

Original Research Article

Evaluation of efficacy & toxicity in Head and neck cancer patients treated with Volumetric Intensity Modulated Arc Therapy (VMAT) Vs. conventional Intensity Modulated Radiation Therapy (IMRT).

Dr. Isha Jaiswal^{1*}, Dr. Chandra Prakash², Dr Rohini Khurana³, Dr Umang Singal⁴

^{1,2}Assistant Professor, Department of Radiotherapy & Radiation Medicine, Institute Of Medical Sciences, Banaras Hindu University, Bhelupur, Varanasi, UP, India

³Professor, Department of Radiation Oncology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Gomti Nagar, Lucknow, UP, India.

⁴Assistant Professor, Department of General Surgery, UNS Autonomous State Medical College, Jaunpur, UP, India.

***Corresponding Author:** Dr. Isha Jaiswal

*Assistant Professor, Department of Radiotherapy & Radiation Medicine, Institute Of Medical Sciences, Banaras Hindu University, Bhelupur, Varanasi, UP, India, E-mail:ishadoc25@gmail.com

ABSTRACT

Background: With the advent of linear accelerator the radiation delivery techniques has shifted drastically from conventional to conformal & intensity modulated radiotherapy (IMRT). Recently, the next generation of IMRT techniques, namely volumetric modulated arc therapy (VMAT) has become widely available. VMAT is an arc treatment that creates highly conformal dose distribution with avoidance of critical structures along with faster delivery time and lowers MU's when compared to IMRT.

Aims and Objectives: To compare dosimetry, toxicity patterns and loco-regional control rates of IMRT & VMAT in head and neck cancer patients treated with concurrent chemo radiation.

Materials and Methods: 50 patients of head & neck squamous cell carcinoma were treated with radical chemo radiotherapy in two arms of twenty five each. All patients weretreated with either IMRT or VMAT and received concurrent chemotherapy Inj Cisplatin 35mg/m² weekly during RT. All Patients were evaluated during & after the treatment for radiation reactions graded according to RTOG toxicity criteria & response assessment according to WHO criteria.

Results and Observations: The study enrolled 55 patients.27 patients were included in the IMRT arm & 28 in the VMAT arm however 2 out of 27 patients in the IMRT arm & 3 out of 28 patients in the VMAT arm were excluded from the study because they did not meet the inclusion criteria. Ultimately each group had 25 patients who completed the treatment& were followed up for response assessment & toxicity.The median age of presentation was 55 years in both the groups & maximum patient belonged to age group 51-60 years. Majority of patients in both the arm had a good KPS score of more than 80.Most common primary site was oropharynx seen in 52 & 56 % of patients of IMRT &VMAT arm respectively followed by hypopharynx 28%-IMRT, 32% -VMAT & larynx cases were the least seen in 20 & 15 % of IMRT & VMAT patients. Most of the patient belonged to stage III seen in 56% of IMRT & 36% of VMAT arm followed by stage IV disease seen in 24% & 32% of IMRT & VMATarm.64% patients in the IMRT arm & 60% in VMAT arm received concurrent chemotherapy.

Conclusion: Both IMRT & VMAT are comparable treatment techniques for head and neck cancer in terms of tolerability & efficacy however VMAT is preferred because of its ,better dosimetric profile & lesser MUs.

Keywords: Intensity Modulated Arc Therapy (VMAT), Intensity Modulated Radiation Therapy (IMRT), head and neck cancer, risk of toxicity, morbidity, Gross Tumor Volume (GTV), high-risk, Clinical Target Volume (CTV), Low-risk CTV, Planning Target Volumes (PTV).

