Impact of Anatomical Variations during Intensity Modulated Radiotherapy on Target Volumes, Organs at Risk, and Dose Volume Histograms in Locally Advanced Head and Neck Cancers – A Prospective Interventional Study from Hyderabad, Telangana

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ABSTRACT

BACKGROUND

Intensity modulated radiation therapy (IMRT) has become the standard treatment in head & neck cancer (HNC). Anatomic changes during IMRT can have impact on dose coverage and organs at risk (OAR) doses. These changes can be compensated by modifying the plan during treatment. The purpose of this study is to evaluate the impact of anatomical variations during IMRT on target volumes, OAR and dose volume histogram (DVH) in locally advanced HNC patients.

METHODS

Twenty-four HNC patients undergoing definitive chemoradiotherapy were planned with initial plan. Repeated computerised tomography (CT) scans were performed at 2nd week (repeat CT1) and 4th week (repeat CT2). Previous plan was transferred to new CT for dosimetric analysis. Patient received remaining fractions with adaptive plan if needed based on triggers (1. more than 5 % deviation in OAR doses 2. If PTV dose did not conform to ICRU83). Plan 1 was generated by re-planning on repeat CT and plan 2 was by superimposition of previous plan. DVH of both plans were compared for volumetric and dosimetric parameters in patients who required re-planning.

RESULTS

Fifty-eight percent of patients required adaptive plan. Seventy-one percent required re-plan at the end of 4th week and 28.5 % at 2nd week. Parotid glands and gross tumour volume (GTV) node reduction were significant in patients who required re-plan compared to patients who did not require re-plan. Patients with significant GTV node reduction experienced grade III/IV mucositis. Patients with significant GTV node and parotid glands reduction experienced grade III/IV dermatitis.

CONCLUSIONS

More than half of HNC patients required re-planning. Most of them required re-planning at 4th week. GTV node and parotid glands reduction can predict the requirement of re-plan, risk of grade III/IV dermatitis. GTV node reduction can predict the risk of grade III/IV mucositis.

KEYWORDS

IMRT, Adaptive Radiotherapy, Anatomical Variations in Head and Neck Cancer, Implementation of Adaptive Plan

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BACKGROUND

IMRT has become the standard modality of treatment in head and neck cancer because of its parotid sparing capability and better dose conformity and OAR sparing.[1] In the past decade, significant progress in image-guided radiotherapy (RT) has revealed that many patients receiving fractionated radiotherapy for HNC have marked anatomic changes during their course of treatment, including shrinking of the primary tumour or nodal masses (GTVs), resolving postoperative changes/oedema and weight loss during course of IMRT for HNC treatment.[2] These volumetric changes during radiotherapy can have impact on target volume dose coverage and delivered doses to the tumour and normal tissues as planned from the initial pre-treatment plan.

These anatomical alterations have a critical impact for IMRT plan than for conventional RT due to the sharp dose gradient between the edges of target volumes and critical OARs. Thus, these changes could potentially lead to overdosing of normal tissues and under dosing or marginal geographical misses of target volumes during course of treatment based on a single initial planning data set. The alterations occurring during the course of RT can be compensated by adaptively modifying the treatment plan during treatment course. This novel approach is known as adaptive radiotherapy (ART).[3,4] In case of head and neck, most anatomic changes take place gradually over the first few weeks of treatment. Thus, there is no need for real-time intervention unless an acute, unforeseen event such as rapid disease progression occurs. Therefore, offline ART appears to be a more practical approach for HNC in majority cases.[3]

Based on previous studies, GTVs significantly decreased throughout the course of RT, and it translated into parallel changes of the corresponding clinical target volumes (CTVs) and planning target volumes (PTVs).[5,6] Hence, the purpose of this study is to evaluate the impact of anatomical variations during radiotherapy on target volumes, OARs and DVH in patients with locally advanced HNC undergoing chemoradiotherapy with IMRT.

Aim

To evaluate the impact of anatomical variations during intensity modulated radiotherapy on target volumes, organs at risk and dose volume histograms in locally advanced head and neck cancers.

