A Prospective Observational Study to Compare the Effect of Adaptive Radiation Therapy in Head and Neck Cancer Patients Treated with Helical Tomotherapy – Bangalore, Karnataka

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ABSTRACT

BACKGROUND

Establishing the usefulness of adaptive radiotherapy in our setting with limited data might help to ensure better conformity and reduce treatment related morbidity. Hence we conducted this study to elicit the benefit of adaptive radiotherapy with helical tomotherapy.

METHODS

This is a prospective study conducted among 25 head and neck cancer patients undergoing radiotherapy with helical tomotherapy. All patients underwent initial radiation therapy treatment planning simulation positron emission tomography computed tomography (PET CT/ CT scan) [CT-1], followed by repeat PET CT/ CT scan at 4th - 5th week of radiotherapy [CT-2]. Planning for full intended dose [66 Gy - 70 Gy] was done on both the scans, keeping the radiation therapy planning parameters same. Changes in the volume of the clinical target volumes (CTV), changes in the volume and dose to spinal cord, bilateral parotids, and mandible were compared. A *p* - value of < 0.05 was considered for statistical significance.

RESULTS

A significant reduction in the volumes of tumour - CTV-1 [CT-1 v/s CT-2: 166.82 cc v/s. 150.63 cc] and of lymph nodal region - CTV-2 [CT-1 v/s CT-2: 260.29 cc v/s 228.00 cc], contra lateral parotid gland [CT-1 v/s CT-2: 33.00 cc v/s 18.72 cc] were observed (P < 0.05). The mean doses received by contra lateral parotid gland [CT-1 v/s. CT-2: 23.14 Gy v/s 21.26 Gy] were significantly lesser in the CT-2 scans (P < 0.05). The mean maximum doses were also significantly lesser to the mandible and spinal cord i.e., CT-1 v/s. CT-2: 68.528 Gy v/s 67.39 Gy and 39.45 Gy v/s. 37.33 Gy respectively (P < 0.05). A significant reduction in standardised uptake value (SUV), values of the primary tumour and involved lymph nodes was observed between CT-1 and CT-2.

CONCLUSIONS

During 4th to 5th week of radiation therapy, significant reductions in the CTVs and in dose to OARs were noted. Thus, we recommend at least one re-simulation scan and re-planning during radiation therapy, irrespective of the type of technique of radiation therapy.

KEYWORDS

Adaptive Radiation Therapy, IMRT, Tomotherapy

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BACKGROUND

The evolution of radiation therapy has been too sophisticated with the introduction of conformal techniques like intensity modulated radiation therapy (IMRT), tomotherapy, etc, has enabled the delivery of radiation with high target conformity and sharp dose gradient. The advantages of these high conformity techniques compared to conventional techniques have been well established in the treatment of head and neck cancers and the usage has also increased in the last decade.[1,2]

Helical tomotherapy, a hybrid between a linear accelerator and a helical CT scanner is one such high conformity techniques that deliver intensity-modulated radiation therapy in a helical fashion. The imaging capacity conferred by the CT component in it allows targeted regions to be visualized prior to, during, and immediately after each treatment in the current technique.[3]

The delivery of such high precision radiotherapy depends on the reproducibility of the initial planning considerations like patient external contour and skin separation, internal target motion, tumour size and patient position during the entire course of radiation therapy. Any changes in these may result in the change of dose delivered to tumour, nodal areas at risk, and surrounding normal structures.[4,5]

Similarly, during the long-fractionated course of 6 - 7 weeks of radiation therapy, there might be regression of primary tumour and nodal disease, reduction in the post-operative soft tissue oedema, alterations in normal glands and mucosa and changes in body habitus due to weight loss.[6,7,8]

The integration of F18-FDG PET/CT images, after administration of tracer, simulation scan done by following a standardized radiation therapy simulation PET CT scan protocol acquired on a dual scanner in the radiotherapy treatment position, along with careful optimization of images within the radiation treatment planning system helps in better delineation of the tumour. On conducting the same with CT alone, there is a potential to avoid a geographic miss of tumour.[9,10]

