

Prospective study of adaptive radiotherapy in head and neck cancers with concurrent chemoradiation in volumetric modulated arc therapy

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Abstract

Introduction: During the course of Head and neck radiotherapy, anatomical changes as body weight and/or tumour volume may result in under dosage or dose inhomogeneity in targets and overdosage in Organs at risk(OARs). so this study is undertaken to provide an overview of magnitude and frequency of these effects and to investigate the benefits of adaptive radiotherapy to patients of Head and neck cancers treated with VMAT. **Aims:** The main aim of the study is to see the benefit of adaptive radiotherapy in Head and neck cancer patients during treatment with Volumetric Modulated Arc Therapy by examining anatomical and dosimetric changes. **Materials and method:** The present study is a prospective, single arm study was conducted at department of Radiation Oncology, at MNJ Institute of oncology and Regional cancer center, Osmania medical college, Hyderabad. 20 patients of Head and neck cancers being treated with radiotherapy will be taken into study over a period of 2 years. **Results:** Mean doses to ipsilateral and contralateral parotids doses decreased to parotids in re-plans but with P value not significant. Mean Dmax doses to spinal cord (with significant P value) and brain stem (non significant p value) are also reduced with re-planning. **Conclusion:** As there is increase in the target volume coverage and decreased doses to OARs with re-planning, ART can be considered in locally advanced head and neck cancers for good tumour control and less side effects

Keywords: Organs at risk(OAR), Volumetric Modulated Arc Therapy(VMAT), Head and neck cancer (HNC).

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Introduction

The term Head and neck cancer (HNC) refers to cancers of the upper aero digestive tract including lips, oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, sinonasal cavities and salivary glands. They account for 4% of all cancers. Approximately 27% of these patients are women. The incidence of head and neck cancer in India in 2012 is about 145,000. This accounts for about 11.5% of all new cases of cancer and about 8.4% of all deaths due to cancer. Epidemiological data shows that head and neck cancers are common in the elderly age group above 40yrs, except for the tumours of the salivary glands and nasopharynx which occur in young people. Life style factors such as tobacco(either smoking or chewing) and alcohol consumption are the major risk factors associated with head and neck cancers. Recently an increasing number of head and neck cancers associated with viral infections such as Human papilloma virus (mostly HPV 16) and Epstein-Barr virus are being diagnosed particularly in the younger age groups. These tumours associated with HPV are found to be associated with better prognosis than the ones not associated with HPV. An increasing incidence of oral tongue squamous cell carcinoma (SCC) in non smoking white women has been reported that does not appear to be driven by prior

HPV infection, whereas the incidence of other oral cavity cancers is declining. There is long standing association between Epstein-Barr virus and Nasopharyngeal cancers (NCC). Occupational exposures are associated with development of sinonasal tract tumours[1]. The primary mode of spread of head and neck squamous cell carcinomas (HNSCC) is either local spread or through the lymph nodes. Factors predicting the risk of lymph node metastasis include the size of the primary tumour, histological grade and presence of lympho vascular invasion. Nodal stage is an important predictor of the risk of distant metastasis, with the N3 tumours having a risk of about 30%. The most common site of distant metastasis is lung. The primary modality of treatment includes surgery and radiation or in some cases both, based on stage of disease. Combined modality treatment can be avoided for lesions with a high cure rate (70% or greater) by either surgery or RT alone. If EBRT is considered, it can be given either through conventional or conformal therapy. Conformal therapy in Head and Neck cancers can be given through IMRT or VMAT technique[2]. During the course of Head and neck radiotherapy, anatomical changes as body weight and/or tumour volume may result in under dosage or dose inhomogeneity in targets and overdosage in Organs at risk(OARs). The largest dose differences between (estimated) delivered and planned OAR dose that have been reported are for parotid glands. A large parotid gland dose than planned will increase the risk of xerostomia with subsequent deterioration of quality of life. Adaptive Radiotherapy is a strategy used to limit or even decrease dose to OARs. In the last decade, many efforts have been to characterize anatomic changes of Head and neck OARs and dosimetric consequences during radiotherapy. Studies on Head and

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neck cancers treated with adaptive radiotherapy particularly with VMAT are not many, so this study is undertaken to provide an overview of magnitude and frequency of these effects and to investigate the benefits of adaptive radiotherapy to patients of Head and neck cancers treated with VMAT.