Objectives

1. To determine the percentage of patients who require implementation of adaptive plan due to either weight loss or tumour shrinkage.
2. To determine the timing of re-planning.
3. To determine the factors which can predict the requirement of implementation of adaptive plan during radiotherapy.
4. To determine the changes in acute toxicities (mucositis grade III/IV & dermatitis grade III/IV) with changes in patient weight, tumour shrinkage and OAR shrinkage.

METHODS

This is a prospective interventional study / single arm open label feasibility study conducted from December 2015 to December 2017 in Apollo Hospital, Jubilee Hills, Hyderabad, Telangana. All histopathologically proven squamous cell carcinoma of head & neck cancer patients (carcinoma of mouth, nasal cavity, nasopharynx, oropharynx, hypopharynx and larynx, paranasal sinuses) receiving chemo radiotherapy in definitive setting were included.

Inclusion Criteria

1. Patients older than 18 years of age.
2. Radiologically bi-dimensionally measurable lesions.
3. Histologically proven locally advanced head and neck squamous cell carcinoma (Stage III and IV).
4. Eastern cooperative oncology group (ECOG) performance status 0 - 2

Exclusion Criteria

1. Prior radiation therapy to the head and neck region.
2. Operated cases.
3. Distant metastases like bone, visceral and distant nodal involvement.
4. Patient not giving consent for study.
5. Patients not fit for chemotherapy.

Radiotherapy Planning

Study protocol was reviewed by the institutional ethics committee and clearance for the study was given. Twenty-four patients with advanced HNC (squamous cell carcinoma) treated with definitive IMRT and concurrent chemotherapy were prospectively analysed. Patients eligible for the study were counselled in detail and after taking informed consent, they have been started on chemo radiation therapy. Patients had pre-treatment CT simulation in our department and were immobilized using custom-fitted thermoplastic head-and-shoulder mask. Contrast-enhanced CT scan was performed with 3-mm interval slices, and data was transferred to eclipse planning system version 13.3. Similar instructions were given to patients during the course of treatment to reproduce immobilization. Initial target volumes and normal structures were contoured on each slice of CT scan as per delineation guidelines for primary tumour by Eisbruch et al.[7] Neck nodes were contoured as per DAHANCA consensus 2014.[8] Plan acceptance based on ICRU 83 guidelines.[9] Treatment was delivered with IMRT and SIB technique on Novalis Tx Linear Accelerator with daily onboard image guidance. Patient was on IMRT with initial plan for 2 weeks (1st and 2nd weeks).

Adaptive Radiotherapy

Repeat CT scans were performed for each patient at the end of 2nd week and at the end of 4th week of radiation therapy. New thermoplastic mask was made in case of ill-fitting mask.

Target volumes and normal structures were recontoured on each slice of repeat CT scans for remaining fractions. Previous plan was transferred to new CT and dosimetric coverage was analysed. Two plans were generated on each repeat scan for each patient. One plan (Plan 1) which was generated by planning on repeat CT scan and another plan (Plan 2) in which previous IMRT plan (including monitoring units) was applied on repeat scan with carefully matched isocenter and bony landmarks. DVH of both plans on each repeat CT scan were compared for volumetric and dosimetric parameters.

Triggers for Implementation of Adaptive Plan

I. Adaptive plan was implemented if there was more than 5 % deviation in doses to OARs.
II. If PTV dose did not conform to International commission on radiation units and measurement (ICRU) 83.[9]

Patient was continued on radiotherapy for remaining fractions with adaptive plan if needed based on triggers for implementation of adaptive plan.

Example 1

Image 1 is showing a case of carcinoma supraglottis, stage IV A in which repeat scan showed gross reduction in GTV primary and GTV node. Superimposed plan which was produced by superimposition of initial plan on repeat CT showed improper dose paint coverage of PTV and DVH showed more than 5% deviation of OAR doses. This patient was re-planned and treated with adaptive plan.

Example 2

Image 2 is showing a case of carcinoma of tonsil, stage IVA in which repeat scan did not show gross reduction in GTV primary and GTV node. Superimposed plan which showed proper dose paint coverage of PTV and DVH did not show more than 5% deviation of OAR doses. This patient did not require implementation of adaptive plan.

Dose Prescription

- All high risk PTV received 66 Gy in 30 fractions.
- All intermediate risk PTV received 60 Gy in 30 fractions.
- All low risk PTV received 54 Gy in 27 fractions.
- Treatment was delivered once daily, 5 fractions per week.

