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Tafaul-Al-Ahsa Cancer Foundation Wins EXCELLENCE AWARD for Cancer Awareness Initiatives at Gulf Cancer Awareness Week 2024





The Gulf Oncology Society meeting resulted in fruitful outcomes, with young doctors showing keen enthusiasm for assuming leadership roles and implementing impactful initiatives.

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

Comparison of Acute Toxicities, Overall Treatment Time and Quality of Life in Head and Neck Cancer Patients Treated with IMRT and Helical Tomotherapy

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Abstract

Introduction: Technical innovations in radiation therapy treatment planning and delivery over the last two decades have changed the practice of radiation therapy dramatically. The benefit of improved dose homogeneity and better sparing of critical structures in helical tomotherapy compared with conventional linac–based IMRT has been reported. This study was conducted to compare acute toxicities (skin, mucous membrane, salivary gland and hematological) during treatment and overall treatment time in Head and Neck Cancer patients treated with IMRT and Helical Tomotherapy and to assess the quality of life of patients during treatment between two groups.

Materials and Methods: The study involved thirty patients with histologically proven Squamous cell carcinomas of Head and Neck. They were treated with concurrent chemoradiotherapy, to a dose of 60–70 Gray in 30–35 fractions. The study consists of 2 arms which are standard IMRT and Tomotherapy arm. Fifteen consecutive patients were treated under IMRT and 15 patients were treated under Helical tomotherapy, along with concurrent chemotherapy. After completion of planning, plans were evaluated and dose to the targets, organs at risk were tabulated. Patients were assessed weekly for acute toxicities (skin reactions, mucositis, xerostomia, haematological toxicities) during the course of the treatment as per RTOG criteria. Quality of life of patients were assessed using FACT/ NCCN HNSI questionnaire in local language at day 1, day 21 and at completion of radiotherapy.

Results: Grade 2–3 skin reactions, mucositis, anemia, leukopenia and thrombocytopenia were predominant in both arms. Treatment time from start of radiotherapy to completion of radiotherapy varied from 39 days to 68 days. Majority of patients completed radiotherapy within 50–56 days. Mean quality of life score did not show much difference between IMRT and tomotherapy arms.

Conclusion: The study did not show any statistically significant difference in overall treatment time, acute toxicities– skin reactions, xerostomia, mucositis & hematological toxicities and quality of life of patients during radiotherapy between IMRT and Helical Tomotherapy. Dosimetric benefits of Tomotherapy over IMRT do not translate into clinical benefit in terms of reduced acute toxicities, lesser overall treatment time and better quality of life of patients.

Key words: Head and Neck Carcinoma, IMRT, Tomotherapy, RTOG, toxicity, FACT/ NCCN HNSI, quality of life

Introduction

Radiotherapy for head and neck squamous cell carcinoma (HNSCC) in many sub sites, has shifted from three–dimensional conformal radiotherapy (3D–CRT) to intensity–modulated radiotherapy (IMRT), resulting in highly conformal and more homogenous dose administration to the target volumes and better sparing of the organs at risk (OARs). Intensity–modulated radiation therapy (IMRT) in head and neck (H&N) cancer has the capability to generate steep dose gradients, leading to an improved therapeutic index. The benefits of linear accelerator–based intensity–modulated radiotherapy (IMRT) in improving PTV conformity, and normal tissue complication probability (NTCP) by sparing OARs have been well documented.[1–5]

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Helical tomotherapy provides image guided IMRT. Helical tomotherapy has been found to produce better homogeneity and normal tissue sparing.[3] Tomotherapy with its integrated mega voltage CT (MV CT) helps in added treatment precision. It permits superior means of delivering conformal radiotherapy. This also allows for ongoing verification and rapid correction of treatment variations, forming core concept of adaptive radiotherapy.[6–8] The benefit of improved dose homogeneity and better sparing of critical structures in helical tomotherapy compared with conventional linac–based IMRT has been reported. We need to investigate whether the dosimetric advantages of Tomotherapy benefit patients by reducing acute toxicities, hence decreasing the treatment breaks and improving the quality of life. Hence the need for the study.

