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Modern Radiotherapy for a Medieval Malady: An Analysis of Treatment Toxicities for Locally Advanced Head and Neck Cancers

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Abstract

Background: Concurrent chemo-radiation has proven to be beneficial in a majority of patients with locally advanced head and neck cancers. Despite modern techniques of radiation delivery, the trade-off is acute and entails late toxicities for a considerable number of patients. Very few studies have reported the outcomes of these patients. We aimed to prospectively assess and report the toxicities of patients undergoing definitive chemo-radiation by the Volumetric Modulated Arc Therapy (VMAT) for the treatment of advanced laryngeal and hypopharyngeal cancer.
Method: This prospective observational study was conducted in a single tertiary care center over a period of two years. We recorded acute and late toxicities during and after the treatment of patients with locally advanced laryngeal and hypopharyngeal cancer treated with definitive chemo-radiotherapy using VMAT. Chi square test and Fisher's exact test were used for comparing the significance of outcome parameters with different variables.
Results: 28 patients who met the inclusion criteria were taken up for analysis. The median age was 59 years. The median treatment time was 48 days. The mean dose to parotid, superior, and mid constrictors was 32, 45, and 64 Grays (Gy). At completion, 7% of the patients had grade 3 or more dermatitis, 4% had grade 3 or higher mucositis, and no patient had grade 3 or higher xerostomia. Five patients treated for hypopharynx cancer developed strictures.
Conclusion: Our results showed that concurrent chemo-radiotherapy using VMAT is a promising method of treatment for advanced laryngeal and hypopharyngeal squamous cell cancer with an acceptable toxicity profile.
Keywords: Larynx, Hypopharynx, Vmat, Dysphagia, Xerostomia

Introduction

Concurrent chemo-radiation has proven effective in a majority of patients with locally advanced head and neck cancers; this method has become the standard of care after its benefit was proven in the meta-analysis of chemotherapy in head and neck cancer.[1]

Despite modern techniques of radiation delivery, the trade-off is acute and ensues late toxicities for a considerable number of patients.[2,3]

This study aimed to report the incidence of acute and late toxicities in patients with locally advanced laryngeal and hypopharyngeal cancer treated with definitive chemoradiotherapy by the volumetric modulated arc therapy technique (VMAT).

Intensity-modulated radiotherapy (IMRT) technique is replacing 3D conformal radiotherapy

(3DCRT) for the definitive treatment of locally advanced head-neck cancer due to its ability to achieve highly conformal dose distribution and reduced dose to organs at risk.[4]

VMAT is a dynamic form of IMRT which has shorter treatment time and superior target coverage in comparison with the step and shoot method and the dynamic field method of IMRT.[5] Thus, it is the preferred type of IMRT.

We hope our analysis can add to the body of knowledge pertaining to the treatment of laryngeal and hypopharyngeal cancer using the VMAT technique.

Materials and Methods

Patient selection

This prospective study was conducted at a tertiary care hospital in a southern part of India. The patients eligible for the study were identified from the departmental and hospital registry between September 2017 and September 2019. We included those in stages III and IV (AJCC 8th edition) of hypopharyngeal and laryngeal squamous cell cancer who were treated with definitive radiotherapy with concurrent chemotherapy. The exclusion criteria were Karnofsky performance status of less than 60%, upfront laryngectomy, histology other than squamous cell carcinoma, or distant metastasis.

All cases were presented and discussed in the interdisciplinary head and neck oncology tumor board. The ethical clearance for the study was obtained from the Institutional Ethics Committee at Manipal Academy of Higher Education, Manipal, Karnataka, India (Ethics code: 552/2017). All the participants signed a written informed consent.

Target volume contouring, dose prescription, and treatment delivery

Gross tumour volume (GTV) comprised the grossly visible disease via clinical examination and imaging. Clinical target volume (CTV) included the GTV with an expansion to account for subclinical disease. The regions at high risk were included in the $CTV_{\text{high risk.}}$ The areas of subclinical disease were designated as $CTV_{\text{intermediate risk}/\text{low risk}}$. The planning target volumes (PTVs) were generated through giving an isometric expansion of 3 mm to all CTVs. PTV high risk/intermediate risk/low risk were prescribed to a dose of 70 Grays, 59.4 Grays, and 56 Grays, respectively using simultaneous integrated boost single phase technique with five fractions weekly. As per the institutional protocol coverage of the primary tumour (V95 of the planning target volumes $\geq$ 95%) over sparing of normal tissues was given precedence. Critical normal structures were given dose constraints according to the QUANTEC guidelines.[6]

Regarding the discretion of the treating physician, weekly concurrent sensitizer chemotherapy with cisplatin (40mg/m2) or

carboplatin (AUC 2) was prescribed for the patient.

