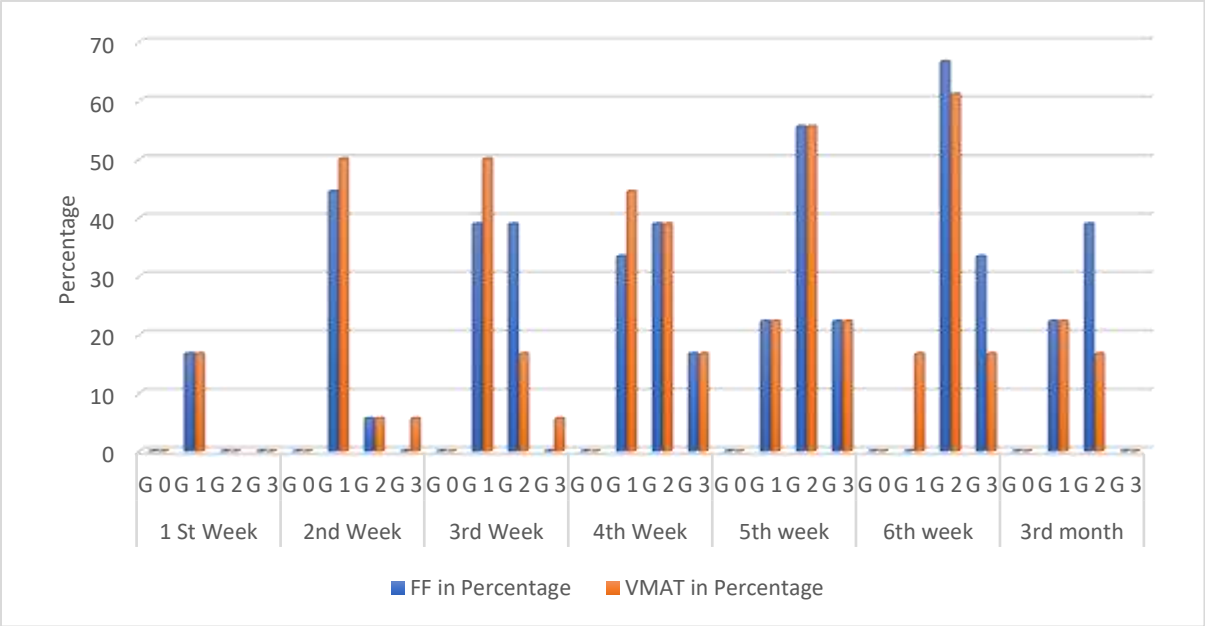

Figure 11: Overall Dysphagia

Evaluation Of Overall Trismus [Figure 12]:

During RT:

1st week – Grade 1: 6 [33.33%], Grade 2: 2 [11.11%], Grade 3: 2 [11.11%] in FF arm and Grade 1: 4 [22.22%], Grade 2: 5 [27.78%], Grade 3: 1 [5.56%] in VMAT arm. Comparison between the two-arm p value with Grade 1 [p=0.4592], Grade 2 [p=0.20766] and Grade 3 [p=0.5483].2nd week – Grade 1: 6 [33.33%], Grade 2:3[16.67%], Grade 3: 2 [11.11%] in FF arm and Grade 1: 4 [22.22%], Grade 2: 6 [33.33%], Grade 3: 1 [5.56%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.4592], Grade 2 [p=0.72786] and Grade 3 [p=0.5483].3rd week – Grade 1: 8 [44.44%], Grade 2: 3 [16.67%], Grade 3: 2 [11.11%] in FF arm and Grade 1: 4 [22.22%], Grade 2 :7[38.89%], Grade 3: 1 [5.56%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.15943], Grade 2 [p=0.13622], Grade 3 [p=0.5483].4th week – Grade 1: 9 [50%], Grade 2: 4 [22.22%], Grade 3: 2 [11.11%] in FF arm and Grade 1: 3 [16.67%], Grade 2: 8 [44.44%], Grade 3: 1 [5.56%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.00001], Grade 2 [p=0.15854] and Grade 3 [p=0.5483].5th week – Grade 1 :9 [50%], Grade 2: 3[16.67%], Grade 3: 3 [16.67%] in FF arm and Grade 1: 4 [22.22%], Grade 2: 7 [38.89%] Grade 3: 1 [5.56%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.00001], Grade 2 [p=0.073], Grade 3 [p=0.2891]. 6th week – Grade 1: 6 [

33.33%], Grade 2: 6 [33.33%], Grade 3: 3 [16.67%] in FF arm and Grade 1 :4[22.22%], Grade 2: 7 [38.89%], Grade 3: 1 [5.56%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.4592], Grade 2 [p=0.72634], Grade 3 [p=0.2891].

