ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 01 | January - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ADAPTIVE RADIOTHERAPY IN LOCALLY ADVANCED OROPHARYNGEAL CANCER – IMPACT ON TARGET VOLUME SHRINKAGE & ORGAN AT RISK

Radiation Oncology

Jayesh Singh Resident, Department of Radiation Oncology, GCRI.
Sumit Goyal Assistant professor, Department of Radiation Oncology, GCRI.
Ankita Parikh Professor, Department of Radiation Oncology, GCRI.
U. Suryanarayana* Professor & HOD, Department of Radiation Oncology. GCRI. *Corresponding Author

ABSTRACT

Aim: To evaluate the volumetric alteration in locally advanced oropharyngeal cancers taking place during image-guided radiotherapy by comparing pretreatment and inter-fractional imaging.
Method: Thirty patients with locally advanced oropharyngeal carcinoma treated with definitive chemoradiotherapy with delivery of 66Gy. All patients re-simulated after 15 fractions. Volumes of rescan was compared with original scan. Acute, late toxicities and tumor control were assessed. Gross tumor volume reduction rate was calculated.
Results: After adaptive rescanning volume change ranged from 3% to 67% in GTV, from 5% to 70% in parotid, 6% to 57% in Submandibular gland. Median tumor volume reduction rate was 28%. Patients with volume reduction rate ≥40% had complete response. Out of 30 patients enrolled in study 20 patients (66.67%) had complete response on clinical evaluation and follow up CT scan while 10 patients (33.33%) had partial response, confirmed on biopsy.
Conclusion: This pilot study suggests that interim replan can diagnosed target & OAR volume change and prevent higher doses to OAR than anticipated during original plan.

KEYWORDS

Adaptive radiotherapy, Oropharyngeal cancer, IGRT, Tumor volume reduction rate

INTRODUCTION:

At present chemoradiation is standard care for oropharyngeal carcinoma with a view of organ preservation approach(1). Radiotherapy can be delivered in conventional 2 dimensional parallel oppose fields or more advanced techniques like 3DCRT or IMRT. But, Conventional radiation is associated with a number of long-term morbidities such as xerostomia, which has been reported in 60–95% of patients, dysphagia in 35–76%, sticky saliva in 33%, decreased sense of taste in 25–50% and dental problems in 33% treated with conventional radiation therapy(2–5). Whereas IMRT is an advanced form of conformal RT permitting more precise cancer targeting and possible escalation of dose while reducing dose to normal tissues and thus side effects(6–10). However, overall survival is similar between patients treated with IMRT and those receiving conventional Radiotherapy(1).

As radiation has biological effect on both tumor and normal tissues, volumetric change can occur in tumor and normal tissue like parotid, submandibular gland, masticator muscles, pharyngeal muscle, larynx, sternocleidomastoid muscle, thyroid gland. Additionally, as patients may have weight loss, it would change the volumetric & dosimetric data implied in treatment planning, which suggest adaptive strategy is valuable(11–13)

METHOD:

Thirty patients with histologically proven squamous cell carcinoma of locally advanced oropharyngeal cancer were enrolled between July 2016 to June 2018 into prospective study approved by Gujarat cancer and research institute investigational review committee.

Radiotherapy planning

Patients were simulated with custom mould thermoplastic head and shoulder mask for pretreatment computer tomography (CT: Siemen's Somatom emotion 6 slice CT) in same position as in thermoplastic mask made. Contrast enhanced CT with 3 mm slice thickness were taken and transferred to MONACO (Elekta; contour and planning system). Radiation was delivered using megavoltage Elekta synergy 6MV photon through dynamic MLC Intensity modulated radiotherapy (IMRT) or Volumetric arc therapy (VMAT) techniques.

Gross tumor was treated with 66 Gy in 30 fractions 2.2 Gy per fraction, high risk Clinical target volume with 60Gy in 30 fractions 2 Gy per fraction, low risk Clinical target volume with 54 Gy in 30 fractions 1.8 Gy per fraction. Cone beam CT was performed twice weekly to monitor anatomical changes.

Concurrent chemotherapy

all patients had received concurrent platinum compound-based chemotherapy as prescribed by medical oncologist at our institute.