Aims and objectives

To compare acute toxicities (skin, mucous membrane, salivary gland and hematological) during treatment and overall treatment time in Head and Neck Cancer patients treated by IMRT with Helical Tomotherapy, and to assess the quality of life of patients during treatment between two groups

Patients and Methods

Study design and study population:

Our study was a prospective, single institute, observational, double arm, comparative study. It was done in HealthCare Global Enterprises Ltd (HCG Hospital) in Bangalore, Karnataka, India, between the time period of June 2016 to May 2017. Institutional scientific review committee and Central ethics committee approvals were taken before starting the study. Patients with histologically proven locally advanced head and neck carcinoma were taken for study. Inclusion criteria were patients with histologically proven squamous cell carcinoma of head and neck (oral cavity, oropharynx, hypopharynx, nasopharynx, supraglottic larynx) with AJCC7th edition TNM staging T3/T4 with N0, any N+, M0, patients suitable for concurrent chemo radiation, with age above 18 years and below 70 years, ECOG 1 & 2; patients with normal renal function tests and patients with or without surgery were considered for the study.

Exclusion criteria were patients not consenting for the study; patients with prior radiotherapy to head and neck; patients with evidence of distant metastasis, simultaneous secondary malignancy, recurrent disease or those who have received neo–adjuvant chemotherapy. Patients with thyroid carcinoma, vocal cord carcinoma and paranasal sinus carcinoma were also excluded from the study.

Sample size calculation:

Sample size was calculated using hypothesis testing of two means formula. As per the formula, the minimum sample required was 12 per arm.[9] Our study had two arms– Standard IMRT arm and TOMOTHERAPY arm. Our study population was formed by 15 consecutive head and neck cancer patients in each arm.

Formula:

$$n = \frac{2s_p^2 \ [z_{1-\frac{\alpha}{2}} + z_{1-\beta}]}{\mu_d^2} \qquad \text{Where,} \quad s_p^2 = \frac{s_1^2 - s_2^2}{2}$$

Where,

s_1^2 : Standard deviation in the first group

s_2^2 : Standard deviation in the second group

μ_d^2 : Mean difference between the samples

α : Significance level

$1-\beta$: Power

Methodology:

A complete informed consent was taken from each patient. All patients underwent complete clinical examination, necessary blood and imaging studies. Immobilization procedure performed with patients in supine position; CT simulation was done using wide bore (80cm) SEIMEN® CT scanner. images were transferred to digital imaging and communication (DICOM) format and sent to ECLIPSE® planning system *(Version11)* (Varian Medical Systems) ®. Patients in IMRT arm were planned using an inverse planning algorithm with step and shoot technique on Eclipse® planning system (Version11), for treatment on Siemens Artiste® linear accelerator (refer figure1) with MLC – 160 leaves, each with a width of 5mm at the isocentre. Treatment was delivered using 6 MV photons. Patients in Tomotherapy arm were planned using an inverse planning algorithm using dynamic delivery technique on Volo® treatment planning system version 5.1 for treatment on Accuray HAD® machine (refer figure 2), with 64 binary MLCs of 0.625cm each. All planning were done with a plan field width of 2.5cm, modulation factor of 2, and pitch depending on size of tumor. Treatment was delivered using 6MV photons. Dose constraints as advised by QUANTEC® was followed for the OAR structures during planning. Prior to delivery, a fluence map check and other quality assurance checks were ensured before starting the treatment.