At 3rd Month:

Grade 1: 4 [22.22%], Grade 2: 6 [33.33%], Grade 3: 2 [11.11%] in FF arm and Grade 1: 2 [11.11%], Grade 2: 4 [22.22%], Grade 3: 1 [5.56 %] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.37343], Grade 2 [p=0.4592] and Grade 3 [p=0.5483].

Overall, there was no statistically significant difference between the two arms in respect to acute toxicities but in week-wise assessment, the incidence of Grade 1 toxicities in 5th week and 6th week in FF arm is more significant than VMAT arm with Z= 2.1213 and p=<0.00001

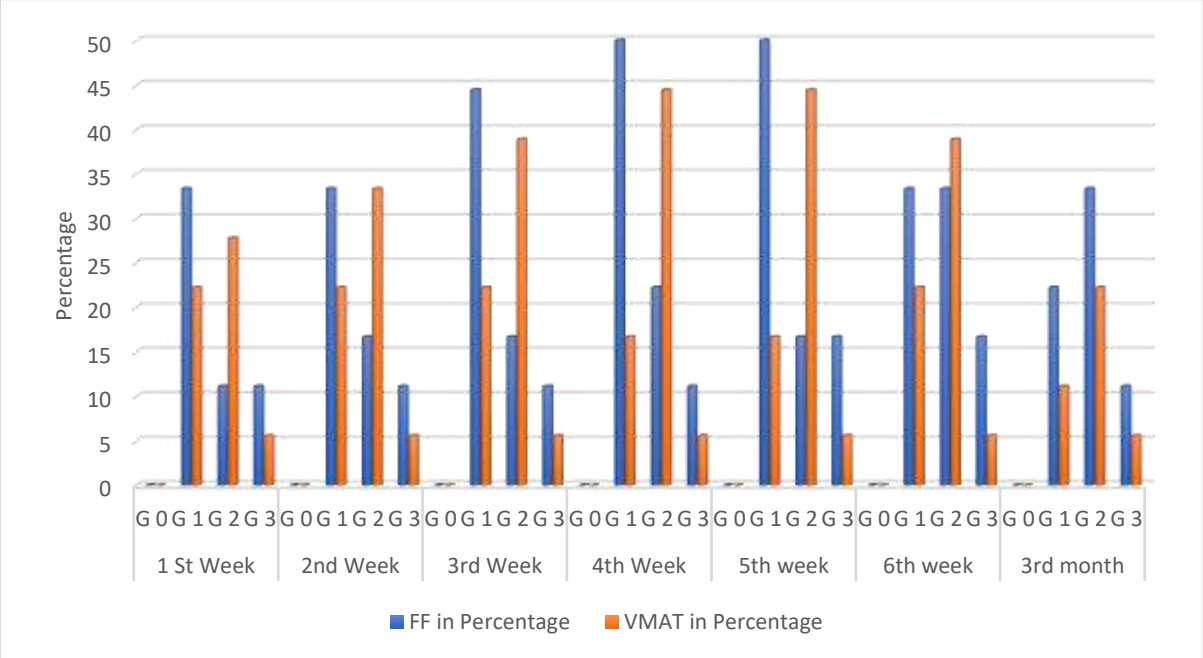

Figure 12: Overall Trismus:

Evaluation Of Overall Xerostomia [Figure 13]:

During RT:

1st week - Grade 1: 0 in FF arm and Grade 1: 1[5.55%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.3125].2nd week-Grade 1 :0 in FF arm and Grade 1: 3 [16.67%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.0703]. 3rd week – Grade 1: 2 [11.11%] in FF arm and Grade 1: 4 [22.22%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.37343].4th week – Grade 1: 4 [22.22%] in FF arm and Grade 1: 6 [33.33%], Grade 2: 1 [5.56%] in VMAT arm. Comparison between the two-arm p value with Grade 1 [p= 0.4592], Grade 2 [p=0.3125]. 5th week – Grade 1: 6 [33.33%] in FF arm and Grade 1: 5 [27.78%], Grade 2: 2 [11.11%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.71884], Grade 2 [p=0.1443].6th week – Grade 1: 6 [33.33%] in FF arm and Grade 1: 6 [33.33%], Grade 2: 2 [11.11%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p =1] and Grade 2 [p=0.1443].