Adaptive radiotherapy

All thirty patients were re-simulated after 15 fractions (after 3rd week). GTV, CTV and OAR were contoured on rescan and volumes of them compared with pretreatment scan. New radiation plan was generated on rescan and delivered.

Patient characteristics

Patients and tumor characteristics were as mentioned in table 1. The maximum patients were in age group of 55-65 years (50%) followed by 45-54 years (33%). 77% patients were younger than 60 years and 23% were in geriatric age group. In this study all patients were oropharyngeal carcinoma, majority had primary base of tongue disease with varying numbers involving other subsites tonsil, soft palate, vallecula, oropharyngeal wall. The group stage distribution was stage III (n=6), stage IVA (n=24).

Follow up

After the treatment completion patients were called for follow up every month. During follow up, patients were asked for side effects of radiotherapy, indirect laryngoscope examinations were done and neck was palpated for nodal status. CT scan was done on 3rd follow up or as clinical findings suggestive of suspicious lesion. If patient had residual disease and confirmed on biopsy or developed recurrent disease were counselled for palliative chemotherapy or salvage surgery.

Table 1. Patient and tumor characteristics

Patient and tumor characteristics	
Characteristics	No of patients
Age (in years)	
<60	23
>60	7
Gender	
Male	27
Female	3
KPS	
70	1
80	4
90	25
Subsite of primary lesion	
Base of Tongue	21
Vallecula	3
Tonsil	5
Soft palate	1

T stage	
cT3	6
cT4	24
N stage	
cN0	16
cN1	13
cN2	1

Toxicity

Patients were monitored at least once a week for acute radiation toxicities (mucositis, dermatitis) and graded as per RTOG grading scale(14). Late toxicities were monitored on follow up.

Tumor volume reduction rate

The changes in total gross tumor volume between original and rescan were evaluated. Tumor volume reduction rate was calculated from Pre-RT GTV and rescan GTV(15).

Statistical Analysis

Comparison between pre-treatment volume of OARs and interval CT-OARs were done using paired sample t test. The differences were considered statistically significant when $p < 0.05$. Tumor volume reduction rate (VRR) was calculated by simple calculation methods and significance of difference was calculated using paired t test.

RESULTS:

Total 30 patients of oropharyngeal carcinoma were evaluated in this study, mean age of the patient was 53 years. The maximum patients were in age group of 55-65 years (50%) followed by 45-54 years (33%). 77% patients were younger than 60 years and 23% were in geriatric age group. All patients had a primary lesion in oropharyngeal structure, majority in base of tongue (n=21,70%) with varying numbers involving other subsites tonsil(n=5,17%), soft-palate(n=3,10%), vallecula(n=1,3%).

The pre- treatment GTV (p-GTV) was ranging from 7.88cc to 94.03cc. The mean p-GTV was 34.00cc with standard deviation (SD) 17.69cc. The volume of i-GTV was ranging from 3.70cc to 58.12cc; mean 20.57cc with SD 10.96cc. The decrease in GTV was ranging from 2.97cc to 44.36cc with percentage ranging from 12% to 67%. The decrease in GTV was statistically significant (p value <0.05).

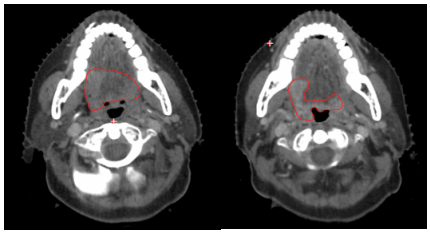

Image 1. Shows contoured GTV (in red) in pre-treatment CT (left image) and interval CT scan at 16 fractions (right image).

Table no. 2 **(n=30)**

	Pre treatment	After 15 #		p-value	Result
Volume (cc) GTV	Mean ± SD	Mean ± SD	Result		
	33.99±17.68	23.54±11.23	volume decrease	<0.0001	S
p value < 0.05 --> S (significant) p value > 0.05--> NS (not significant)					

Volumetric change in GTV and organ at risk contoured for the purpose of this study pre-treatment and at interval CT scan (16#) has shown in table 3. GTV and all OAR except mandible has significant change in volume with p value <0.05 which is statistically significant. Change in volume of spinal cord can be due to difference in contouring technique.