Chemotherapy Details

Concurrent chemotherapy was administered with cisplatin 40 mg/m2 every weekly. Chemotherapy for the week is deferred or delayed if serum creatinine > 2 mg/dl or absolute neutrophil count < 1500 cumm or total platelet count < 1,00,000/cumm.

Dosimetric Analysis

Doses to OARs (spinal cord D max, brain stem D max, parotid glands D mean) and target volume coverage of adaptive plan on repeat CT (plan 1) and superimposed plan (plan 2) were recorded. The dosimetric effects were quantified by comparing DVH of plan 1 and plan 2.

Clinical Outcomes

All patients were evaluated for weight loss during treatment. Complete blood picture was repeated to evaluate the chemotherapy toxicity. Analysis of toxicities was repeated every week during treatment and at the end of the treatment. Total number of cycles of chemotherapy received and treatment breaks were documented. All toxicities were evaluated using the RTOG acute radiation morbidity scoring. Acute effects of dermatitis and mucositis were recorded.

Statistical Analysis

Appropriate statistical tests were used including independent student's t test and Pearson's correlation coefficient. Independent students t test was used to determine the changes in acute toxicities (mucositis grade III/IV & dermatitis grade III/IV) with changes in patient weight, tumour shrinkage and OAR shrinkage. Pearson's correlation coefficient was used to correlate the percentage of changes in doses to PTVs and OARs as a function of percentage of change in patient weight and anatomical variations like tumour shrinkage and OAR shrinkage during radiotherapy. P value of < 0.05 was considered as significant for this study.

RESULTS

Patient Characteristics

Table 1 highlights the patient and tumour characteristics of the 24 patients who were analyzed in this study. Of note, the median age was 53 years (range: 21 to 80). Most common subsite of head and neck cancer is nasopharynx (29 %), followed by hypopharynx (21 %), tonsil (16 %), supra glottis (16 %), paranasal sinuses (8 %), tongue (8 %). Most common stage is stage IV A (62 %) followed by stage III (25 %), stage IV B (12 %). Most common histology grading was moderately differentiated carcinomas: (50 %), poorly differentiated carcinoma: 35 %, well differentiated carcinomas: 15 %.

Requirement of Implementation of Adaptive Plan

14 patients (58 % of patients) required adaptive planning and 10 patients (41.67 % of patients) did not require adaptive planning.

Timing of Implementation of Adaptive Plan

10 patients (71.5 % of patients) required implementation of adaptive plan at the end of 4th week. 4 patients (28.5 % of

patients) required implementation of adaptive plan at the end of 2nd week.

	Characteristics	No. of Patients
Age	< 60	12
	➢ 60	12
Gender	Male	17
	Female	7
Sub site	Nasopharynx	7
	Para nasal sinus tumour	2
	Tongue	2
	Tonsil	4
	Hypopharynx	5
	Supraglottis	4
	Stage: III	6
	IVA	15
	IVB	3
Grading	Well differentiated	3
	Moderately differentiated	10
	Poorly differentiated	7

Table 1. Patient and Tumour Characteristics

Factor	Implementation of Adaptive Plan Required (Mean +/- SD)	Not Required (Mean +/- SD)	P Value
Percentage of weight reduction	9.56 ± 4.553	8.90 ± 4.974	0.738
percentage of reduction in GTV primary	27.86 ± 24.137	13.20 ± 10.163	0.085
percentage of reduction in GTV node	41.23 ± 22.133	18.75 ± 13.997	0.019*
Percentage of reduction in Parotid glands volume	25.91 ± 16.513	7.02 ± 8.865	0.003*

Table 2. Comparison between Group of Patients Who Required Implementation of Adaptive Plan and Group of Patients Who Did Not Require Implementation of Adaptive Plan

	Reduction in parotid Glands D mean	Reduction in Brain Stem D max	Reduction in Spinal Cord D max	Increase in PTV Primary D50	Increase in PTV Node D50
GTV node reduction (Pearson correlation coefficient)	- 0.657	0.568	0.223	- 0.145	0.249
GTV node reduction (P value)	0.015*	0.043	0.464	0.636	0.413