Materials and method

It is a prospective, single arm study was undertaken with prior approval from hospital scientific and ethical committees. It was conducted at department of Radiation Oncology, at MNJ Institute of oncology and Regional cancer center, Osmania medical college, Hyderabad. 20 patients of Head and neck cancers being treated with radiotherapy will be taken into study over a period of 2 years from August, 2017 to June, 2019. Patients meeting the following criteria will be included in the study.

Tumour classified as stage I-IV located in oropharynx, nasopharynx, hypopharynx, larynx or oral cavity according to the TNM (Tumour Node Metastasis) classification. Histopathological diagnosis of invasive Squamous cell carcinoma at the primary site.

Inclusion criteria: Age 18-60 years, Performance status 0-2 according to Eastern Cooperative Oncology Group (ECOG) criteria, Patients with KPS >40. Patients with prophylactic dental evaluation done before RT planning, Normal CBC and normal liver and kidney function tests.

Exclusion criteria: Distant metastases, Prior surgical excision (except biopsy), Planned elective surgery, Patient not willing to get involved in the study, Previously irradiated patients, the existence of synchronous multiple malignancies or previous history of head and neck cancer, severe active co-morbidity and people with HIV and those who cannot tolerate concurrent chemoradiation

The patient was explained about the treatment and consent was taken. Before starting of treatment patient weight is measured and noted. Pre-RT dental prophylaxis was done to patient for dental caries, sharp teeth, other dental problems

Immobilization and Simulation: All the patients were subjected for dental evaluation and those who had dental extraction were given adequate time for healing minimum of 2 weeks. Then the Patient was immobilized in supine position using a thermoplastic facial mask of 5 clamps with neck slightly extended and hands are placed by side to ensure reproducible daily setup and to minimize patient motion. A proper head rest was also used to ensure that the patient was comfortable. Patient was aligned properly with the help of laser alignment beams.

- Each patient underwent a planning CT plain and with I.V. contrast from vertex to mid thoracic region with slice thickness of 3mm using a Philips Bigbore 16 – slice CT simulator.
- Orthogonal room lasers were used to place skin markers to verify that no shift occurred between scans.
- The CT images were transferred online to the ECLIPSE tm (Varian medical system, Palo Alto, CA, USA) treatment planning system (TPS).

The patient was made to get CT Sim done before start of RT planning and original plan(O) is made, every week CBCT is done along with monitoring of weight of patient and checking the status of thermoplastic ray cast (whether it was being correctly fit or getting loose due to weight loss or disease regression). During mid treatment which is approximately around completion of 3 to 3 and half weeks, if there is weight loss of >10%, the fitting of thermoplastic ray cast was checked and if it was adequate then with same ray cast, re-simulation with plain and I.V contrast CT was done. If at all, the ray cast got loose, then a new thermoplastic ray cast was done in order to avoid the mobilisation of patient, then with new ray cast re-simulation with plain and I.V contrast CT scanning with same isocentre was kept. Initially original plan with initial contours is made, then the patient is made monitored during treatment and during mid treatment on the new rescan based on the then contours a new adaptive plan(R) is made. To check the difference in volumes in

Results

PTV and doses received by OARs, the original contours are super imposed on the adaptive rescan by matching the bony land marks and then the original plan is copied on to the adaptive re-sim contours and then a hybrid plan(H) is made.