All the patients treated with 60–70 Gy, 2 Gy /fraction, 30–35 fractions, 5 fractions/week, along with weekly concurrent chemotherapy (cisplatin / carboplatin). Concurrent chemotherapy administered weekly with

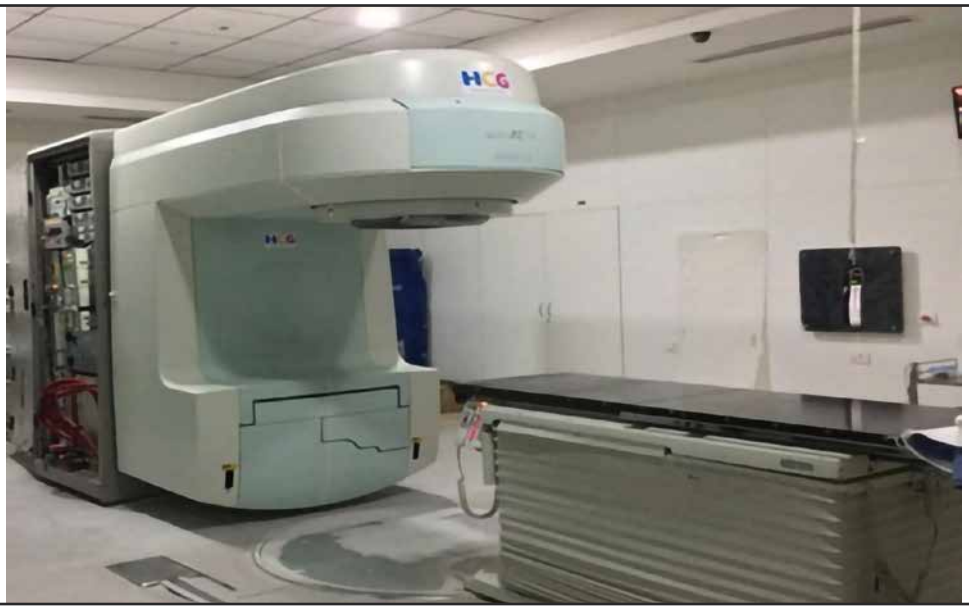


Figure 1. Siemens Artiste Linear Accelerator



Figure 2. Helical Tomotherapy Machine – Accuray HAD

Inj. Cisplatin 40mg/m^2. Inj. Carboplatin was used in patients with compromised renal parameters (e.g.: higher creatinine clearance) and /or where cisplatin was not expected to be tolerated. Dose of carboplatin calculated by area under curve (AUC) based on glomerular filtration rate (AUC–2).

Patient evaluation:

Patients were assessed weekly for acute toxicities during the course of treatment as per RTOG criteria. Grades of skin reactions, mucositis, xerostomia were noted. Blood examinations were done weekly. Hematological parameters (Hemoglobin, total count, differential count, platelet count, serum Creatinine) were checked and grade of toxicity noted. Quality of life questionnaire was given to all patients in their local language on first day, middle (day 21) and completion of radiation treatment. Quality of life assessment was done using FACT/NCCN HNSI questionnaire (in their local language). License was obtained for the use of FACIT Questionnaire.

Statistical methods:

All study data were manually entered into an electronic spread sheet. Each patient was assigned a unique trial recruitment number and the spread sheet was encrypted with a password. Data was analysed using SPSS version

(IBM Software) version 23 for Windows. Descriptive data statistics on patient demographics, toxicity scores, hematological scores have been presented in tabular or graphic forms whichever appropriate.

The descriptive data statistics – frequency analysis, percentage analysis was used for categorical variables and the mean and standard deviation were used for continuous variables. Association between two variables was tested using Chi–square test. The results of Tomotherapy and IMRT compared with the two–sided Mann – Whitney U test. The threshold for statistical significance is $p< 0.05$.

Results

Patient and tumor characteristics are detailed in table 1 and table 2. Mean age was 48.67years (range 33–70 years) in IMRT arm and 56.93years (range 35–70years) in Tomotherapy arm. Male population was predominant in our study [IMRT – 11/15(73.3%), Tomotherapy–14/15(93.3%)]. All sub sites of head and neck were taken. Maximum cases were of oral cavity (IMRT– 11/15, Tomotherapy 11/15). Sub sites were matched in both arms. All patients had locally advanced disease. All the patients received bilateral neck irradiation. Prescription dose ranged from 60–70Gy in 30–35 fractions, with majority of patients having prescription dose of 66Gy [IMRT – 7/15(46.7%) and Tomotherapy 9/15(60%)].