At 3rd Month:

Grade 1: 6 [33.33%], Grade 2: 1 [5.56%] in FF arm and Grade 1: 4 [22.22%], Grade 2: 3 [16.67%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p = 0.4592] and Grade 2 [p = 0.2891].

Overall, there was no statistically significant difference between the two arms in respect to acute toxicities but in week-wise assessment, the incidence of Grade 2 toxicities in the VMAT arm is numerically higher than FF arm though which is statistically insignificant.

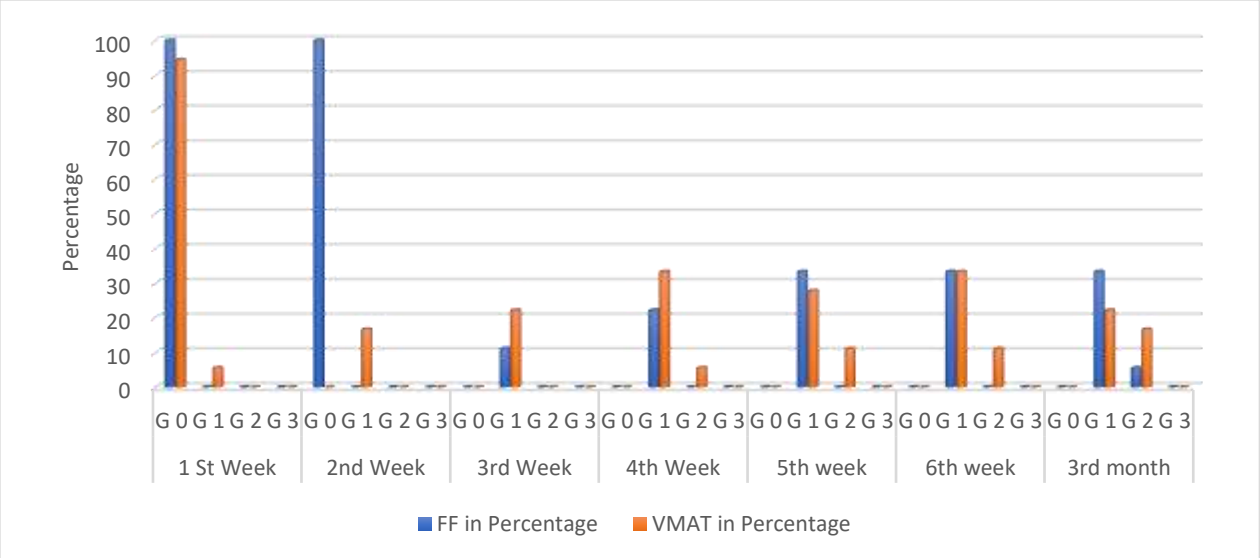

Figure13: Overall Xerostomia

Late Toxicity

Evaluation of Trismus [Figure 14]:

6th Month:

Grade 1: 3 [16.67%], Grade 2: 5 [27.78%] in FF arm and Grade 1: 4 [22.22%], Grade 2: 2 [11.11%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.3125] and Grade 2 [p= 0.20766].

9th Month:

Grade 1: 1 [5.56%], Grade 2: 4 [22.22%] in FF arm and Grade 1: 1 [5.56%]. Grade 2: 2 [11.11%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p= 1] and Grade 2 [p = 0.37343].

12th Month:

Grade 1: 3 [16.67%], Grade 2: 2 [11.11%] in FF arm and Grade 1: 1 [5.56%] and Grade 2: 1 [5.56%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.2891] and Grade 2 [p=0.5483].

Overall, there was no statistically significant difference between the two arms in respect to late toxicities.