The following structure sets were contoured in the treatment planning:

- a. Gross tumour volume (GTV): visible tumour and/ or enlarged (or) suspicious lymph nodes identified either clinically or radiographically. It was divided into
 - Gross primary tumour volume (GTVp) and
 - Gross nodal volume (GTVn)
- The clinical target volume (CTV): tissues felt to harbour risk of microscopic, but not gross disease.

They were divided into:

CTV High Risk (CTVHR): GTV +5mm and areas of high risk are included based on site of disease.

CTV Intermediate risk (CTVIR): based on anatomical site of involvement, intermediate risk areas are contoured,

CTV Low Risk (CTVLR): uninvolved neck nodal levels are included whenever needed.

Neck nodal regions were contoured as per recently updated consensus

Contouring done for initial original plans and also for the re-sim adaptive plans to know the volume difference of target volumes and OARS because of weight loss or decrease in gross tumour volumes.

Planning target volumes (PTV): PTVHR, PTVIR, and PTVLR were generated by adding uniform margin of 5 mm to CTVHR, CTVIR and CTVLR respectively.

The OARs (Organs at Risk) include the Spinal cord, Brain stem, Parotid glands, Cochlea, Lips, Oral cavity, Mandible, Pharynx, Larynx, Pituitary gland, optic chiasm, lens, eyes, unspecified tissue. Not more than 1cc of unspecified tissue outside the targets can receive 74 Gy or more.

Treatment planning

VMAT Planning:

Double Arc plans consisted of 2co-planar arcs with the first arc in the clockwise (181 to 179 degrees) and the other arc in the counter clockwise (179 to 181 degrees) direction. Plan evaluation was done using isodose lines superimposed on CT slices, 3D surface dose displays, and dose-volume histograms [DVHs]. After plan approval, VMAT plans were delivered in Varian True beam linear accelerator. Parameters that were analyzed using the Dose Volume Histograms are:

PTV V95% (Dose received by 95% volume of the PTV)

GTV V100% (Dose received by 100% volume of the GTV)

Doses to OARS like spinal cord, parotids, brain stem, larynx, lens, eye, optic chiasm, cochlea are within normal limit or not whenever possible not compromising the dose to PTV. This evaluation is done during re-plan also. During treatment patient was given concurrent chemotherapy with weekly cisplatin of 40mg/m² after evaluating their CBP, Renal function status. Patient was also monitored for acute reactions of radiation and treated if needed. After the completion of treatment, patient was asked to come for first follow up after 6 weeks and response evaluation was done by clinical examination and if needed CT Head and Neck.

Statistical analysis: The information collected regarding all the selected cases was recorded in a Master Chart. Data analysis was done with the help of computer using MS-Excel, SPSS 22.0 (Trail version). Using this software, frequencies, percentage, range, mean, standard deviation. Student t' test and p' values were calculated. A p value <0.05 is shown to have significant relationship.

Terms used for Statistical significance

NS: not significant

S: significant

HS: highly significant

Table 1: Distribution among head and neck cancer patients treated with adaptive radiotherapy

Age (in years)	Number of cases	Percentages
Males		
20 TO 30	0	0
30 TO 40	4	20%
40 TO 50	3	15%
50 TO 60	8	40%
Total	15	75%
Female		
20 TO 30	1	5%
30 TO 40	1	5%
40 TO 50	1	5%
50 TO 60	2	10%
Total	5	25%
Site		
Ca Nasal Cavity	1	5%
Hypopharynx	3	15%
Larynx	3	15%
Nasopharynx	1	5%
Oral Cavity	9	45%
Oropharynx	3	15%
STAGE		
T2N2bM0	2	10%
T2N3bM0	1	5%
T3N0M0	3	15%
T3N1M0	2	10%
T3N2bM0	3	15%
T3N2cM0	1	5%
T3N2M0	1	5%
T4aN1M0	1	5%
T4aN2bM0	1	5%
T4aN2cM0	3	15%
T4aN2M0	1	5%
T4bN2cM0	1	5%

Table 2: Pathology of head and neck cancer patients treated with adaptive radiotherapy