Table 3. Correlation between GTV Node Reduction and Changes in Doses in Group of Patients Who Required Implementation of Adaptive Plan

Factor	Grade III/IV Mucositis Yes (Mean +/- SD)	No (Mean +/- SD)	P Value
Percentage of weight reduction	10.39 ± 4.655	7.98 ± 4.475	0.212
Percentage of reduction in GTV primary	25.46 ± 24.768	17.36 ± 14.158	0.348
Percentage of reduction in GTV node	41.82 ± 24.551	22.60 ± 14.104	0.043*
Percentage of reduction in parotid glands volume	22.84 ± 17.730	12.36 ± 13.807	0.126

Table 4. Comparison between Group of Patients Who Experienced Grade III/IV Mucositis and Group of Patients Who Did Not Experience Grade III/IV Mucositis

Comparison between Group of Patients Who Required Implementation of Adaptive Plan and Group of Patients Who Did Not Require Implementation of Adaptive Plan

The factors that were significantly correlated with requirement of implementation of adaptive plan are reduction of GTV node and reduction in parotid gland volume with P value 0.019 and 0.003 respectively. Weight reduction and reduction of GTV primary did not show significant correlation with requirement of implementation of adaptive plan. Table 2

B/L Parotid Gland Doses in Patients Who Required Implementation of Adaptive Plan

There was significant reduction in B/L parotid glands D mean with implementation of adaptive plan in patients who required implementation of adaptive plan with P value 0.003. B/L parotid glands D mean without implementation of adaptive plan was 44.29 Gy (Std. Deviation: 9.148) and with implementation of adaptive plan was 42.19 Gy (Std. Deviation: 8.355).

Correlation between GTV Node Reduction and Changes in Doses in Group of Patients Who Required Implementation of Adaptive Plan

There was significant negative correlation between GTV node reduction and reduction in parotid glands D mean with adaptive planning during radiation therapy with P value 0.015. GTV node reduction did not show significant correlation with Brain stem D max, Spinal cord D max, PTV primary D50 and PTV node D 50. Table 3. Significant correlation between GTV node reduction and reduction in parotid glands D mean is not strong enough to fit into regression formula to find value of dependent variable with known value of independent variable.

Comparison between Groups of Patients Who Experienced Grade III/IV Mucositis and Group of Patients Who Did Not Experience Grade III/IV Mucositis

There was significant reduction in GTV node in group of patients who experienced grade III/IV mucositis compared to group of patients who did not experience grade III/IV mucositis with P value 0.043. There was no significant difference in reduction in GTV primary, parotid glands and patient weight between group of patients who experienced grade III/IV mucositis and group of patients who did not experience grade III/IV mucositis Table 4.

Comparison between Groups of Patients Who Experienced Grade III/IV Dermatitis and Group of Patients Who Did Not Experience Grade III/IV Dermatitis

There was significant reduction in GTV node and parotid glands volume in group of patients who experienced grade III/IV dermatitis compared to group of patients who did not experience grade III/IV dermatitis with P value 0.047 and 0.033 respectively. There was no significant difference in reduction in GTV primary and patient weight between group of patients who experienced grade III/IV dermatitis and group of patients who did not experience grade III/IV dermatitis. Table 5