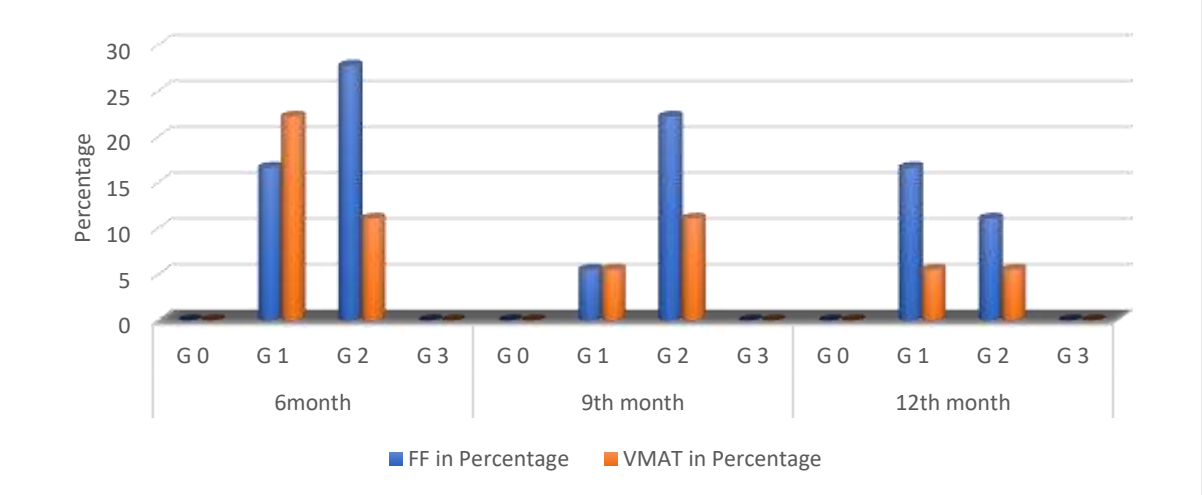

Figure14: Overall Trismus

Evaluation of Xerostomia [Figure 15]:

6th Month:

Grade 1: 4 [22.22%], Grade 2: 1 [5.56%] in FF arm and Grade 1: 6 [33.33%], Grade 2: 2 [11.11%] in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.4592] and Grade 2 [p=0.5483].

9th Month:

Grade 1: 2 [11.11%], Grade 2: 1 [5.56%] in FF arm and Grade 1: 5 [27.78%], Grade 2: 0 in VMAT arm. Comparison between the two-arm p value in Grade 1 [p=0.20766], Grade 2 [p=0.3125].

12th Month:

Grade 1: 3 [16.67%], Grade 2: 1 [5.56%] in FF arm and Grade 1: 5 [27.78%], Grade 2: 0 in VMAT arm. Comparison between the two-arm p-value in Grade 1 [0.42372], Grade 2 [p=0.3125]

Overall, there was no statistically significant difference between the two arms in respect to late toxicities.