		IMRT		TOMOTHERAPY	
		No	%	No	%
Age of the patients	31–40 years	5	33.3	1	6.7
	41–50 years	4	26.7	3	20
	51–60 years	3	20	5	33.3
	61–70 years	3	20	6	40
	Total	15	100	15	100
	Mean ± SD	48.67±11.94		56.93±10.65	
Sex of the patients	Male	11	73.3	14	93.3
	Female	4	26.7	1	6.7
Subsite of disease	Hypopharynx	3	20	3	20
	Oral cavity	11	73.3	11	73.3
	Oropharynx	1	6.7	1	6.7
Group stage	III	2	13.33	7	46.66
	IVA	13	86.66	8	53.33
Radiation dose	60Gy	3	20	4	26.7
	66Gy	7	46.7	9	60
	70Gy	5	33.3	2	13.3

Table 1. Showing patient and tumor characteristics and radiation dose received in IMRT and TOMOTHERAPY arms. SD – standard deviation

Toxicities

Patients were assessed weekly for skin reactions, mucositis, xerostomia, hematological toxicities. The acute toxicities during treatment between IMRT and Tomotherapy groups are summarized in table 3 and 4.

Hematological toxicities:

With regard to hemoglobin, two patients in Tomotherapy arm developed grade 2 anemia. Three patients in IMRT arm and two patients in Tomotherapy arm developed grade 2 leukopenia. One patient in IMRT arm and three patients in Tomotherapy arm developed grade 3 leukopenia. One patient in tomotherapy arm developed grade 2 thrombocytopenia. We did not observe statistically significant difference in hematological toxicities between two arms. (Refer table 3 and figure 3)

	IMRT			Tomotherapy		
	Total cases	STAGE III	STAGE IVA	Total cases	STAGE III	STAGE IVA
Hypopharynx	3	0	3	3	1	2
Oral cavity	11	2	9	11	5	6
Oropharynx	1	0	1	1	1	0

Table 2: Showing total number of cases in different stages in each sub site

	RTOG GRADING	IMRT (15)		TOMOTHERAPY (15)		p value
		No.	%	No.	%	
Hemoglobin	Grade 2	0	0	2	13.3	0.193
	Grade 3	0	0	0	0	
WBC	Grade 2	3	20	2	13.3	0.49
	Grade 3	1	6.7	3	20	
Platelets	Grade 2	0	0	1	6.7	0.309
	Grade 3	0	0	0	0	