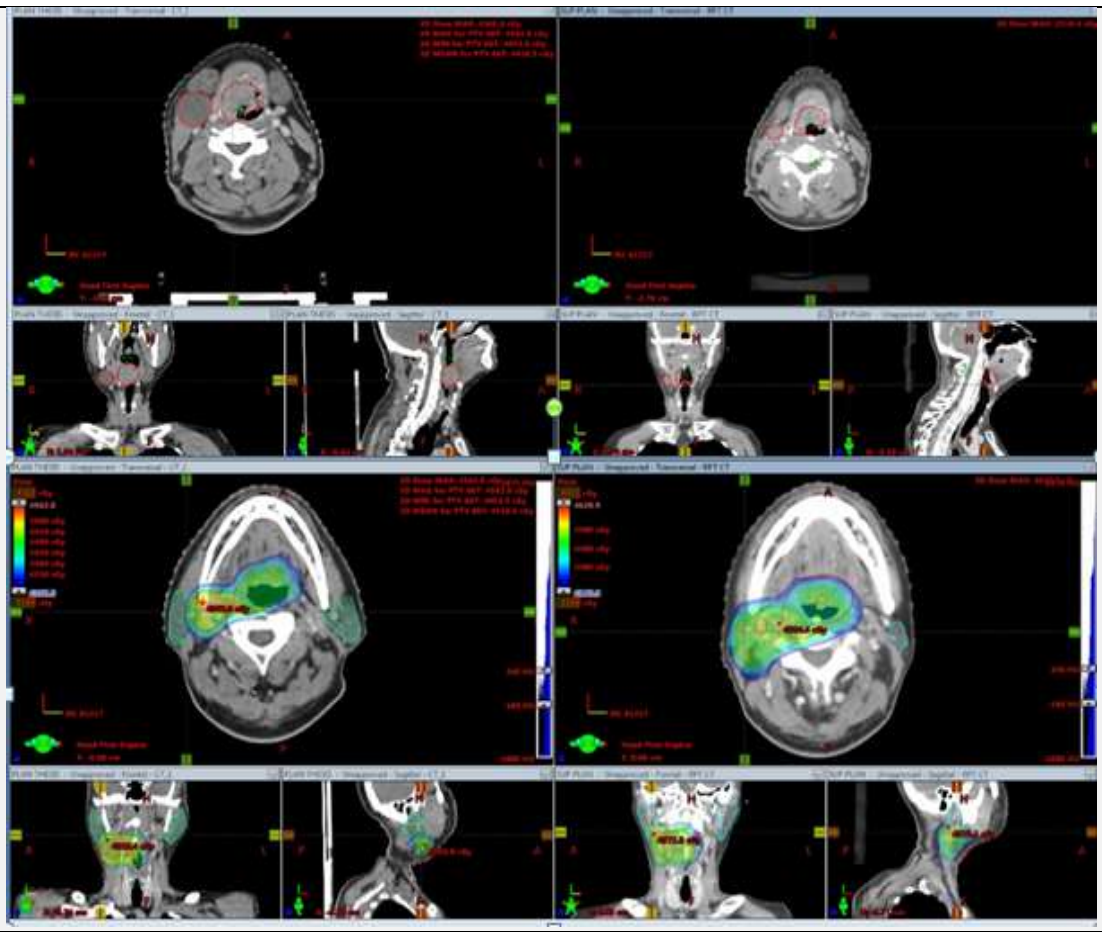

Image 1. Case of Carcinoma Supraglottis, Stage IV A in Which Repeat Scan Showed Gross Reduction in GTV Primary and GTV Node