Though the theoretical gain has been achieved from recalculating the dose distribution throughout the course of radiotherapy using adaptive radiotherapy (ART) and has been demonstrated earlier, an appropriate time to assess the response during the radiation therapy remains unclear and few literatures report minimum of two weeks to be favourable.[11,12]

To the authors knowledge till date, there is limited data on adaptive radiation therapy for squamous cell carcinoma of the head and neck (SCCHN) treated with helical tomotherapy in Indian setting and hence this study was conducted.

In addition to this, comparison of SUV values adds more strength to this study. Hence with the objectives to compare the volumetric, dosimetric changes and SUV values with adaptive radiotherapy this study was taken up.

METHODS

This is a comparative cross sectional study which was prospectively conducted between August 2016 and July 2018 in the department of radiation oncology at a premier oncology institute, Bangalore. Those with histologically proven stage II, III, IVa, or IVb squamous cell carcinoma of the head and neck region aged above 18 years with Karnofsky performance status 0 to 2 planned for radical radiation therapy,[13,14] those who underwent surgery for primary tumour and were eligible for adjuvant radiation therapy and the patients who received induction chemotherapy before radiation treatment were included in the study. Patients with diagnosis of cancer except for those who were appropriately treated for localized epithelial skin cancer, or prior radiation therapy to the head and neck region were excluded. Ethical clearance has been obtained from the Institutional Ethical Committee and informed consent was taken from the patients.

Procedure of Simulation

Using a neck support and a customized four-point thermoplastic mask extending down to the shoulders along with shoulder retractors, patients were immobilized. 18F-FDG-PET/CT scans were acquired on Siemens Biograph Vision 600 in three-dimensional mode using an axial field of view of 15.7 cm.

Radiation planning CT scanfrom vertex to diaphragm with contrast were acquired using a matrix of 512 X 512 pixels with 2.5mm slice thickness and reconstruction interval of 2.5mm and standard reconstruction kernel. The PETCT scan was initiated 1 hour post-intravenous injection of 18F-FDG. Following CT acquisition, a limited body PET image was acquired with maximum of 3 beds, 2 min acquisition time for each bed position, with 15% overlap. Patients planned for radical Radiation therapy underwent limited PET CT simulation scans and those planned for post-operative adjuvant radiation therapy underwent contrast enhanced CT simulation scans.

Procedure of Contouring and Planning

The organs at risk and the target regions were delineated in Eclipse planning system (Varian Medical Systems, Palo Alto, CA). After the delineation, the digital imaging and communications in medicine (DICOM) images along with the RT structure set were pushed to VoLO- Accurayprecision® Treatment planning system by Accuray for planning and optimization.

On the basis of previous literatures, we adopted 40 % of the SUV values for delineating the gross tumour volumes.[10] Spinal cord, bilateral parotids, mandible, the gross tumour volume of primary disease and involved nodes were contoured and clinical treatment volume 1 was accordingly created encompassing both the gross and nodal tumour. In CTV-2, immediately adjacent lymph node levels and soft tissues were considered and in CTV-3 prophylactic cervical nodal regions were covered.

All the CTVs were expanded uniformly with 3 mm margin to create respective planning target volume (PTV) 1, 2 and 3. PTV 1 was prescribed with 70 Gy in 35 fractions, PTV 2 with 60 Gy in 30 fractions and PTV 3 with 56 Gy in 28 fractions.

In patients receiving post-operative adjuvant radiation therapy, the CTV 1 encompassed tumour bed, adjacent soft tissues and involved nodal regions. In CTV 2, ipsilateral lymph node levels were included. In node positive neck, contra lateral neck nodes were included in CTV 3. All the CTVs were expanded uniformly with 3 mm margin to create respective PTVs 1, 2 and 3.60 Gy in 30 fractions to the PTV 1, 54 Gy in 27 fractions to PTV 2 and PTV 3 were prescribed.