Table 3: RTOG Acute toxicities on Hemoglobin, WBC and Platelets

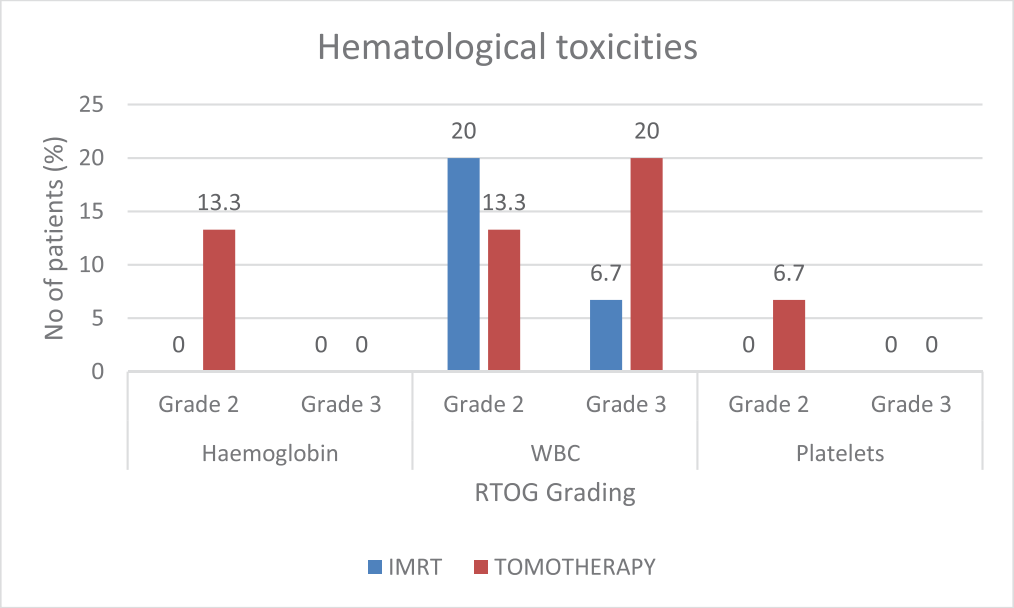


Figure 3. RTOG Acute toxicities on Haemoglobin, WBC and Platelets

RTOG Acute toxicities in Skin, Mucosa and Salivary gland;

From table no 4, it is noted that during the course of treatment in IMRT arm, four patients developed grade 2 skin reactions and none developed grade 3 skin reactions. In tomotherapy arm, during the course of treatment one patient developed grade 2 skin reactions and one developed grade 3 skin reactions.

In IMRT arm, twelve patients developed grade 2 mucositis and three developed grade 3 mucositis. In tomotherapy arm, ten patients developed grade 2 mucositis and five developed grade 3 mucositis.

In IMRT arm, eleven patients developed grade 2 xerostomia, in tomotherapy arm ten patients developed grade 2 xerostomia.

We did not observe statistically significant difference in acute toxicities between two arms. (Refer table 4 and figure 4)

Overall treatment time:

Treatment time from start of radiotherapy to completion of radiotherapy varied from 39 days to 68 days. Majority of patients completed radiotherapy within 50–56 days. There was no statistically significant difference between two groups (p–0.288) (Refer table 5 and figure 5)

Quality of life

Quality of life questionnaire scoring done using FACT/NCCN Head & Neck Symptom Index (FHNSI) Scoring Guidelines (Version 4). Mean quality of life score in IMRT

	RTOG GRADING	IMRT (15)		TOMOTHERAPY (15)		p value
		No.	%	No.	%	
Skin	Grade 2	4	26.7	1	6.7	0.227
	Grade 3	0	0	1	6.7	
Mucositis	Grade 2	12	80	10	66.7	0.682
	Grade 3	3	20	5	33.3	
Xerostomia	Grade 2	11	73.3	10	66.7	0.69
	Grade 4	0	0	0	0	

Table 4: RTOG Acute toxicities in Skin, Mucosa and Salivary gland

OVERALL TREATMENT TIME	IMRT		TOMOTHERAPY	
	No.	%	No.	%
<=42 days	2	13.3	0	0
43–49 days	1	6.7	3	20
50–56 days	9	60	6	40
>56 days	3	20	6	40
Total	15	100	15	100
Mean ± SD	51.67±7.27		53.73±5.05	
p	0.288			