SITE	PATIENTS	PERCENT
MD SCC	9	45%
WD SCC	4	20%
SCC	7	35%
Total	20	100%

Table 3: Pre Rt Weight Vs Mid Rt Weight Distribution

Weight In Kgs	Pre Rt Weight	Mid Rt Weight
30 To 40	1 (5%)	5 (25%)
40 To 50	4 (20%)	7 (35%)
50 To 60	9 (45%)	4 (20%)
60 To 70	6 (30%)	4 (20%)
Total	20 (100%)	20 (100%)
Mean	54.475	47.525
Sd	9.95	9.80

Table 4: Distribution among head and neck cancer patients treated with adaptive radiotherapy.

TV V95%	MEAN	SD	P-VALUE
Original Plan	96.50	1.65	0.00018 *HS
Hybrid plan	92.49	4.27	
Re plan	97.39	1.81	
USING ANOVA TEST AT 95% CI			
GTV V100%			
Original Plan	97.21	1.70	0.00011 *HS

Hybrid plan	93.07	5.14	
Re plan	98.19	1.52	
USING ANOVA TEST AT 95% C			
GTV VOLUME (cm³)			
Original Plan	62.54	30.60	
Hybrid plan	46.09	33.36	0.112 NS
USING ANOVA TEST AT 95% CI			
Ipsilateralparotid			
Original Plan	34.17	7.50	
Hybrid plan	33.99	9.62	
Re plan	30.80	8.29	0.377 NS
USING ANOVA TEST AT 95% CI			
C/L Parotid			
Original Plan	24.60	7.43	
Hybrid plan	24.10	5.33	
Re plan	21.83	5.69	0.331 NS
USING ANOVA TEST AT 95% CI			
Spinal Cord			
Original Plan	43.71	3.29	
Hybrid plan	43.90	4.78	
Re plan	40.83	4.50	0.044 *S
USING ANOVA TEST AT 95% CI			
Brainstem			
Original Plan	49.02	7.19	
Hybrid plan	48.85	7.15	
Re plan	45.45	7.94	0.239 NS
USING ANOVA TEST AT 95% CI			

Here in original plan the mean PTV V95% is 96.50 but on hybrid plan evaluation it is only 92.49, which is not the appropriate dose that should be received. But on re-plan which is done on the new contours based on changes in volumes of patients either due to loss of weight or disease regression, the PTV coverage which might have been not appropriate if same plan was continued is corrected ON re plan the PTV coverage mean is 97.39 . The P value is also 0.00018 which is highly significant indicating adaptive radiotherapy in head and neck cancer patients is helpful in providing adequate coverage. In initial plan done, the mean value of GTV V100% is 97.21 In hybrid plan, it is 93.07 indicating chances of tumour miss. In re plan it is 98.19.P value:0.00011 which is highly significant. The mean of maximum dose received by spinal cord in original plan is 43.71Gy The mean of maximum dose received by spinal cord in hybrid plan is 43.9Gy The mean of maximum dose received by spinal cord in re plan is only 40.83Gy P value is 0.044