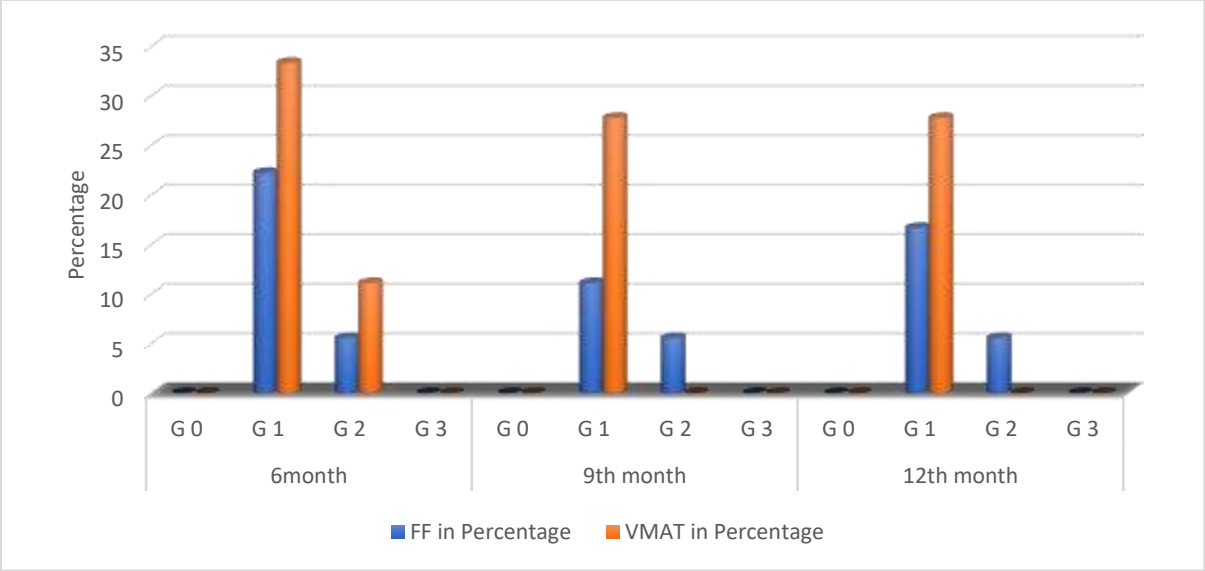

Figure15: Overall Xerostomia:

Discussion

Brief Overview:

Over the last several decades, RT combined with concurrent systemic chemotherapy has become an integral component [18,19] in the curative-intent management of HNSCC, both in the definitive, non-surgical as well as post-operative adjuvant setting. Conventional techniques although capable of delivering tumoricidal doses, resulted in unintentional and unwarranted high-dose irradiation of surrounding normal critical structures situated in the vicinity of target tissues, resulting in undesirable acute as well as late toxicity [20,21] with a potentially negative impact upon health-related QOL [22,23]. Modern advances in treatment planning and delivery, particularly IMRT, have revolutionized contemporary oncologic practice with its potential to tightly conform high-doses to target tissues [24] with resultant better sparing of OARs such as salivary glands, uninvolved mucosa, spinal cord, brainstem, and optic pathway.

A study published by Mellon et al., (2015) shows that VMAT had more homogeneous target coverage and a shorter treatment delivery compared with 7 fields IMRT for prostate cancer treatment. In another study published by Mahantshetty et al.,[25] (2010) comparing IMRT vs VMAT in the treatment of Ovarian cancers using whole abdomen radiotherapy concluded that PTV homogeneity, conformity index, and OAR sparing were better in the cohort of patients treated by RapidArc. Smet et al., [26] (2015) retrospectively compared sliding window IMRT and RapidArc techniques in locally advanced head and neck carcinomas, CT datasets of 79 patients treated with Rapid Arc and 78 patients treated with IMRT were included. They concluded that the target coverage with the 95% isodose line was in favor of the RA plans. In addition, dose homogeneity and organ at risk sparing were again better in the arc plans. A 62% reduction in MU was achieved in the RA plans when compared to the sliding window IMRT technique. Clinical toxicity outcomes were also assessed in this study showing that the grade of acute toxicity was lower for RA than for sliding window IMRT except for the grade of dermatitis. Studies by Lee et al.,[27] (2011) and Stieler et al., [28] (2011) both pointed out that the main difference between VMAT and IMRT was a significantly faster delivery time and lower number of MUs in favor of VMAT with a minimal advantage of better target coverage and OAR sparing (2%) as compared to the IMRT technique. The main drawback of IMRT is the higher number of MUs and longer delivery time. Such prolonged delivery may have an impact on treatment outcome, particularly for tumors with short repair halftime and have a low alpha/beta ratio (Wang et al., 2003).

Study	n	Technique	PTV			OAR sparing	MU
			Coverage	CI	HI		
Vanetti et al. [29]	29	sw IMRT sa VMAT da VMAT	Similar	Similar	da VMAT	da VMAT	1126 vs 463 vs 584
Verbakel et al. [30]	12	sw IMRT sa VMAT da VMAT	Similar	Similar	da VMAT	Similar (Parotis: da VMAT)	1108 vs 439 vs 459
Johnston et al. [31]	10	sw IMRT da VMAT	Similar	sw IMRT	sw IMRT	Similar (Contralateral parotis: da VMAT)	529 vs 1628
Fune Kee Fung et al. [32]	20	sw IMRT RA	Similar	sw IMRT	Similar	Similar	542.85 vs 1612.58
Van Gestel et al. [33]	5	ss IMRT RA sw IMRT SA Tomo	Tomo (swIMRT and RA similar)	RA	Tomo (swIMRT and RA similar)	Tomo (RA better than swIMRT)	415 (RA) vs 1125 (swIMRT)
Wiehle et al.	15	ssIMRT da VMAT	da VMAT	daVMAT (conformity function)	/	da VMAT	/
Guckenberger et al. [34]	15	ssIMRT 1–3 arc VMAT	Post-op: 3 arc pharynx: 3 arc = IMRT	/	ssIMRT	Similar	430–688 vs 358–440 vs 460–519 vs 506–560