Table 5. Overall treatment time. SD – standard deviation

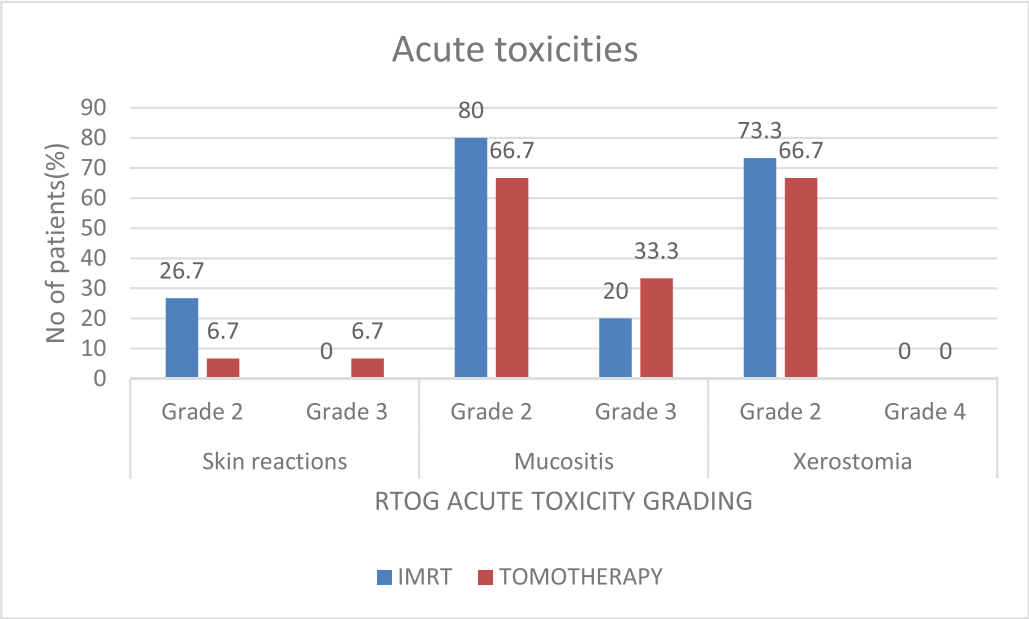


Figure 4. RTOG Acute toxicities in Skin, Mucosa and Salivary gland

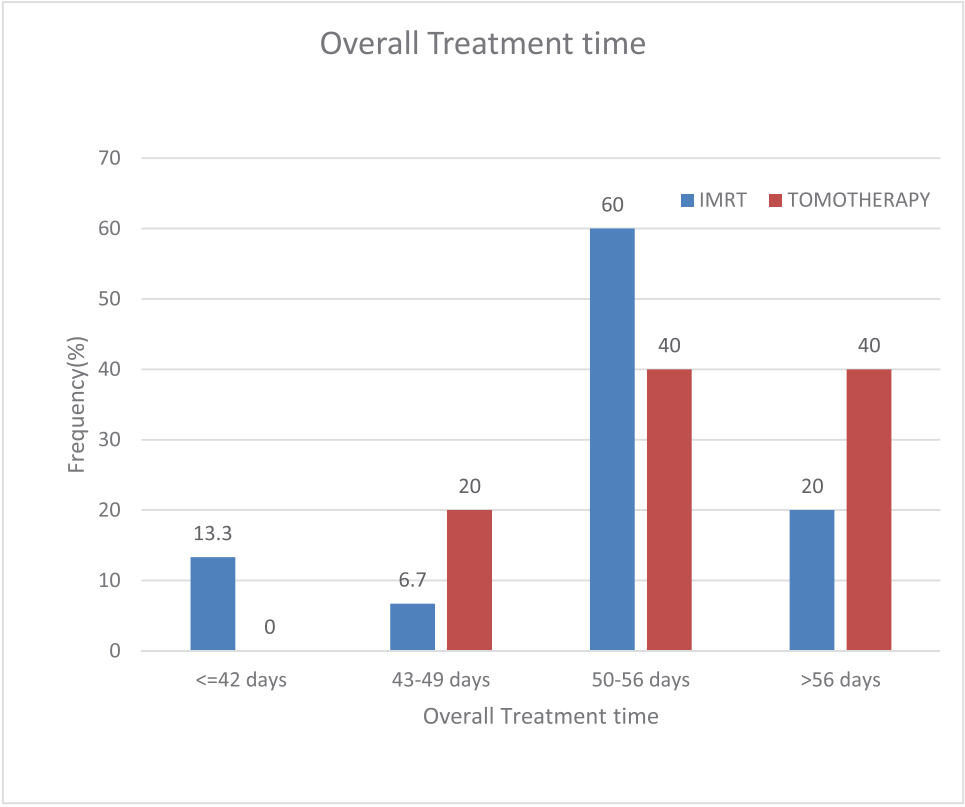


Figure 5. Overall treatment time

Arm was 25.87, 21.87 and 22.4 at day1 (QoI–1), day21 (QoI–21) and at completion of radiotherapy (QoI–End) respectively. And for tomotherapy arm, it was 25.87, 22.33 and 23.20 at day1 (QoI–1), day21 (QoI–21) and at completion of radiotherapy (QoI–End) respectively. There was no statistical difference in quality of life between two groups. (Refer table 6)

Discussion

Various studies have shown dosimetric benefit of Tomotherapy over IMRT.[8–10] Very few studies in head and neck malignancies, have investigated whether the dosimetric benefit of tomotherapy over conventional IMRT getting translated clinically in terms of toxicity reduction .