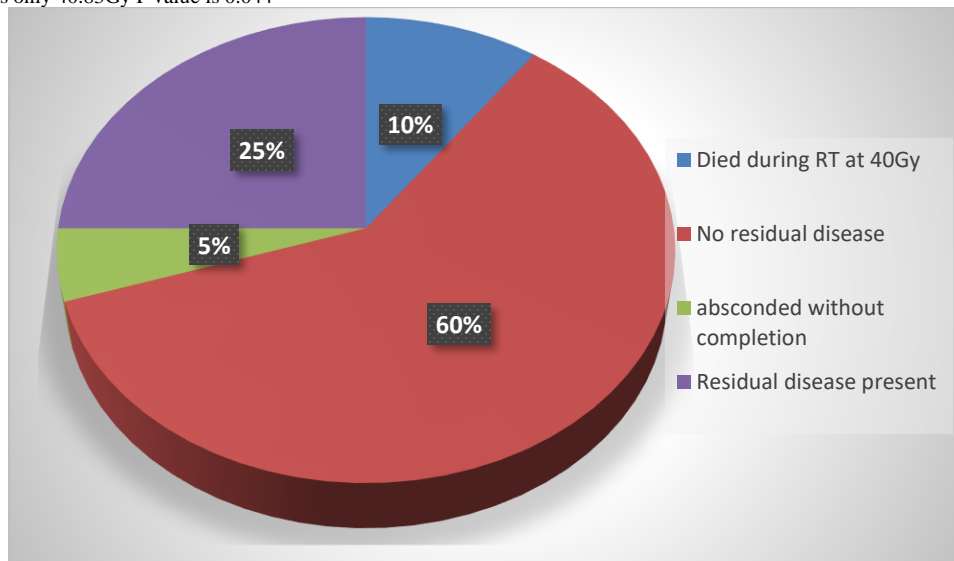


Fig 1: Locoregional control at 1st follow up distribution among head and neck cancer patients treated with adaptive radiotherapy

Discussion

In India, Head and neck cancers in advanced stages are of in great number because of many risk factors like tobacco chewing, alcohol (which has a synergistic role with tobacco) and viral infections like Human papilloma virus and Epstein Barr viruses. In many of these patients, as surgery is not feasible because of very advanced stages, Radiation do play a vital role in the treatment modality with concurrent chemotherapy. With the latest techniques that are evolving in the field of Radiation, IMRT and VMAT are in wild use because of their conformal dose to target area and help in dose escalation with sparing of normal tissues as much as possible. With these huge burden of disease, the tumour might regress during radiation or patient might loose weight during treatment which causes the changes in body contours or thermoplastic ray cast get loosened resulting in more difference in immobilisation of patient finally leading to less coverage to target volumes and more doses to Organs at risk(OARs) nearby. Hence the concept of adaptive radiotherapy might be beneficial. Murat surucu et al[3]conducted a study with 51 patients to investigate the effects of adaptive radiotherapy on dosimetric, clinical and toxicity outcomes for patients with advanced H&N cancers with IMRT by doing a re sim at median dose of 37.8Gy. The results are also in favour showing a decrease in maximum dose to brainstem and spinal cord, the ipsilateral and contralateral parotid mean doses also decreased with increase in target volume coverage. Nagarjuna Burela et al[4]had done a study in Bhagwan Mahaveer cancer Hospital at Jaipur, India to see the anatomic and volumetric changes that occurs in head and neck cancer patients during radiation and to see the role of adaptive radiotherapy in tumour coverage and OARs. Results has adaptive re-planning has increased tumour coverage and normal tissue sparing. Hansen et al[5]retrospectively reviewed plans for 13 patients with locally advanced HNC who had repeat CT imaging and re-planning during the RT course in response to weight loss or tumour shrinkage. When compared with a re-plan, the original plans demonstrated decreased dose to target tumour volumes as well as an increase in dose to the brainstem and spinal cord. Schwartz et al[6]showed that adaptive re planning led to a mean reduction of parotid doses. They concluded that head and neck ART dosimetrically outperforms IMRT.

Castelli et al⁷had done a study to see the benefits of adaptive re-planning in locally advanced H&N cancer patients. The results showed overdosing of parotid gland with standard IMRT plan and with adaptive re-planning there is a significant decrease in mean dose that is delivered to parotid gland and thereby xerostomia risk.