INTRODUCTION

Head & neck cancer is a major health problem in India. More than 50% of cases are from the developing world including India. Worldwide it accounts for 5,99,637 cases as per Globocan 2012. [1] of which 141140, cases are from India accounting of 25% of global burden in contrast to 45780(7.5%) cases from USA (SEER data 2015). [2]. In India it accounts for 30-45 % of all cancers in males & 11 to 15% in females [3] reflecting nearly similar sex ratio. Among the various sub site lip (ASR=9.8; Canada) and tongue cancers(9.7; France), have the highest incidence in world followed by oropharynx & hypopharyngeal cancers (ASR=12.5; France)[4]. While in India the ASR ranges from 9.3, 7.5& 2.7 per 100,000 cases for oral cavity larynx, hypopharynx & lip cancers respectively [5]. Five districts (Wardha, Kanyakumari, Pondicherry, Tiruvanthapuram and Kollam) have mouth cancer incidence ranging from 9.1 to 14.1 - much higher than recorded worldwide [6]. Common age group in India is 40-60 years & in fact, 60 to 80% of patients present with advanced disease in India, as compared to 40% in developed countries [7]. 61% to 79% of oral and pharyngeal cancers have been attributed to tobacco use alone and 75% with smoking plus alcohol drinking [8-9]. Cancer of the nasopharynx has been linked to Epstein Barr virus infection and oropharynx to human papilloma virus infection [10]. Some studies have also implicated precancerous lesions such as erythroplakia and leukoplakia as an as an important etiological factor of oral cavity cancer [11]. Significant correlation has been found between the stage of the primary tumor, the presence of involved cervical lymph nodes, and 5-year survival. Pérez et al [12] showed actuarial 10-year disease-free survival rates were 65% for patients with T1 tumours, 60% for T2, 60% for T3, and 30% for T4 disease. Patients with no cervical lymphadenopathy or with For Oropharyngeal cancers the results of M.D Anderson cancer centre & University of Florida from 1975-1998 suggest that the 5-year local-regional control and cause-specific survival rates with conventional treatment for stage I, 84-98% and 69-89%; for stage II, 80-85% and 75-87%; respectively [13]. The 5 years locoregional control & cause specific survival when considered for various sub sites in T1 & T2 lesions of base of tongue is 92-98%^[13], tonsil-90-92% [14-15], & soft palate-85-90% [16]. For pharyngeal tumours the 5 year locoregional control rates for stage I & II pyriform sinus, supraglottic & glottic cancers are 85% [17-18] 86-93% [19] & 100 % [19] respectively. High rates of loco regional control have also been achieved using interstitial brachytherapy in early stage (T1) & EBRT directed at primary and bilateral neck followed by interstitial brachytherapy boost to primary in T2 stage with a loco regional control of 82 % to 94 % at 5 years which is similar to various surgical series.[20-23]. Lee and co-workers [24] reported locoregional control and disease free survival as 93-100 % & 91 % respectively for 60 patients of supraglottic cancers at the M.D. Anderson Hospital between 1974 and 1987. The results of micro laser surgery & trans oral resection for early Supraglottic & glottic larynx cancers show 5 year local control rates ,recurrence free survival & overall survival of 100%,83% & 78% respectively[25]. Head & neck cancers have emerged as major public health problem in India. In our country more than 1.5-2 lakhs cases of head and neck are reported every year. It constitutes about 30% of all cancer in males and 11-16% in females accounting for a sex ratio of 3:1. Most patients are between 40 and 60 years. Indians are disproportionately affected by head and neck cancer with younger ages of incidence and more advanced disease at presentation. In patients with advanced carcinomas of the head and neck, locoregional control poses a major therapeutic

challenge. For tumors considered to be unresectable, the treatment has been conventionally fractionated radiation therapy up to total doses of 70 Gy and resulted in 2-year survival rates of less than 30%. Attempts to improve this poor outcome have been made by combining conventional radiotherapy regimen with simultaneously chemotherapy as well as introducing different alterations of radiation fractionation using hyper fractionated and or accelerated treatment schedules. Also here have been made significant advances in the delivery of RT in past few decades from 2D conventional to 3D conformal (3D-CRT) to intensity modulated radiotherapy (IMRT). These developments have been mainly driven by the need to reduce the dose to normal tissues & hereby minimize the risk of toxicity and morbidity associated with H&N radiotherapy. IMRT can be delivered via multiple fixed fields (conventional IMRT) or arc therapy (VMAT). VMAT is a novel radiation technique that creates conformal dose distributions with variable gantry speed, dynamic movements of MLC and variations in dose-rate. The basic concept of arc therapy is the delivery of radiation from continuous rotation of the radiation source. Arc therapies have the ability to achieve highly conformal dose distributions and are essentially an alternative form of IMRT. Various retrospective and few prospective dosimetric planning studies have compared these two techniques in head and neck cancer. These reports suggest that VMAT produces dose distribution comparable to IMRT for a variety of treatment sites including head and neck with at least similar or better plan quality. However there have been very few studies comparing VMAT & IMRT in terms of their clinical response to patients. This study aims to prospectively evaluate and compare both the techniques of radiotherapy for efficacy & toxicity in head and neck cancer patients..