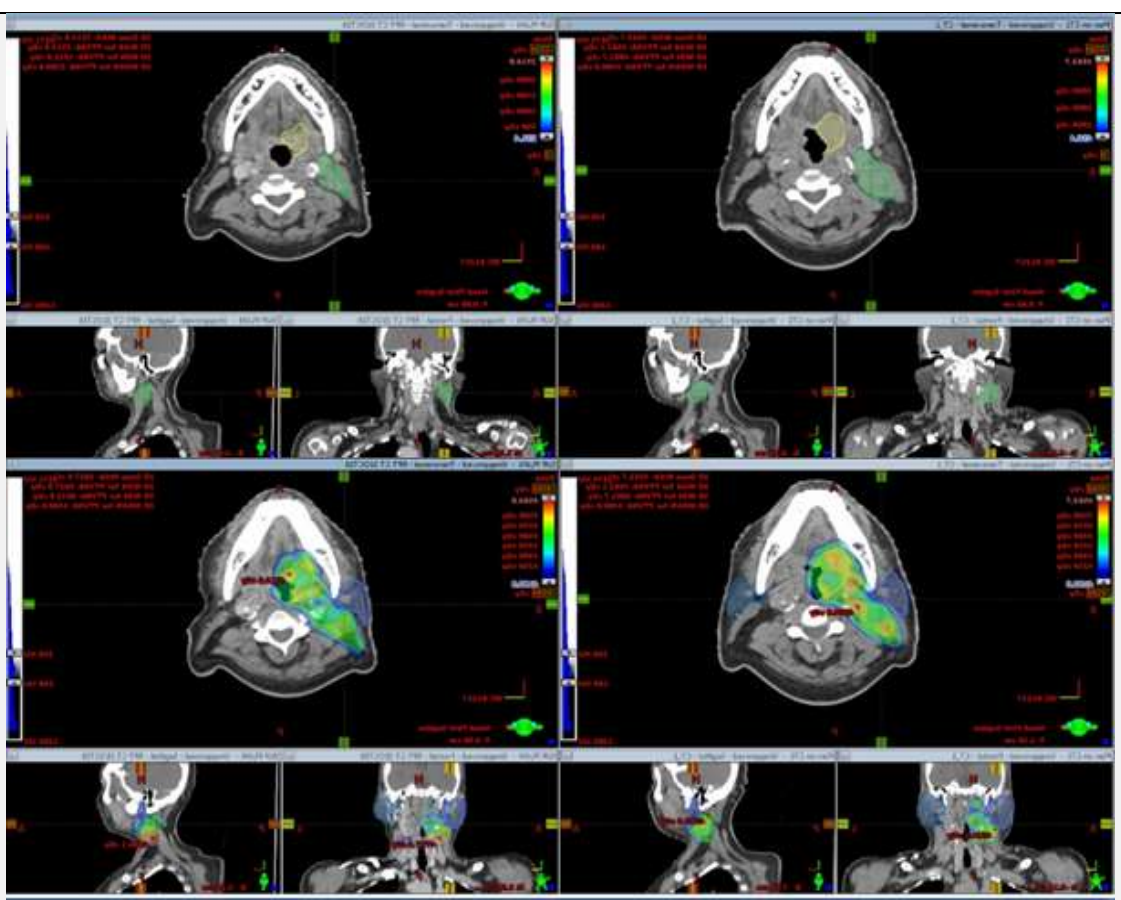

Image 2. A Case of Carcinoma Tonsil, Stage IVA in Which Repeat Scan Did Not Show Gross Reduction in GTV Primary and GTV Node

Factor	Grade III/IV Dermatitis Yes (Mean +/- SD)	No (Mean +/- SD)	P Value
Percentage of weight reduction	11.26 ± 4.841	8.10 ± 4.236	0.108
Percentage of reduction in GTV primary	23.44 ± 15.396	20.73 ± 23.633	0.762
Percentage of reduction in GTV node	43.56 ± 24.729	24.50 ± 16.495	0.047*
Percentage of reduction in parotid glands volume	27.19 ± 20.163	12.55 ± 11.574	0.033*

Table 5. Comparison between Group of Patients Who Experienced Grade III/IV Dermatitis and Group of Patients Who Did Not Experience Grade III/IV Dermatitis

DISCUSSION

Adaptive radiotherapy is conceptually an attractive approach to compensate for tumour and normal tissue variations during treatment but limited work exists currently to guide its clinical application in day to day practice. Little practical evidence exists regarding issues like the timing of rescan, the dose at which adaptive planning to be executed, the basis of patient selection for adaptive planning. Our study was designed to determine the percentage of patients who require implementation of changed plan due to either weight loss or tumour shrinkage.

In our study, 58% of patients required implementation of changed plan. In the past, studies have been done to find out the optimum timing of adaptive re-planning. Wu et al.[10] performed such a study where 11 patients underwent weekly helical CTs during routine IMRT. The authors reported that one adaptive re-planning during midcourse improved parotid mean dose sparing by 3 %, two re-planning by 5 %, and six re-planning by 6 %, assuming that adaptive re-planning transpires one week prior to actual treatment delivery. If six weekly re-plans were used immediately, parotid dose sparing improved by 8 %. In our study 71.5 % of patients required re-planning at the end of 2nd week. 28.5 % of patients required re-planning at the end of 4th week.

In literature few studies have reported volumetric changes during adaptive planning. In a study by Barker et al.[2] The median GTV decreased at a rate of 0.2 cc per day corresponding to 70 % reduction on last day of RT. In this study both primary tumour and involved nodes lost volume at approximately same rate of 1.6 % per day. In addition, the center of the mass of shrinking tumours changed position with time, indicating that GTV loss was frequently asymmetric.