A constraint of 26 Gy mean dose, 46 Gy and 72 Gy maximum doses were set to parotid gland, spinal cord and mandible respectively. Patients who were planned for concurrent chemotherapy received Cisplatin 40 mg/m2 or Carboplatin AUC-2, weekly injections for 5 to 6 weeks.

Procedure of Adaptive Radiation Therapy

The initial planning was done on PET CT/ CT scan (CT-1) before starting the radiation therapy. At 4 to 5 weeks of radiation therapy, as the changes in skin contour and skin separation is maximum due to weight loss, re-moulding of the thermoplastic cast was done followed by re-simulation radiation planning PET CT/ CT scan (CT-2) were done.[15] On CT-2 scan also spinal cord, bilateral parotids, mandible, the gross tumour volume of primary disease and involved nodes were contoured and clinical treatment volume 1 was accordingly created encompassing both the gross and nodal tumour. CTV-2 and CTV-3 were created following the same norms that of CT-1 scan. All the CTVs were expanded uniformly with 3 mm margin to create respective planning target volume 1, 2 and 3.

Plans for full intended dose were done by keeping the planning parameters same on both CT-1 and CT-2. Once re-simulation was done, all the patients were treated with new radiation plan done on CT-2 till the completion of radiation therapy.

All the patients were contoured by single radiation oncologist and planned by single radiation physicist to avoid difference in the delineation of the target volumes, organ at risks (OARs), and the planning procedure. To avoid observational bias, the same oncologist and physicist evaluated the radiation plans. No any formal sample size calculation was done and all the patients in the defined time period were assessed for eligibility and taken into the study.

The changes in the volumes of CTV of the gross tumour (both primary and involved nodes), lymph nodal regions, volumes of the contra lateral parotid glands and the distance of the contra lateral parotid gland surface to the patient skin at the tip of the styloid process level, maximum dose for the mandible and spinal cord, mean dose for the contra lateral parotid gland were noted in both CT-1 and CT-2. For the study purpose we combined both immediate adjacent lymph node levels CTV-2 and prophylactic cervical nodal regions CTV 3 as CTV -2

The outcomes were measured in terms of volumetric changes, dosimetric changes and SUV values of the lesions and lymph nodes. The volumetric changes were assessed with respect to clinical target volume and parotid volume evaluations and the dosimetric changes were assessed with respect to mean and maximum doses delivered to organs at risk.

Statistical Analysis

All the data were entered into Microsoft Excel sheet. The continuous variables were expressed in means or medians based on the parametric or non-parametric distribution of the data. The categorical variables were expressed in proportions or percentages. The difference in the medians of volumetric changes was compared using Wilcoxon signed-rank test. Paired t - test was used to compare the difference in means of dosimetric changes. Friedman test was used to compare the median SUV values of the lesions and lymph nodes.

The data was analysed using Statistical Package for Social Sciences (SPSS) version 18.0. A p - value of < 0.05 was considered statistically significant.

RESULTS

The median age of the patients was 57 years, and it ranged from minimum of 18 years to a maximum of 69 years. Majority i.e., 96.0 % of the study subjects were males. Out of 25 patients accrued, 16 (64.0 %) of them were planned for radical radiation therapy with or without concurrent chemotherapy and remaining 9 (36.0 %) of them were for post op-adjuvant radiation therapy. Majority i.e., 40.0 % of the patients had oral cavity cancer among which 80.0 % underwent surgery and planned for adjuvant RT. Nearly 50.0 % of the patients belonged to stage-IV cancers irrespective of the primary site. [Table-1]

The difference in the medians of the clinical tumour volumes (CTV 1 and CTV 2) of the contra lateral parotid, the distance of the parotid gland to the surface of the skin were significantly lesser in CT-2 (120.8 cc, 251 cc, 18 cc and 34 mm) compared to CT-1 (124 cc, 280 cc, 24.9 cc and 51 mm) respectively, hence indicating the significant reduction in the volumes of the primary tumour and lymph nodal regions, shrinkage of contra lateral parotid glands and also reduction in the distance from skin to parotid gland surface ($P < 0.05$). [Table-2]