MATERIALS AND METHODS:

Patient selection:

Fifty patients with non-metastatic Stage II-IV head and neck squamous cell cancer registered in the department of radiation oncology from July 2014 to December 2015 were enrolled in either treatment groups after written informed consent. Ethical clearance for the conduction of the study was obtained from the institutional ethics committee prior to the commencement of the study. It was a 2 arm study; Arm A: 25 patients of head and neck cancer treated with conventional IMRT & Arm B: 25 patients of head and neck cancer treated with VMAT. The selection criteria included histologically proven squamous cell carcinoma of oropharynx, hypopharynx & larynx with age more than 18 years, clinical stages III -IVb, Karnofsky Performance Status (KPS) of more than 70, and absence of serious uncontrolled comorbidities. Patients with recurrent & metastatic disease were excluded from the study.. Staging was done as per American Joint Committee on Cancer (AJCC, 7th edition, 2010). Baseline workup included a chest x-ray, complete haemogram, kidney and liver function tests, Direct laryngoscopy, contrast enhanced computed tomography (CECT) and other imaging were performed as indicated and as per clinician preference. Complete dental and nutritional assessment was also done before starting treatment.

Those patients fit for study were enrolled and assigned into one of the treatment groups either VMAT or IMRT on random number basis. Radical radiotherapy & chemotherapy was given to patients depending on clinical stage and general condition of the patient.

Radiotherapy:

Simulation & Contouring: All patients were immobilised in supine position with a 5clamp thermoplastic head & neck mask & contrast enhanced CT simulation was performed. Using multislice CT simulator (Siemens Somatom) images were transferred to the treatment planning station (MONACO version 3.3) for contouring & planning. The gross tumor volume (GTV) was delineated. The high-risk clinical target volume (CTV) encompassed the GTV with an additional 1-1.5 cm margin, correcting for anatomical boundaries. The low-risk CTV included the elective nodes according to internationally accepted guidelines (18). An isotropic 5 mm margin was then added to CTVs to obtain the planning target volumes (PTV). PTVs were cropped 3 mm inside the Skin.

Normal structures, including the parotid glands, oral cavity, mandible, optic nerves and chiasm, brainstem, larynx, pharynx, oral cavity, thyroid, and spinal cord, were also contoured on the CT scans.

Radiotherapy Planning: The IMRT plans were generated using five-seven coplanar beam directions of 6 MV. Each VMATV plan consisted of two 6 MV arcs with an arc length of 360°, one clockwise and one counterclockwise.

Dose Fractionation: All patients were treated with either IMRT or VMAT with Simultaneous integrated boost technique. Two SIB dose levels were prescribed. The patients were treated with either 66 Gy/60Gy/54Gy to high risk/intermediate-risk/low-risk planning target volume in 30 fractions. Treatment planning was done using 3D Computerized Treatment Planning System (TPS)(MONACO version 3.3) with inverse planning module, image fusion Algorithm, DICOM and MOSAIQ electronic record verification system

Planning Objectives and Plan Evaluation. Plans were deemed acceptable if 95% of the prescribed dose covered $\geq 95\%$ of the respective PTVs and no more than 2% of the PTV received $\geq 107\%$ of the prescribed dose. Concerning OARs Standard IMRT constraints for OARs were followed as per the Mobius chart.

Treatment delivery: Quality assurance (QA) was done for each patient before treatment delivery. Treatment was delivered on ELEKTA Infinity linear accelerator machine, with dynamic multileaf collimation (40-pair MLC), leaf width of 1 cm at the isocentre. Set-up image verification was done in the form of cone beam computed tomography (CBCT) prior to treatment delivery for first three fractions. Subsequent CBCTs were acquired twice in a week and online corrections were done when setup error ≥ 3 mm was noted in any directions defined in ICRU 50, 62 & 82

Chemotherapy: The chemotherapy regimen planned was Inj. cisplatin 50 mg weekly during radiotherapy to a total 6 cycles. Patients who were not candidate of concurrent chemotherapy due to low performance score, malnourishment, deranged renal function, uncontrolled systemic illness or any combination of above were treated by radiotherapy alone.

Toxicity assessment and follow-up: During treatment weekly assessment was done for each patient and. Radiotherapy associated toxicity will be evaluated along with complete Haemogram, liver function test and kidney function test. The first post-treatment visit was done 3 weeks after completion of radiotherapy. Subsequent visits were scheduled as monthly interval for the first 3 months, then 2 monthly for the next 6 months & 3 monthly thereafter. At each follow-up a complete assessment of the primary disease & toxicity was done. Acute toxicity were graded using the RTOG acute radiation morbidity scoring criteria up to 90 days from the treatment initiation. Late toxicity was graded using RTOG Late Radiation Morbidity Scoring Schema 90 days after treatment initiation. Radiological and endoscopic evaluation was done initially at 3 months and then at the decision of treating physician later to evaluate locoregional disease status. Response will be categorized as complete response, partial response, stable disease, or progressive disease based on WHO criteria for response evaluation. SPSS version 19.0 was used for statistical analysis. The dosimetric & clinical results of IMRT and VMAT were compared with the two-sided matched-pair t-test. P value of 0.05 and less was considered to be statistically significant for all analysis..