In line with institutional policy, all patients had an endoscopic guided nasogastric tube placed prior to treatment. They were prescribed a hospital diet as per requirement by the team of nutritionists during the entire course of the treatment. Monaco treatment planning system was used for VMAT planning and treatment was delivered on Elekta Versa HD linear accelerator.

Assessment

Following treatment, history and physical examination was performed on a monthly basis for the first three months, a three-monthly basis for the first two years, and six monthly thereafter. Acute and late radiation toxicities was graded according to the Radiation Therapy Oncology Group (RTOG) acute and late morbidity scoring criteria, respectively. Hematological toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE 3.0). Acute toxicity was recorded at treatment completion and late toxicity at 6 months.

Data analysis

Data was analyzed using Microsoft Excel 2017 and SPSS (Statistical Package for Social Sciences,IL,Chicago) version 20. Chi square test and Fisher's exact test were used to compare the significance of outcome parameters with different variables. A value of 0.05 was taken as the level of significance.

Results

A total of 28 patients who met the inclusion criteria were analyzed. Demographic details are summarized in table 1. Median treatment time was 48 days (44 to 53 days). The mean volume of GTV_{70} and PTV_{70} was 32.1 cc and 113.6 cc, respectively. Across the cohort, the mean coverage of PTV_{70} which received 95% of the prescribed dose was 98.4 % and that of PTV_{70} receiving 98% of the prescribed dose was 94.4%. The mean homogeneity index was 1.05, and the mean conformity index was 0.74. The mean dose to organs at risk, such as parotids, submandibular, oral cavity, superior constrictor, mid constrictor, and thyroid was 32Gy, 60Gy, 40Gy, 45Gy, 64Gy, and 65Gy, respectively.

93% of the patients lost weight during the course of the treatment. 76% lost more than 5% of their baseline body weight. Two patients gained weight during the course of the treatment. The effect of different variables on weight loss was assessed and the results are depicted in table 2.

Haematological and acute toxicities recorded during the course of the treatment are summarized in table 3. The late toxicities of the 16 patients who had a follow-up of 6 months or more were also recorded (Table 3).

Table 4 summarizes the effects of different variables on acute xerostomia and dysphagia.

The comparison of toxicity with dose to organ at risk is shown in table 5.

One case of carcinoma hypopharynx underwent emergency tracheostomy for laryngeal edema five months post treatment. Five patients treated for cancer of the hypopharynx developed strictures. Six months after treatment, two patients developed nasogastric tube dependence due to persistent aspiration with oral feeds. Both patients died of aspiration after 7 and 10 months of treatment, respectively. Three other patients died due to causes unrelated to therapy. Two of these patients died of myocardial infarction, and the other's cause of death was unknown.

Discussion

Over a study period of two years, 28 patients who met the inclusion criteria were

assessed, and their median follow-up was 6.5 months. The most common age group among the patients in the study was 60-65 years. The median treatment time was 48 days and no patient had a delay of more than four days.

Weight and nutrition

Two of the patients in our study gained weight during treatment, and both had a nasogastric tube placed before starting the treatment. Three-quarters of our patients had a weight loss of greater than 5% of their body weight during the course of the treatment, and there was a mean 5% loss of initial body weight. Significant weight loss was observed in patients receiving carboplatin sensitizer as compared to those receiving cisplatin. (P= 0.008)

A higher percentage of weight loss was detected in males compared to females and patients with a hypopharyngeal primary in comparison to a laryngeal primary, but it was not statistically significant. The placement of a percutaneous endoscopic gastrostomy tube prophylactically has been shown to improve the nutritional status of head and neck carcinoma patients who undergo definitive concurrent chemoradiotherapy. However, this remains a controversial topic.[7,8]

Toxicity

Among the haematological toxicities, leucopenia was the most common, likely due to the concurrent chemotherapy. Higher rates of haematological toxicities were observed with the increase in the number of chemotherapy cycles. Acute toxicities were assessed at the end of the treatment and a majority were grade 1 or less, and none of the patients developed grade 4 toxicities. Concurrent chemoradiotherapy involves a greater risk of severe late toxicity.