	Baseline Characteristics	n (%)
Age group in years (n = 25)	≤ 30	2 (8 %)
	31 - 50	8 (32 %)
	51 - 60	7 (28 %)
	> 60	8 (32 %)
Gender	Male	24 (96 %)
	Female	1 (4 %)
Sub-sites	Oral cavity	10 (40.0)
	Nasopharynx	5 (20.0)
	Oropharynx	4 (16.0)
	Hypopharynx	4 (16.0)
	Larynx	1 (4.0)
	Para-nasal sinuses	1 (4.0)
Stages	Stage- II	4 (16.0)
	Stage-III	9 (36.0)
	Stage-IV	12 (48.0)

Table 1. Baseline Characteristics of the Cases

Variables	CT-1 Medians (Range)	CT-2 Medians (Range)	Z-Value (*p* -Value)
CTV-1 (cc)	124.1 (8 – 502)	120.8 (8 - 417)	-4.20 (< 0.001)*
CTV-2 (cc)	280 (2.1 - 485)	251 (1.4 - 424)	-4.19 (< 0.001)*
C/L Parotid volume (cc)	24.9 (15 – 38)	18 (11 – 31)	-4.37 (< 0.001)*
Skin to parotid distance (mm)	51 (24 - 85)	34 (20 - 64)	-4.37 (< 0.001)*

Table 2. Volumetric Evaluation of Target Volume and Parotids

* indicates statistically significant difference at P < 0.05

The difference in the median SUV values of the primary tumour and the involved lymph nodes also significantly reduced in CT-2 (5.5 and 4) compared to CT-1 (16.8 and 7) respectively (P < 0.05). [Table-3]

Gross Tumours	PET CT - Median SUV Values CT-1	CT-2	X^2- Value (*p* -Value)
Primary tumour (n = 16)	16.8	5.5	22.66 (< 0.001)*
Involved lymph nodes♀ (n = 13)	7.0	4.0	22.22 (< 0.001)*

Table 3. Comparison of SUV Values of the Primary Tumour and Lymph Nodes

♀-3 cases were excluded as they did not have any lymph nodal SUV uptake,
*- indicates statistically significant difference at P < 0.05

OARs		Doses in Mean ± SD CT-1	CT-2	t-Value(*p* -Value)
Mandible	Mean Dose (Gy)	53.7±7.3	52.2±7.1	4.77(<0.001)*
	Maximum Dose (Gy)	68.5±3.3	67.4±3.6	12.09(<0.001)*
C/L Parotid	Mean Dose (Gy)	23.2±5.7	21.3±5.8	8.12(<0.001)*
	Maximum Dose (Gy)	59.2±4.5	57.6±4.8	5.16(<0.001)*
Spinal Cord	Maximum Dose (Gy)	39.5±4.7	37.3±5.3	6.81(<0.001)*

Table 4. Comparison of Means of Mean and Maximum doses to OARs

* indicates statistically significant difference at P < 0.05

The means of the mean doses to mandible and contra lateral parotid decreased significantly in CT-2 (52.2 Gy and 21.3 Gy) compared to CT-1 (53.7 Gy and 23.2 Gy) (P < 0.05). Similarly, even the difference in the means of maximum doses to the contra lateral parotid gland and spinal cord also was statistically significant wherein, the doses to parotid gland and spinal cord in CT-2 were 57.6 Gy and 37.3 Gy and CT-1 were 59.2 Gy and 39.5 Gy respectively (P < 0.05). [Table-4]

DISCUSSION

Marked anatomical changes have been observed during treatment either due to shrinkage of primary tumour and nodal volumes or weight loss.[16,17] Weight loss during RT treatment as demonstrated by Bhandari et al. is 10 % after the 3rd week of RT.[18] Helical tomotherapy a technique of IMRT, increases therapeutic ratio by increasing dose to target and reducing doses to OARs. Due to its high conformity, steep dose gradients exist around tumour volume (TV). A small change in anatomical/positional variations results in under dosage to TV and higher doses to OARs. In our study, we have quantified the changes that happen during the course of radiation therapy treatment and the dosimetric impact of re-planning.