Results and Observations: Patient and tumor characteristics: The study enrolled 55 patients. 27 patients were included in the IMRT arm & 28 in the VMAT arm however 2 out of 27 patients in the IMRT arm & 3 out of 28 patients in the VMAT arm were excluded from the study because they did

not meet the inclusion criteria. Ultimately each group had 25 patients who completed the treatment & were followed up for response assessment & toxicity. The median age of presentation was 55 years in both the groups & maximum patient belonged to age group 51-60 years. Majority of patients in both the arm had a good KPS score of more than 80. Most common primary site was oropharynx seen in 52 & 56 % of patients of IMRT & VMAT arm respectively followed by hypopharynx 28% -IMRT, 32% -VMAT & larynx cases were the least seen in 20 & 15 % of IMRT & VMAT patients. Most of the patient belonged to stage III seen in 56% of IMRT & 36% of VMAT arm followed by stage IV disease seen in 24% & 32% of IMRT & VMAT arm. 64% patients in the IMRT arm & 60% in VMAT arm received concurrent chemotherapy.

Table 1: Age distribution of patients

Table -1

Age in years	IMRT (N=25)		VMAT (N=25)	
	No.	%	No.	%
Mean ± SD	55.76±8.40		55.80±12.39	
Median	55		55	
Range	43-74		45-77	

N=total number of patients

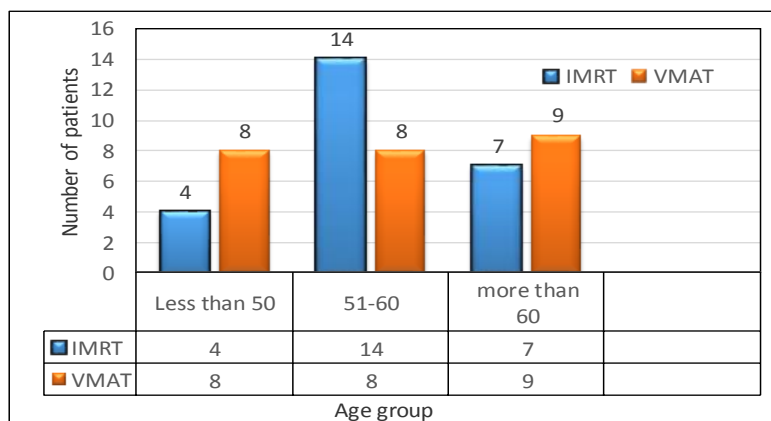


Figure-1

Table -1 & figure -1 shows that the age of the patients enrolled in our study ranges between 43 to 77 years with mean & median age of presentation being 55 years in both the groups & maximum patient belonged to age group was 51-60 years. The patient age distribution was symmetrical in both the arms of study with no significant difference

Gender Distribution of Patients (Figure-2)

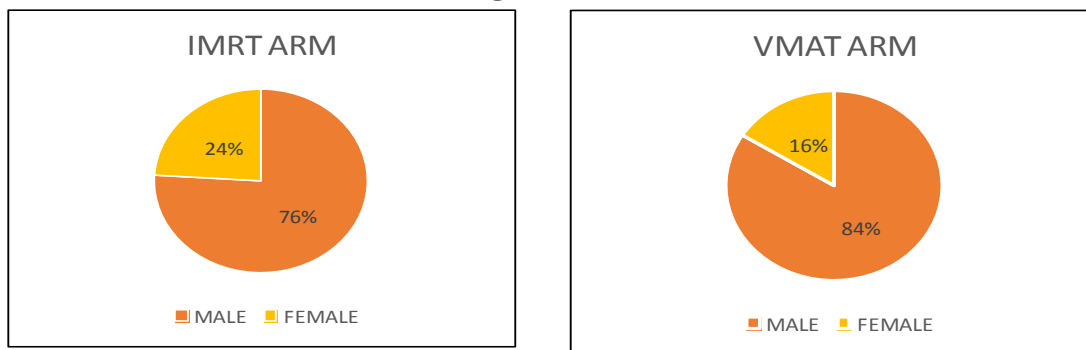


Figure-2

Figure -2 shows that male outnumbered females with a ratio of 3:1 in IMRT arm & 5:1 in VMAT arm however the difference was not statistically significant.