CI conformity index, *HI* homogeneity index, *OAR* organs at risk, *MU* monitor units, *swIMRT* sliding-window IMRT, *sa VMAT* single arc volumetric-intensity modulated therapy, *da VMAT* double arc VMAT, *RA* RapidArc, *ssIMRT* step and shoot IMRT, *Tomo* tomotherapy

Table 7: Overview of published planning studies comparing IMRT and VMAT.

Patient Selection and Assessments:

Between Oct 2019 to March 2021, 36 patients accrued for this study. We formed robust patient inclusion and exclusion criteria after referring to the various available literature. The mean age of the patient population in our study was 51 yrs. and it ranged from 30 to 70 yrs., all belonged to the Indian population.

All post-operative HNSCC patients with risk factors like advanced tumor stage [T3 and T4], presence of a positive margin, extracapsular spread outside lymph nodes, Lymphovascular invasion, perineural invasion, presence of a lymph node > 3cm, multiple positive lymph nodes those required adjuvant radiation with or without concurrent chemotherapy are randomized to two different techniques of IMRT [FF and VMAT].

We followed the standard dose fractionation regime for postoperative setting: 6000cGy in 30 fractions @ 200cGy per fraction, 5 days a week, over 6 weeks, and patients with risk factors like positive margins and ECE positive received at least 6600cGy in 30 fractions @180cGy per fraction, 5 days a week over 6 weeks along with weekly concurrent chemotherapy with Inj.CISPLATIN 40mg/m2. The technique of radiation delivery modality is decided according to the preference of the treating doctor. At our center, in most of the HNSCC patients, radiation delivery is planned by IMRT technique either Fixed Field or VMAT.

In our study, we assessed the toxicity outcomes using CTCAE [versions 5.0], RTOG, and LENT SOMA grading system between these two techniques during the treatment for 6 weeks and every 3 monthly follow-ups till 12 months. However, we intend to continue the follow-up of patients in the future to look out for Overall survival and Disease-free interval and development of late toxicities between these two modalities.

Research Question:

In our study, we asked the question, "Is there any difference in clinical outcomes in terms of toxicities between the two different IMRT techniques. Our Null Hypothesis was designed as "There is no difference in clinical outcomes in terms of toxicities" and our alternative hypothesis naturally formed to be "There is a difference in clinical outcomes in terms of toxicities"

Toxicities:

In our study, acute toxicities are assessed weekly during the radiation and 3rd-month post-radiation. Overall, Weight Reduction: there is a significant Grade 1 weight reduction is seen in the FF arm compared to the VMAT arm with p-Value <0.0001 but the incidence of Grade 2 weight reduction is significant in the VMAT arm in the 5th and 6th week of radiation with a p-value <0. 0001. Overall assessment of dermatitis: there was no significant difference between FF and VMAT arm but the incidence of Grade 3 toxicity is higher in the 5th week of FF arm compared to VMAT arm with Z score = 2.1213 and p-value=0. 014. Overall assessment of Mucositis: there is no significant difference between FF and VMAT arm but the incidence of Grade 3 toxicity in the 6th week of the FF arm is higher than VMAT though it's not statistically significant with Z score = 0.7071 and p-value=0.4775. Overall assessment of dysphagia there is no significant difference between FF and VMAT arm but the incidence of Grade 2 toxicity in 6th week in FF arm is more significant than VMAT arm with Z score = 2.0599 and p-Value = 0. 039.Overall assessment of Trismus: There was no significant difference between the FF and VMAT arm but the incidence of Grade 1 toxicities in the 5th week and 6th week in the FF arm is more significant than the VMAT arm with a Z score = 2.1213 and a p-value <0. 0001.Overall Xerostomia: there was no significant difference between the FF and VMAT arm but the incidence of Grade 2 toxicities in the VMAT arm is higher than the FF arm though which is insignificant. Late toxicities are assessed from the 6th month till the 12th month @ 3 monthly intervals Trismus: there was no significant difference in the prolonged