In our study mean loss of GTV node is 41.2 % and 18.7% corresponding to 1.47 % and 0.66 % decrease per day in patients who required implementation of adaptive plan and in patients who did not require implementation of adaptive plan respectively. Mean loss of GTV primary is 27.8 % and 13.2 % corresponding to 0.99 % and 0.47 % decrease per day respectively. In the present study three patients did not have nodal disease (GTV node) where these patients were not considered for analysis of the volume loss as it is inappropriate. Using independent t test, both the groups of patients were compared in terms of reduction in GTV node. There was significant difference in reduction in GTV node with P value of 0.019. There was no significant difference in reduction in GTV primary with P value of 0.085.

In our study, mean loss of weight is 9.5 % (ranging from 3 % to 18.4 %) and 8.8 % (ranging from 4.3 % to 15.7 %) corresponding to 0.33 % and 0.31 % decrease per day in patients who required implementation of adaptive plan and in patients who did not require implementation of adaptive plan respectively. There was no significant difference in reduction in weight with P value of 0.738.

In study by Barker et al.[2] Parotid glands also decreased in volume (median: 0.19 cm^3 / d, range: 0.04 – 0.84 cm^3 / d), generally shifted medially (median, 3.1 mm; range, 0–9.9 mm) with time.

Regarding normal tissue changes, Lee et al.[11] acquired data using megavoltage CT imaging. Parotid volumes decreased with a median loss of 21.3 % or 0.7 % per day. Hansen et al.[12] performed a study on 13 head and neck cancer patients treated with IMRT. Planning CT scans were performed before treatment and after an average dose of 36 Gy. A mean reduction in the parotid volume of 21.5 % and 15.6 % was observed for the left and right gland, respectively. No changes were observed for the GTV. Osorio et al.[13] looked at the 3D anatomical changes of tumours, irradiated or spared parotids, and submandibular glands by performing CT scan analysis at 0 and 46 Gy. Irradiated and spared parotid glands had a volume loss of 17 % ± 7 % and 5 % ± 4 %, respectively.

In our study rate of volume loss of parotid glands per day is 0.92 % and 0.251 % in patients who required implementation of adaptive plan and in patients who did not require implementation of adaptive plan respectively. Parotid glands volume decreased with a mean loss of 25.9 % and 7.02 % in patients who required implementation of adaptive plan and in patients who did not require implementation of adaptive plan respectively. Both the groups of patients were compared in terms of reduction in parotid glands volume. There was significant difference in reduction in parotid glands volume with P value of 0.003.

In patients who required the implementation of adaptive plan, correlation between reduction in patient weight, tumour volumes (GTV primary and GTV node), Parotid glands shrinkage and changes in doses to target volumes (PTV primary D50, PTV node D50), doses to OAR was analysed. There was significant negative correlation between reduction in GTV node and reduction in parotid glands D mean (P value – 0.015). There was apparently significant positive correlation between GTV node reduction and reduction in brain stem D max (P value – 0.043).

Yan et al.[10] investigated the prognostic value of volume reduction rate (VRR) in head and neck cancer patients treated with IMRT. Multivariate analysis of the primary tumour relapse-free survival revealed that VRR is an outcome predictor for local control in oropharyngeal and hypopharyngeal cancer patients. Those with large tumour volumes or a VRR < 0.5 should be considered for a salvage or a dose escalation scheme. This can be tested in our cohort of patients in future by following these patients for a longer duration.

CONCLUSIONS

More than half of the patients with head and neck carcinoma required re-planning during radiation therapy. Most of the patients required re-planning at the end of 4th week. GTV node reduction and parotid glands reduction are the factors which can predict the requirement of implementation of adaptive plan, risk of grade III/IV dermatitis during radiotherapy. GTV node reduction is the only factor which can predict the risk of grade III/IV mucositis. GTV node reduction is the only factor which showed significant negative correlation with reduction in doses to OARs (parotids D mean) with adaptive planning in this study. Large sample size and long follow up is recommended in future to overcome the above limitations of the study.

Limitations

In our study, sample size was small. Subset analysis was also not possible because of small sample size. Follow up was short to assess the outcome. Prognostic value of volume reduction rate was not analysed because of short follow up. Response assessment was not done in the present study.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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