Reduction in the CTV of primary tumour in our study was in line with the findings by Burela et al. (13.1 %) and Cheng et al. (12.0 %) wherein, our study noted 11.0 % reduction at 4 to 5 weeks of radiation therapy.[17,19] Bhinde et al. showed 5.46 % and 7.9% reduction in the CTV of the primary tumour during 4th and 5th week respectively which was noted to be slightly lower when compared to our study which might be due to the inclusion of the postoperative patients in our study where the volume of the reconstructed flap and post-operative oedema decreased during the course of radiation therapy.[20] Schwartz et al. have also mentioned regarding reduction in the nodal masses and Cheng et al. demonstrated around 30 % reduction in the CTV of the lymph nodes, which in contrast to our study was only 11 % because in the present study we have considered even the post-operative patient.[19,21]

Burela et al. and Dewan et al. found nearly 25.0 % and 31 % reduction in the mean contra lateral parotid volume which is in concordance with the present study wherein, it was 25 % reduction in the contra lateral parotid gland volume.[17,22] The reduction in the mean doses to parotid was 2 Gy as noted in our study and is in parallel to findings as reported by Castelli et al. in their systematic review wherein the reduction of around 0.6 - 6 Gy was noted. However, the wide range of mean reductions as reported by Castelli et al. might be due to different re-planning schedules ranging from 1 to 16 weeks. Burela et al. also demonstrated around 4 Gy reductions in the mean dose received by contra lateral parotid gland.[17] The current study records a statistically significant reduction of 33 % in the distance of skin to lateral edge of the contra lateral parotid gland at the level tip of styloid process, which is due to weight loss leading shrinkage in the subcutaneous fat, leading to decrease in the distance between skin and parotid gland. The maximum dose to mandible reduced by around 1.1 Gy in CT-2 compared to CT-1, which was similarly shown by Simone et al. where they noted 2 Gy reductions.[23] The maximum dose to spinal cord reduced by 2 Gy in CT-2 compared to CT-1 similar to results reported by Castelli et al. wherein it ranged from 0.1 to 4 Gy.[24]

Significant reduction in SUV values of primary lesions and involved lymph nodes have been observed in our study which is due to radiation therapy per se and in correspondence to it, Bhatnagar et al. also noted reduction in the metabolic activity of the tumour.[25]

In order to generalize the results, the study needs to be conducted in a larger setting among larger samples. Doses to the submandibular glands, oral cavity, larynx and pharynx have not been elicited in the present study. Sensitivity and specificity of different durations of re-planning sessions could not be elicited as the weekly re-plans could not be considered due to logistic constraints.

CONCLUSIONS

The volume reduction during the course of treatment were significant which ranged from 0 % - 78.0 % for primary tumour volumes, 0 % - 90.0 % for nodal volumes and 4.0 % - 91.0 % for parotid volume (P < 0.05). The significant reduction in the mean doses to mandible ranging from 2 Gy

to 12 Gy, contra lateral parotid from 1 Gy to 20 Gy were recorded ($P < 0.05$).

Similarly maximum doses also significantly reduced for mandible ranging from 1 Gy to 3 Gy, contra lateral parotid from 0 Gy to 9 Gy and spinal cord from 2 Gy to 12 Gy ($P < 0.05$). SUV uptakes of lesions and lymph nodes also significantly reduced over the treatment course ($P < 0.05$). Hence, at least one re-simulation scans at around 4th to 5th week of radiation therapy followed by re-planning and delivery of the new radiation treatment plan accordingly are recommended.

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