duration of trismus in both FF and VMAT arm exception few patients prolonged trismus as a post-surgical complication. Xerostomia: there was no significant difference between the FF and VMAT arm. There was no incidence of Edema of the Face and Neck and Osteoradionecrosis of Jaw within 12 months of assessments between both FF and VMAT arm.

From our study results newer hypothesis can be generated states that "Is there any correlation among Mucositis and Weight Reduction between VMAT and Fixed Field IMRT"

The main limitation of our study will be less sample size, due to COVID 19 pandemic and restriction due to that we can't able to achieve the desired numbers of patients. And the follow-up period in our study was only 1 year. The outcome of late toxicities needs a longer duration of follow-ups.

Conclusion

Even though VMAT treatment have a faster fraction delivery time and lower MU compared to FIXED FIELD IMRT, from our study we found out there is no significant clinical benefit in terms of Acute and Late toxicities in postoperative HNSCC patients. Since our study has a limited number of patients and the duration of follow-up was also limited, we suggest a prospective randomized study with a larger number of patients and a longer period of follow-up will be needed in the future to conclude about the superiority between the two techniques.

References

1.GLOBOCON 2020 https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21660.

2. Kelly C, Paleri V, Downs C, Shah R. Deterioration in quality of life and depressive symptoms during radiation therapy for head and neck cancer. Otolaryngology Head Neck Surg 2007; 136:108–11. Crossref, Medline, Google Scholar.

3.WijersOB, Levendag PC, Braaksma MM, Boonzaaijer M, Visch LL, Schmitz PI. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. Head Neck 2002; 24:737–47. Crossref, Medline, Google Scholar.

4. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al... Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without

chemotherapy: a systematic literature review. RadiotherOncol2003; 66:253–62. Crossref, Medline, Google Scholar.

5. Mendenhall WM. Mandibular osteoradionecrosis. J Clin Oncol 2004; 22:4867–8. Crossref, Medline, Google Scholar.

6. BhideSA, Harrington KJ, Nutting CM. Otological toxicity after postoperative radiotherapy for parotid tumors. CLIN Oncol (R CollRadiol) 2007; 19:77–82. Crossref, Medline, Google Scholar.

7. HammerlidE, Taft C. Health-related quality of life in long-term head and neck cancer survivors: a comparison with general population norms. Br J Cancer 2001; 84:149–56. Crossref, Medline, Google Scholar.

8.Eisbruch A, Marsh LH, Martel MK, Ship JA, Ten Haken R, Pu AT, et al... Comprehensive irradiation of head and neck cancer using conformal multisegmented fields: assessment of target coverage and noninvolved tissue sparing. Int J DEAs Phys 1998; 41:559–68. Crossref, Medline, Google Scholar.

9.Butler EB, Teh BS, Grant WH, Uhl BM, Kuppersmith RB, Chiu JK, et al... Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity-modulated radiotherapy. Int J RadiatOncolBiol Phys 1999; 45:21–32. Crossref, Medline, Google Scholar.

10. Khan’s The Physics of Radiation Therapy [Page No: 430].

11.Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. J Clin Oncol 2007; 25:938–46. Crossref, Medline, Google Scholar.

12.Verbakel WF, Cuijpers JP, Hoffmans D, Bieker M, Slotman BJ, Senan S. Volumetric intensity-modulated arc therapy vs. conventional IMRT in head-and-neck cancer: a comparative planning and dosimetric study. Int J RadiatOncolBiol Phys 2009; 74:252–9. Crossref, Medline, Google Scholar.

13. Real-life assessment of Volumetric Modulated Arc Therapy (VMAT) toxicity in Head and Neck Squamous Cell Carcinoma (HNSCC) treatment.

14.CTCAE https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

15.RTOG https://www.rtog.org/ResearchAssociates/AdverseEventReporting/CooperativeGroupCommonToxicityCriteria.aspx.