In this study 20 patients of locally advanced H&N cancer with ECOG score of 1-2 are included. All of them were treated with concurrent chemoradiation. An original VMAT plan is done at beginning of RT, at mid treatment that corresponds to range of 33Gy – 36Gy, almost 3 to 3 1/2 weeks a re-adaptive VMAT plan was done on new re-sim contours and Hybrid VMAT plan was made on new contours with original plan by matching the bony and soft tissue landmarks. During this study, the significant (>10%) weight loss of patients at mid treatment compared with their initial weight before treatment is observed in almost all of the patients except two patients. This weight loss has led to alteration in fitting of thermoplastic ray cast in some patients. In 4 patients along with weight loss, there is significant nodal size decrease leading to the change in thermoplastic ray cast for proper immobilisation. The Original (O) VMAT plan made at the beginning of RT, adaptive VMAT Re-plan (R) on the mid treatment re-sim contours and a Hybrid VMAT plan (H) on re-sim by copying the initial plan. In all these plans, PTV V95%, GTV V100%, mean doses to ipsilateral and contralateral parotid glands and maximum dose (Dmax) received by the spinal cord, brainstem is compared to know the difference in tumour coverage and doses difference to OARs. It is defined as the percentage of volume of the PTV that is receiving 95% of prescribed dose. In this study, the PTV coverage is increased in re-plan when compared to original plan.

(The P value is 0.00018 significant) In this study, the GTV coverage is increased in re-plan when compared to original plan. (P value:0.00011 which is highly significant).The mean dose that is received by ipsilateral parotid is less in re-plan when compared to original plan. P value is 0.377 (not significant). The mean dose that is received by contralateral parotid is less in re-plan when compared to original plan. (P value is 0.33). The mean of maximum dose received by spinal cord in re-plan is less when compared to original plan. (P value is 0.044, which is significant). The mean of maximum dose received by brainstem in re-plan is less when compared to original plan. (P value is 0.23 not significant).

All patients had weight loss during treatment. Among 20 patients, 16 had significant weight loss i.e.>10% from initial weight and 12 requiring the need for nasogastric tube. The mean weight loss among patients is observed to be 7kg. The mean weight loss in percentage is 15.2% after 3 weeks of RT. Bhandari et al[8]reported 10% weight loss after 3 weeks of treatment. Burela, et al[4]reported a mean weight loss of 7.99% after 4 weeks of treatment. The weight loss in this study is with more significant value, the initial weight being low, built of the patients, nutritional status of patients, socioeconomic conditions might have shown a vital role in more weight loss comparing to the western studies. This show the need for adaptive radiotherapy in locally advanced H&N cancer patients whenever required. The PTV V95% in re-plan has shown an increase of mean 0.93% from initial plan which increases more target volume coverage area and there by reducing the chances of local recurrences. In original plan the mean PTV V95% is 96.50. In hybrid plan evaluation it is only 92.49, had the same plan is continued with the changed contours and not taken into consideration for re- sim and re-planning, the mean dose received by the PTV is reduced to below 95% which might not be acceptable. Due to Re plan the PTV coverage is corrected and tried to increase the coverage to the new volumes to a mean of 97.39. The P value is also 0.00018 which is highly significant indicating adaptive radiotherapy in head and neck cancer patients is helpful in providing adequate coverage. In muratsurucu et al³ the PTV V95% median coverage was improved by 0.5% by adapted re plan. In Jensen et al⁹ there is improvement of coverage by 8%. In Capelle et al¹⁰ the PTV coverage improved by 0.5Gy(D1%). In Dewan et al[11] has shown more uniform coverage and decrease V110% by 2%. In Olteanu et al[12]has shown higher minimum and lower maximum doses. In Schwartz et al[3]the results shown increase coverage and dose homogeneity. In Burela et al[4] D95% did not differ much but with significant difference in D2%. In the above studies, in some re planning is done weekly and in some after 2 weeks or at the end of 4th week of starting of RT with significant p value. But in some studies, like Castelli et al[7] there is no difference or improvement in target volume coverage. With many studies showing improvement in target volume coverage and p value being significant, adaptive re-planning can be considered in locally advanced H&N cancer. The GTV volume receiving 100% dose is increased by 0.92% in study with significant p value of 0.00011 which is highly significant. In initial plan the mean percentage of GTV receiving 100% dose is 97.21. Due to re-plan based on changed volumes now it has improved to 98.19. Though in re-plan we are appreciating the increase in mean but by continuing the same plan there are chances of tumour miss due to change in body contours which is being depicted by hybrid plan. In hybrid plan the mean volume is only 93.07 increasing the chances of local failure. Sometimes there might be increase in tumour volume during RT also, re-planning avoids the missing of increase tumour area. In Surucu et al[3]there is a median increase in GTV coverage by 0.8%. There are not many studies focussing particularly on GTV V100% as target volume coverage includes both GTV and PTV. Hence all studies depicting the increase in target volume coverage can also consider increase in coverage of GTV. So adaptive planning should be considered for improvement in GTV coverage and to avoid the miss in tumour tissue. In this study it is observed that the ipsilateral