Table 3: volumetric change in GTV and OARs **(n=30)**

	Structure	Mean	Std. Deviation	Volume change	p value	Result
1	P GTV	33.9953	17.68805	decrease	<0.0001	S
	i GTV	23.547	11.23931			
2	p-rt parotid	20.3	4.98547	decrease	<0.0001	S
	i-rt parotid	14.3264	4.7375			
3	p-lt parotid	20.934	6.14307	decrease	<0.0001	S
	i-lt parotid	14.5726	5.52839			
4	p-rt SMG	7.75	1.67399	decrease	<0.0001	S
	i-rt SMG	5.4557	1.43329			
5	p-lt SMG	7.683	1.54776	decrease	<0.0001	S
	i-lt SMG	5.249	1.25092			
6	p-mandible	64.58	9.0256	decrease	>0.05	NS
	i-mandible	63.1697	8.83744			
7	p-spinal cord	26.1283	4.78847	decrease	<0.0001	S
	i-spinal cord	24.18	4.95191			
8	p-thyroid	11.6763	2.13961	decrease	<0.0001	S
	i-thyroid	8.9323	1.75423			
p value < 0.05 -> S (significant), p value > 0.05 -> NS (significant)						

Out of 30 patients enrolled in study 20 patients (66.67%) had complete response on clinical evaluation and follow up CT scan done 3 months after completion of concurrent chemoradiation, while 10 patients (33.33%) had partial response, confirmed on biopsy. All six patients with stage III disease had a complete response in comparison to eleven out of twenty-four patients with stage IV disease.

DISCUSSION

IMRT is the treatment modality technique of choice for management of oropharyngeal carcinoma. As we know radiation has biological and structural effect on tumor as well as the normal tissue; further patients may have significant weight loss during treatment because of the acute mucositis and nutritional deficiency. Treatment would be delivered on the basis of plan made on pre-treatment CT scan. In view of volume changes in normal tissues and as well as the target, OARs may receive higher doses with compromised target coverage, which may result in unnecessary toxicities. So, it is a logical step to replan at a specified interval to evaluate tumor volume reduction rate (VRR) which has prognostic significance and reduce dose to normal tissue leads to decrease in late toxicities.

In our study change in volume of GTV ranged from 3% to 67% after 3 week (at 16 fraction) which is statistically significant (p value < 0.0001).

Hyebin Lee et al (14). had documented the patients who achieved loco-regional control had a higher tumour VRR than those with loco-regional failure (p = .010), and those with the tumour VRR >35% achieved significantly higher loco-regional control at 3 years (94.4% vs 72.4%; p = .018). In our study patients who had VRR ≥40% at interim re-plan done after 15 fractions at 3rd week has complete response at 1 year after treatment while in patients with VRR <40%, 54.55% has complete response at year.

Kataria et al (15). has investigated efficacy and toxicities of adaptive radiotherapy and documented median reductions in gross primary disease volumes on mid-treatment scans was 34%; 16 patients experienced grade 3 acute mucositis; four patients developed local recurrences, all within the RT field. In our study median reduction in GTV was 28%; 13 patients had grade 3 acute mucositis; 1 patient had local recurrence, 1 had neck recurrence and 1 had distant metastasis in chest wall but no disease at primary site.

Francesco Ricchetti et al (16). documented the parotid glands showed the largest average absolute volume change with a shrinkage of 10 mL; next, and smaller reductions involved both the submandibular and the thyroid glands. In our study average shrinkage in volume of right parotid-5.97cc, left parotid-6.36cc, right SMG-2.29cc, left SMG-2.43cc and thyroid gland-2.74cc.

Shih-Neng Yang et al (17). has shown primary tumor volume and T staging as a prognostic factor for primary tumor relapse-free survival for OPC: T4 tumor (p = 0.0001, hazard ratio 7.38), pGTV ≥20 mL (p = 0.01, hazard ratio 10.61). In our study, we found stage III tumor responded well and 100% complete response while in stage IV 45.83% had complete and 54.17% had partial response. But we didn't find significant co-relation between pre-treatment GTV and clinical response.