Chief presenting complaint of the patients (Figure-3)

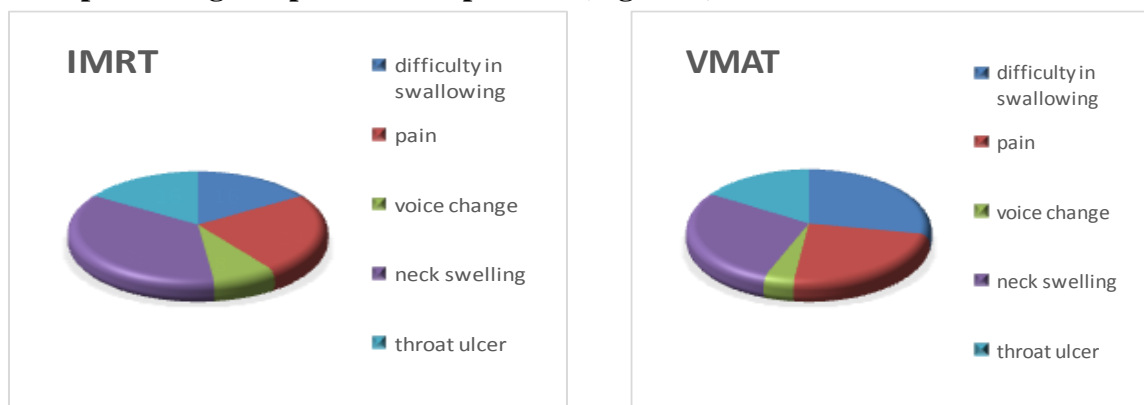


Figure-3

Figure -3 states that the most common presenting complaint in our study. Neck swelling was seen in 36% & 28% of IMRT & VMAT followed by difficult in swallowing & pain during swallowing seen in 40% & 52% of IMRT & VMAT patients. Throat ulcer seen in 16% patients in both the groups & the least common presentation was voice change

Median duration of symptoms prior to diagnosis (Table-2)

Table-2

ARM	IMRT	VMAT
Months	4.5 months	3.8 months

As shown in table -2 the median duration of symptoms was 4.5 months in the IMRT arm & 3.8 months in the VMAT

Distribution of the patients according to diagnosis (Table -3)

Table-3

Diagnosis	IMRT (N=25)		VMAT (N=25)		p-value
	No.	%	No.	%	
Oropharynx	13	52.0	14	56.0	0.877
Hypopharynx	7	28.0	8	32.0	0.728
Larynx	5	20.0	3	12.0	0.511

N=total number of patients

As shown in table-3 the most common primary site was oropharynx seen in 52 & 56 % of patients of IMRT & VMAT followed by hypopharynx 28%-IMRT, 32% -VMAT & larynx case were the least seen in 20 & 15 % of IMRT & VMAT patients.

Target volume coverage and monitor units

Table reports the results dosimetric comparison of IMRT & VMAT. All plans in both groups achieved acceptable target coverage for all the included parameters, respecting the planning objectives. The mean of the doses to target were similar in the both the arm with non-significant difference. However, there was a trend towards a better target coverage in the VMAT arm compared to IMRT arm.

Organs at risk

There was no statistical difference between the Dmax of spinal cord, PRV cord & brainstem &

Dmean of parotids.

Mean MU for VMAT arm was significantly less than IMRT arm and VMAT treatment were faster than IMRT .

Clinical evaluation

Results for acute toxicity:

On clinical analysis though no statistical significance was observed in acute radiation toxicity, a trend toward lesser toxicity was observed in VMAT arm compared to IMRT arm Comparing the grade 3 acute toxicity, mucositis was the most common acute toxicity in both the arms seen in 68% - IMRT & 52 % -VMAT arm followed by skin toxicity (48% & 44%) & oesophageal toxicity (32% & 24%). Grade 3 skin toxicity was seen in 44% patients in VMAT vs. 48% in IMRT. Highest skin toxicity was grade 4-skin ulceration seen in 12 % in IMRT & 4 % in VMAT in 6th week of radiotherapy but this was statistically insignificant For grade, 3 dysphagia nasogastric tubes placed in 5 patients in IMRT group & 4 patients in VMAT. Rest of the patient given intravenous fluid support & no patient had grade IV toxicity.

Figure -1 show that the incidence of grade 3 toxicity was lower in the VMAT arm compared to IMRT arm however, the difference was statistically non-significant..

Clinical Response Assessment

Direct Laryngoscopy and CECT face & neck ± PET-CT was performed in all patients after 3 months of completion of radiotherapy. All patients showed good response to treatment. 19 out of 20 in IMRT arm & 20 out of 22 patients in the VMAT arm had complete clinical response to treatment. One patient in the IMRT arm & two in VMAT arm had partial response to treatment.

Table-4.