parotid gland has received a lesser mean dose by 3.3Gy in re-plan when compared to the mean dose in initial original plan. P value being 0.37 which is not significant. In this study it is observed that

the contralateral parotid gland has received a decreased mean dose by 2.8Gy in re-plan when compared to the initial original plan. P value being 0.33 which is not significant.

Table 5: Comparison of mean doses in Ipsilateral and contralateral parotid original, hybrid plans

Ipsilateral parotid	Original plan	hybrid plan	P value
Cheng et al[13]	53.8	57.5	<0.001
Dewan et al[11]	15.1	18.4	0.01
Burela et al[4]	23	22.9	0.9
Present study	34.17	33.39	0.37
Contralateral parotid			
Cheng et al[[13]	29.9	37.1	0.005
Dewan et al[11]	14.7	14.5	0.08
Burela, et al[4]	20	22	0.338
Present study	24.6	24.1	0.37

In this study it is observed that due to adaptive re-planning the maximum dose received by the spinal cord is decreased. The mean of max dose to spinal cord in original plan is 43.7Gy but with re planning it is reduced to 40.8Gy and the p value is also significant of 0.044. The mean of maximum dose received by the brainstem in re-plan is reduced in comparison with the original plan. The mean decrease is by 9.18%. (P value is 0.2.NS)

Table 6: Comparison of Dmax dose to spinal cord in original plan, hybrid plan and re-plan

Studies	Original plan	Hybrid plan	Re-plan	P value
Cheng et al[13]	41±2	43±4		0.008
Hansen et al[5]	25.7	23.3	19.3	0.003
Burela et al[4]	20.67	24	19.7	<0.05
Dewan et al[11]	17	19.45	13.2	0.001
Present study	43.7	43.9	40.8	0.04

In this study the locoregional control at 6mths is 60% with adaptive radiotherapy. As the patient recruitment for this study is conducted till April 2019 a minimum of 6 months follow up is only considered. Out of 20 patients, 12 patients had good locoregional control (LRC) with no metastasis elsewhere, one patient had absconded and lost to follow up, 2 patients died during treatment due to disease, 5 patients had residual disease at first follow up. The patients with residual disease were advised surgery and opinion regarding surgical feasibility is taken but none could get surgery done either due to medical reasons or inoperability of disease, so all were considered for palliative chemotherapy.

Limitations

Subjects considered in this study is less which could not result in significant and decision changing outcomes. The timing of adaptive radiotherapy itself is not clear after still these many studies because of nonuniform results. For re-planning there are no clear guidelines or consensus. There are no characteristic patients based on stage who can be considered for ART. Even in LAHNC patients, the role of physical factors like weight reduction in patients in ART is not clear. Very time consuming and Costly.

Conclusion

As there is increase in the target volume coverage and decreased doses to OARs with re-planning, ART can be considered in locally advanced head and neck cancers for good tumour control and less side effects. Though it is such a cumbersome procedure, which is time consuming, costly, but with promising results in increasing the target volume coverage and decreased doses to OARs, ART can be considered in locally advanced head and neck cancers for good tumour control and less side effects. But there is no clear consensus guidelines on ART and for clinical correlation with xerostomia with decreased parotid doses further studies are needed.

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