CONCLUSION

Adaptive radiotherapy for locally advanced oropharyngeal carcinoma is excellent strategy for curative intent to avoid missing target coverage and to reduce toxicities to OAR. Larger cohorts and randomized design can unlock the further hidden benefits of adaptive radiotherapy in head and neck carcinoma.

REFERENCES

1. Pfister DG, Foote RL, Gilbert J, Gillison ML, Ridge JA, Rocco J. NCCN Guidelines

Index Table of Contents Discussion. 2018;227.
2. Bundgaard T, Tandrup O, Elbrønd O. A functional evaluation of patients treated for oral cancer. A prospective study. Int J Oral Maxillofac Surg. 1993;22(1):28–34.
3. Constine LS. What else don't we know about the late effects of radiation in patients treated for head and neck cancer? Int J Radiat Oncol Biol Phys. 1995;31(2):427–429.
4. Epstein JB, Emerton S, Kolbinson DA, Le ND, Phillips N, Stevenson-Moore P, et al. Quality of life and oral function following radiotherapy for head and neck cancer. Head Neck J Sci Spec Head Neck. 1999;21(1):1–11.
5. Harrison LB, Zelefsky MJ, Pfister DG, Carper E, Raben A, Kraus DH, et al. Detailed quality of life assessment in patients treated with primary radiotherapy for squamous cell cancer of the base of the tongue. Head Neck J Sci Spec Head Neck. 1997;19(3):169–175.
6. Wu Q, Manning M, Schmidt-Ullrich R, Mohan R. The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. Int J Radiat Oncol Biol Phys. 2000;46(1):195–205.
7. Chao KC, Majhail N, Huang C, Simpson JR, Perez CA, Haughey B, et al. Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. Radiother Oncol. 2001;61(3):275–280.
8. Dogan N, King S, Emami B, Mohideen N, Mirkovic N, Leybovich LB, et al. Assessment of different IMRT boost delivery methods on target coverage and normal-tissue sparing. Int J Radiat Oncol Biol Phys. 2003;57(5):1480–1491.
9. Li Y, Taylor JM, Ten Haken RK, Eisbruch A. The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy. Int J Radiat Oncol Biol Phys. 2007;67(3):660–669.
10. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys. 2006;66(4):981–991.
11. Bando R, Ikushima H, Kawanaka T, Kudo T, Sasaki M, Tominaga M, et al. Changes of tumor and normal structures of the neck during radiation therapy for head and neck cancer requires adaptive strategy. J Med Invest. 2013;60(1.2):46–51.
12. Castadot P, Geets X, Lee JA, Christian N, Grégoire V. Assessment by a deformable registration method of the volumetric and positional changes of target volumes and organs at risk in pharyngo-laryngeal tumors treated with concomitant chemo-radiation. Radiother Oncol. 2010;95(2):209–217.
13. Bhide SA, Davies M, Burke K, McNair HA, Hansen V, Barbachano Y, et al. Weekly volume and dosimetric changes during chemoradiotherapy with intensity-modulated radiation therapy for head and neck cancer: a prospective observational study. Int J Radiat Oncol Biol Phys. 2010;76(5):1360–1368.
14. Lee H, Ahn YC, Oh D, Nam H, Kim YI, Park SY. Tumor volume reduction rate measured during adaptive definitive radiation therapy as a potential prognosticator of locoregional control in patients with oropharyngeal cancer. Head Neck. 2014;36(4):499–504.
15. Kataria T, Gupta D, Goyal S, Bisht SS, Basu T, Abhishek A, et al. Clinical outcomes of adaptive radiotherapy in head and neck cancers. Br J Radiol. 2016 Jun;89(1062):20160085.
16. Ricchetti F, Wu B, McNutt T, Wong J, Forastiere A, Marur S, et al. Volumetric change of selected organs at risk during IMRT for oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2011;80(1):161–168.
17. Yang S-N, Liao C-Y, Chen S-W, Liang J-A, Tsai M-H, Hua C-H, et al. Clinical implications of the tumor volume reduction rate in head-and-neck cancer during definitive intensity-modulated radiotherapy for organ preservation. Int J Radiat Oncol Biol Phys. 2011;79(4):1096–1103.