	IMRT N=20		VMAT N=22	
	No.	%	No.	%
CR	19	95	20	90.9
PR	1	5	2	9.1
SD	0	0	0	0
PD	0	0	0	0

Table-5 Patients who had partial response to treatment

	IMRT N=1/20	VMAT N=2/22	
		Pt. 1	Pt. 2
Age/ gender	55/M	55/F	70/M
KPS	90	70	80
Site	Oropharynx (BOT)	Oropharynx (BOT)	Hypopharynx (Pyrimiform Sinus)
Initial Stage	IV	IV	IV
Treatment received	CTRT	RT	RT
Residual Disease status	Nodal	nodal	Local + nodal
Management	Palliative chemotherapy		

Table – 4, 5 shows the details of patients who had partial response to treatment. One patient in

IMRT arm had partial response was a 55 years male, KPS 90 suffering from stage IV Oropharyngeal cancer treated with concurrent chemo radiotherapy as per schedule & on post RT investigation showed residual disease at primary & nodal site. Two patients had partial response in VMAT arm. One among them was a 55 years female, KPS 70 stage IV oropharynx treated with RT alone considering her age & performance status. & had residual nodal disease. The other patient was also a 70 years male, KPS=80, stage IV hypopharyngeal cancer treated with RT alone & had both primary & nodal residual disease. All patients were referred to surgical oncology for expert opinion regarding feasibility of salvage surgery. None of the patient could be taken up for surgery due to either patient refusal & comorbid condition & therefore are now treated with cisplatin based palliative chemotherapy.

DISCUSSION

In this prospective single-center study we compared dosimetric and clinical outcomes of 50 patients treated with either standard sliding window IMRT or VMAT in locally advanced HNC regarding the dose & fractionation schedule, all patients were treated with simultaneous integrated boost radiotherapy via IMRT or VMAT technique. SIB-IMRT gives the advantage of better target conformity with less dose spillage in critical organs. At the same time, it allows delivery of a higher dose of radiation to smaller sub volumes in the target in a shorter period of time. SIB-IMRT fractionation regimen in our study was 66/60/54Gy to PTV-HR, PTV-IR and PTV-LR respectively. In the view of biological equivalency to conventional doses of 70Gy, 60Gy and 50Gy, respectively [26-27] the regimen was used as an alternative to conventional 70Gy in all patients. Same fractionation was used in RTOG H-0022 and also by Vosmik et al. [27]. This is the most common fractionation schedule used in various trials of SIB-IMRT. However, this fractionation scheme is considered inadequate for locally and regionally advanced head and neck cancer There are various possible approaches to enhance the radiobiological effect of radiotherapy on the tumor in locally and regionally advanced disease. The most common practice is the use of a higher dose than 66Gy in 30 fractions (70Gy or more) [28]. However there are data showing that dose escalation beyond 66Gy had led to severe acute reaction & poor compliance to radiotherapy. Lauve et al [28] in a study of high dose SIB –IMRT concluded that the maximal tolerable dose is 70.8Gy in 30 fractions (dose per fraction 2.36Gy) however it is associated with greater incidence of acute grade 3 toxicities which required a treatment break and dose reduction. The high number of grade 3 acute side effects corresponds to the escalation of dose per fraction. Furthermore, there is still limited evidence that the higher dose per fraction cannot increase the late effect probability. In our study we found that the SIB-66Gy schedule was well tolerated by all patients in both arms & only 5 patients in the IMRT arm & 3 in VMAT arm had treatment breaks ranging from 2-4 days in the last week of radiotherapy. With the median treatment time of 42 days most of the patients completed treatment at scheduled time. Since the treatment interruption was less than a week so no patient required dose modification or gap correction. As far as the dose constrains to the organ at risk is considered it is in accordance with the standard dose constrains used in various clinical trials of 3D conformal radiotherapy & intensity modulated radiotherapy. The planning objective of 95% of the planning target volume to be covered by more than 95% of the prescribed doses was fulfilled in all patients in both arms & for all target volumes. The prescribed doses & the mean of the doses to target & Organ at risk were similar in the both the arm with non-significant difference. However there was a trend towards a better target coverage & sparing of OAR in the VMAT arm though this did not reach any statistical significance. Several planning studies have compared dosimetric results achieved with VMAT plans with fixed field IMRT plans. The authors of these studies observed better PTV coverage and conformity as well as better sparing of OARs for VMAT compared to IMRT, while delivery times were shortened. Study by Vanetti et al [29] compared single and double arc VMAT with 7-9 field fixed field IMRT (SW) in 29 patients with tumours of the oropharynx, hypoharynx and larynx. The results of the study showed similar PTV coverage and conformity but VMAT was