STRUCTURE	PARAMETER	IMRT	TOMOTHERAPY	Mean difference	p–value
		Mean ± SD	Mean ± SD		
Quality of life	Qol–1	23.73 ± 5.64	25.87 ± 2.13	2.14	0.148
	Qol–21	21.87 ± 3.98	22.33 ± 3.28	0.46	0.802
	Qol– End	22.40 ± 4.45	23.20 ± 4.52	0.8	0.632

Table 6. Quality of life of patients between two groups. SD – standard deviation; Quality of life at day1 (Qol–1), day21 (Qol–21) and at completion of radiotherapy (Qol–End)

As per the literature, studies have shown that there is no significant difference in acute toxicities between both the IMRT techniques, in fact few studies have the hypothesis that there is more integral dose in conformal techniques than conventional techniques.[11] In this context, we studied the dosimetries and acute toxicities of two different IMRT delivery techniques.

In our study, all patients were treated with concurrent chemo radiotherapy, to a dose of 60– 70 Gray in 30–35 fractions. Dosimetric part of the study is already reported in another article.[12] The dosimetric analysis showed that there was statistically significant reduction in spinal cord maximum dose and point doses in tomotherapy plans compared to IMRT plans (43.07 Gy in IMRT and 34.41 Gy in tomotherapy). The decrease in spinal cord dose can increase the tolerance reserve which can be useful in dose escalation or re–irradiation if required. There was significant improvement in V95% in tomotherapy arm compared to IMRT arm, indicating the significantly superior coverage of target volumes in helical tomotherapy plans compared to IMRT plans. V110% (hot spots) inside the target was very minimal in tomotherapy arm compared to IMRT arm. Conformity index, homogeneity index between two arms were comparable. There was slight decrease in contra lateral parotid doses which is not statistically significant.[12] However literature shows that a drop as low as 1 Gy mean dose can cause reduction in incidence of xerostomia.[13] There by the study concluded that there are dosimetric benefits seen in Tomotherapy group. We investigated whether these dosimetric benefits translated into clinical advantage during radiotherapy in terms of reduced acute toxicities, better quality of life and decreased overall treatment time.

Kruser et al reported the occurrence of acute mucositis and hematological toxicities in head and neck cancer patients treated with 3DCRT, IMRT and helical Tomotherapy. Their analysis showed no significant difference in acute hematological and mucosal toxicities between 3 groups. [14] Likewise in our study also, we didn't see any significant difference in acute mucositis and hematological toxicities. The acute skin reactions and xerostomia were also comparable between 2 groups in present study.

The radiation related toxicities during RT impair the quality of life of patients causing breaks in the treatment course and prolonging the overall treatment time. To get good tumor control, it is necessary to complete the treatment in stipulated time. Jose A. Gonzalez et al in their review regarding the effect of overall treatment time in Head and neck cancer patients, showed that delay in completion of RT may result in average loss of locoregional control ranging from as low as 1.2% per day to as high as 12–14% per week.[15] In our study, mean overall time for IMRT arm is 51.67 days and for Helical tomotherapy is 53.73days. The difference between 2 groups was not statistically significant (p– 0.288). In our study, we assessed quality of life of patients using FACT questionnaire in their own language at day1, day21, and at the end of radiotherapy. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient. QOL score was 23.73, 21.87 and 22.40 for IMRT and 25.87, 22.33 and 23.20 for Helical tomotherapy on Day1, Day21 and completion of radiotherapy respectively. There was no statistical difference between 2 groups.

Conclusion

With our present study and dosimetric comparison studies done previously, it is noted that Helical Tomotherapy gives better homogeneity and superior dose distribution with regard to both organ at risk and target volume. But it did not reflect in reducing acute toxicities. Dosimetric advantages of Helical Tomotherapy are important in reducing long term complications. Larger sample size and longer follow up will disclose more reliable clinical benefits of Tomotherapy techniques over conventional IMRT techniques.

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