16.LENT SOMA GRADING SYSTEM: https://www.thegreenjournal.com/article/0167-8140(95)90055-1/pdf

17. Target delineation for postoperative treatment of head and neck cancer https://www.sciencedirect.com/science/article/abs/pii/S1368837518303014?via%3Dihub.

18.Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomized trials and 17,346 patients. Radiotherapy Oncol 2009; 92:4–14. doi: 10.1016/j.radonc.2009.04.014

19. Gupta T, Agarwal J, Bannerjee S, Ghosh-Laskar S, Murthy V, Budrukkar A. IMRT and IGRT in head and neck cancer: have we delivered what we promised. Ind J Surg Oncol 2010; 1:166–185.

20. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiotherapy Oncol 2003; 66:253–262.

21. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol 2008; 26:3770–3776. doi: 10.1200/JCO.2007.14.6647

22. Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer 2010;18:1039–1060. doi: 10.1007/s00520-010-0827-8

23. Ramaekers BL, Joore MA, Grutters JP, van dan Ende P, Jong Jd, Houben R, et al. The impact of late treatment-toxicity on generic health-related quality of life in head and neck cancer patients after radiotherapy. Oral Oncol 2011;47(8):768–774. doi: 10.1016/j.oraloncology.2011.05.012

24. Gregoire V, De Neve W, Eisbruch A, Lee N, Van den Weyngaert, Van Gestel D. Intensity-modulated radiation therapy for head and neck carcinoma. Oncologist 2007;12(5):555–564. doi: 10.1634/theoncologist.12-5-555.

25.Mahantshetty U, Jamema S, Engineer R, et al (2010). Whole abdomen radiation therapy in ovarian cancers: A comparison between fixed beam and volumetric arc-based intensity modulation. Radiation Oncol, 5, 106.

26. Smet S, Lambrecht M, Vanstraelen B, Nuyts S (2015). Clinical and dosimetric evaluation of RapidArc versus standard sliding window IMRT in the treatment of head and neck cancer.

27.Lee TF, Chao PJ, Ting HM, et al (2011). Comparative analysis of SmartArc-based dual arc volumetric-modulated arc radiotherapy (VMAT) versus intensity modulated radiotherapy (IMRT) for nasopharyngeal carcinoma. J ApplClin Med Phys, 12, 3587.27.

28. Stradlater Onkol, 191, 43-50. Stieler F, Wolff D, Schmid H, et al (2011). A comparison of several modulated radiotherapy techniques for head and neck cancer and dosimetric validation of VMAT. Radiother Oncol, 101, 388–93.

29. Vanetti E, Clivio A, Nicolini G et al (2009) Volumetric modulated arc radiotherapy for carcinomas of the oro-pharynx, hypo-pharynx and larynx: a treatment planning comparison with fixed field IMRT. Radiotherapy Oncol 92:111–117.

30 Verbakel WF, Cuijpers JP, Hoffmans D et al (2009) Volumetric intensity-modulated arc therapy vs. conventional IMRT in head and-neck cancer: a comparative planning and dosimetric study. Int J Radiat Oncol Biol Phys 74:252–259.

31.Johnston M, Clifford S, Bromley R et al (2011) Volumetric-modulated arc therapy in head and neck radiotherapy: a planning comparison using simultaneous integrated boost for nasopharynx and oropharynx carcinoma. Clin Oncol (R Coll Radiol) 23:503–511.

32. Fung-Kee-Fung SD, Hackett R, Hales L et al (2012) A prospective trial of volumetric intensity-modulated arc therapy vs conventional intensity modulated radiation therapy in advanced head and neck cancer. World J Clin Oncol 3:57–62.

33.Van Gestel D, Van Vliet-Vroegindeweij C, Van den Heuvel F et al (2013) RapidArc, Smart Arc and TomoHD compared with classical step and shoot and sliding window intensity modulated radiotherapy in an oropharyngeal cancer treatment plan comparison. Radiat Oncol 8:37.

34. Guckenberger M, Richter A, Krieger T et al (2009) Is a single arc sufficient in volumetric-modulated arc therapy (VMAT) for complex-shaped target volumes? Radiotherapy Oncol 93:259–265.