better than IMRT at sparing spinal cord (D2%, mean dose), brainstem (D2%, mean dose) and parotid glands (mean dose). Our study failed to reflect any significant dosimetric difference between VMAT & IMRT because it was not a pure dosimetric study. The volumes of target planned with VMAT & IMRT were different for all patients & for all plans. On the contrary various studies which documented dosimetric difference between the 2 techniques has VMAT & IMRT plans generated and compared for same target volumes & organ at-risk. In conventional RT guidelines there is now a widely accepted standard for use of concurrent chemotherapy. The analogical CT schemes can be considered to be useful in SIB-IMRT techniques. Concurrent CT usually belongs to IMRT protocols for nasopharyngeal cancer. The toxicity profile in these trials was acceptable. Lee et al [30], recently published a study with SIB-IM-RT regimen with dose 70 Gy, 59.4 Gy and 54 Gy in 33 fractions and concurrent CT (mostly two cycles of cisplatin 100 mg/m² every 3–4 weeks) in 41 patients with locally advanced oropharyngeal cancer. Acute grade 3–4 mucous toxicity was reported in 66% of patients, and late xerostomia grade ≥ 2 was reported in 12% of cases. Considering the results of these studies concurrent chemotherapy was prescribed to all the patients with advanced stage (III&IV) of presentation. The role of concurrent chemo radiotherapy as the standard mode of treatment in locally advanced tumours of pharynx and larynx have been proved by MACH-NC meta-analysis by Pignon and many other randomized control trails. MACH-NC in a study on 93 phase III trials and 17,346 patients concluded that OS benefit was 4.5% at 5 years when chemotherapy was added to RT, with greater benefit for CCRT vs. induction chemo followed by RT (6.5% OS benefit with concurrent chemo-RT). It also states that there was no difference between mono or poly chemotherapy regimens, but increased benefit with platinum-based compounds. So in this study cisplatin was chosen as the drug for concurrent chemotherapy regimen. The chemotherapy schedule was Cisplatin 50 mg weekly during radiotherapy for 6 cycles. However 3 patients in the IMRT arm & 2 in the VMAT arm could not be given CCRT because of poor performance status & medical comorbidity. 69% in IMRT arm & 66% in VMAT arm received at least 4 cycles of chemotherapy. Since various clinical trial & meta-analysis including MACH-NC have proven the benefit of chemotherapy was decreased with increasing age, with no benefit observed if age more than 70 year so in our study also patient with age more than 70 were exempted from concurrent chemotherapy treatment.

For early stage disease single modality treatment in the form of altered fractionated radiotherapy was considered adequate based on the results of MARCH, meta-analysis which states that there is a significant survival benefit of 3.4% in altered fractionation as compared to conventional fractionation.

The present study confirms the feasibility and very good tolerance of this regimen in head and neck cancer. Assessment of acute toxicities during radiotherapy reflected a trend towards lower incidence of grade 3 toxicities in the VMAT arm compared to IMRT arm however the statistical analysis showed non-significant results. The incidence of acute toxicities depends largely on the tumor volume, target delineation & dose prescription that determine the amount of normal tissue irradiated during radiotherapy. Comparing the acute toxicities encountered in our study with the various studies of SIB IMRT, incidence of grade 3 toxicity as the worst toxicity during radiotherapy was skin: 48% in IMRT vs. 44% in VMAT, mucositis 68% vs. 52% in IMRT vs. VMAT, pharynx & oesophageal toxicity 32% vs. 24% & laryngeal toxicity 20% vs. 16% in IMRT vs. VMAT. There was a trend towards lesser toxicity in the VMAT arm compared to IMRT arm however the difference failed to achieve a statistical significance.

In our study the incidence of grade 3 skin toxicity was 48% in IMRT arm vs. 44% in VMAT arm. 12% of IMRT patients & 4% of VMAT patients also encountered grade 4 skin toxicity. This is in contrast to the findings of Chao ET al. in whose series almost 21% of the patients had experienced grade III dermatitis during treatment. Lee et al have highlighted the importance of the angle of beam entry and the bolus effect produced by the thermoplastic casts in the production of this kind of dermal toxicity. They have recommended the trimming of the PTV to a depth of 5 mm from the

skin surface and giving separate constraints to the skin. One of the possible reason for increased skin toxicity in our study may be that we used a 3mm margin for trimming the PTV from skin surface. In our experience, we have also observed that giving constraints to the skin results in dose calculation errors. Several authors have reported substantial preservation of the parotid gland saliva flow rates in early head & neck cancer with significant reduction in the incidence of severe xerostomia when the mean parotid dose was below 25.8–26 Gy in patients treated with IMRT. However, the amount of the parotid gland that will be spared or irradiated is directly related to the volume overlap between the treatment target and the parotid glands. Since the most common lymph node involved in head & neck cancer is level II jugular nodes, so contouring of these nodes with margin & inclusion in the high risk PTV results in irradiation of inferior pole of parotids to higher doses. Even then there is a probability of keeping the mean dose to parotid below 26 Gy in early tumours but in advanced tumours, with bilateral lymph node involvement, parotid sparing may not be possible in the same amount as in early head and neck cancers. This is because large amount of normal tissue, from the base of skull to the supraclavicular fossa which has to be included in the irradiation fields for advanced tumours. As mentioned before in our study 80 % patients in IMRT arm & 68% in VMAT arm were locally advanced tumours so the dose constraint to the parotid was not strictly followed. PTV coverage was given preference over parotid sparing & so 80% of our IMRT & 72 % of VMAT patients experience grade 2 salivary changes at end of RT. However the incidence of severe xerostomia fell drastically on subsequent follow ups & at 3months the incidence of grade 2 xerostomia was 40 % vs. 22.50% in IMRT vs. VMAT. The recovery of xerostomia was earlier in the VMAT arm compared to IMRT however, the difference was statistically insignificant. The acute toxicity data in the present study are not different from estimated values experienced from conventional radiotherapy of 70 Gy in seven week. We also observed that median time of persistence of maximum grade toxicity in our study is less as compared to conventional RT, suggesting early recovery as a result of lower dose to surrounding normal tissue.

As far as local control is considered IMRT having potential to deliver higher doses to tumours near critical structures when compared to 2D-RT or 3D-CRT, can influence loco-regional control & survival. However due to the high dose-gradient generated by the characteristics of IMRT isodoses, concerns about loco-regional control and survival have arisen. Only one large study (616 patients with nasopharyngeal tumours) with a long follow-up (5 years) has shown an improvement in both loco-regional control and overall survival more evident in locally advanced tumours. Many other small randomized trials with shorter follow-up did not reflect these results. As our study also has a short follow up period & locoregional control was not our endpoint so any comment upon the difference in loco regional control & overall survival cannot be made but the treatment response assessment at 3 months showed complete response in 95% of IMRT patients & 91% of VMAT patients. Although the difference in response rate was statistically insignificant but the probable reason for it may be that VMAT arm had more stage IV patients (32% vs. 24%) & all the patients with partial response had stage IV disease.

Considering the late toxicities we are yet to observe results with more follow-up visits. We have results with median follow-up of 5 months and in our study, all acute toxicities resolve at 2-3 months follow up, earlier in VMAT compared to IMRT arm. Mucosal toxicity, skin toxicity rates improved after completion of treatment. Unlike several contemporary series of concurrent chemo radiation reporting a high incidence of laryngo-pharyngeal toxicity, we are yet to observe significant morbidity in this area. Xerostomia was the only toxicity that persisted after 3 months however the incidence decreased with increasing time interval from the end of radiotherapy.

CONCLUSIONS:

In the present study, the results of the study showed comparable demographic profile between the 2 arms of the study and good tolerance to the prescribed regimen. As far as the acute toxicities during radiotherapy are concerned the analysis of most severe acute toxicities as grade 3 in both the arms

reflected that overall mucositis was the most common acute toxicity in both the arms seen in 68%-IMRT & 52 % -VMAT arm followed by skin toxicity (48% & 44%) & oesophageal toxicity (32& 24%). Least common incidence was seen in laryngeal toxicity (20% & 16%) in both the arms. Overall the incidence of all grade 3 toxicities were lower in the VMAT arm compared to IMRT arm however, the difference was statistically non-significant. The analysis of response to treatment shows that all patients had response to treatment. Nineteen out of 20 in IMRT arm & 20 out of 22 patients in the VMAT arm had complete response while one patients in the IMRT & two in VMAT arm had partial response as assessed by WHO criteria. These results support the use of IMRT& VMAT as an acceptable technique to treat patients in order to more efficiently plan radiotherapy while reducing the toxicity rates compare to the previous techniques (conventional, 3DCRT). Although the study sample is a heterogeneous in terms of primary tumour location (oropharynx, hypopharynx and larynx) and stage of the disease, the present data confirms the feasibility of IMRT & VMAT techniques of radiotherapy & tolerability of IMRT-SIB with concurrent chemotherapy in patients with advanced head and neck cancer.

LIMITATIONS:

Limitations of the present study is small sample size and shorter duration of follow up. Therefore, a study on larger sample size and longer duration of follow up is required in order to find out the statistically significant difference between IMRT & VMAT for long term control & toxicities.

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