Advanced T-stage, old age, and primary tumor in the larynx and hypopharynx are strong independent risk factors of late radiation toxicity.[9] Late toxicities were assessed in the 16 patients who had a follow-up duration of six months or longer; there was no incidence of grade 2 or higher xerostomia.

Nancy et al. also reported that xerostomia improved over time, and in their cohort, no grade 2 or more xerostomia was observed at two years post treatment.[7]

Dysphagia and xerostomia are the two important late radiation-induced toxicities known to significantly impair the quality of life after treatment. New radiation delivery techniques help minimize the dose to the salivary glands and anatomic structures involved in swallowing, such as the pharyngeal constrictor muscles.[10]

Numerous studies have reported a relationship between reduced salivary flow or xerostomia and dose distribution in salivary glands. [11,12,13]

In our study, the mean dose to the parotid gland was 32Gy (range of 10 to 53Gy), which is above the 26Gy threshold established by Eisbruch *et al.*[11] A higher rate of xerostomia was seen in patients who received high doses to the salivary glands, but this was not statistically significant.

Levendag et al. studied oropharyngeal cancer patients who received radiotherapy; they found that the swallowing complaints were significantly associated with the increase in mean dose to superior pharyngeal constrictor and mid pharyngeal constrictor muscles.[14]

In laryngeal and hypopharyngeal cancer, the structures related to swallowing dysfunction are usually the primary targets, hence cannot be spared. However, in a study by Eisbruch et al., the patients with a hypopharyngeal primary tumour and a laryngeal primary tumour had a significant sparing of the pharyngeal constrictor muscles using IMRT.[15]

In our study, the mean dose to the superior and mid pharyngeal constrictor muscles was 45.63 (12 to 71) and 64.38 (54 to 72),

respectively. This is slightly higher than the recommended dose to pharyngeal constrictors, which is 50 to 55Gy.
This can be explained by the fact that in many patients, the pharyngeal constrictor muscle was in close proximity to the GTV volume.
Comparison of the dysphagia grade and doses to the constrictor muscles showed a higher rate in those receiving high doses, but this was not statistically significant.
In a review of 222 patients with cancers related to the head-neck region, 21% of those treated with definitive concurrent chemoradiation developed strictures, and hypopharyngeal carcinoma was a significant predictor of stricture formation.[16]
In our study, we observed similar rates of stricture on follow-up. 20% of the patients (5 out of 25) developed a stricture that required dilatation. All 5 of these patients were cases of carcinoma hypopharynx. All patients underwent a biopsy at the time of dilatation which showed only therapy-related changes.

Limitations

Among the limitations, mention can be made of the small number of patients and the short duration of follow-up. Furthermore, we did not analyze the toxicity profile three months post treatment, which would have helped us better understand the trends of toxicity improvement or its lack. The toxicities assessment at 6 months did not take into account the voice quality after treatment. We are planning on improving these shortcomings by incorporating these factors in our future studies.

Conclusion

Definitive chemoradiotherapy for advanced cases of laryngeal and hypopharyngeal cancers in the modern era have acceptable toxicities. Although hypopharyngeal malignancies have poorer prognosis, more studies are required to assess the efficacy and toxicity of organ preservation treatment modalities and identify subgroups that will benefit the most.

Conflict of Interest

None declared.

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Table 1. Demographics summary

Factors	Frequency
Age	
 <60 years ≥60 years	Median = 59 years 14(50%) 14(50%)
Gender	
Males Females	**19 (68%)** 9 (32%)
Primary Site	
Larynx Hypopharynx	12 (43%) **16 (57%)**
Subsite	
Supraglottis Glottis Subglottis Pyriform sinus Post cricoid Posterior pharyngeal wall	**7 (25%)** 5 (18%) 0 4 (14%) **7 (25%)** 5 (18%)
'T' Stage	
T1 T2 T3 T4	0 1(4%) **25(89%)** 2(7%)
'N' Stage	
N0 N1 N2 N3	9(32%) **11(39%)** 8(29%) 0
Stage Group	
Stage III Stage IV A Stage IV B	**19 (68%)** 7 (25%) 2 (7%)
Histological grade	
WDSCC MDSCC PDSCC	7 (25%) **19 (68%)** 2 (7%)
Chemotherapy	
Cisplatin Carboplatin	**18 (64%)** 10 (36%)

T – Tumor stage , N- Node stage; WDSCC**:** Well differentiated squamous cell cancer; MDSCC**:** Moderately differentiated squamous cell cancer; PDSCC: Poorly differentiated squamous cell cancer

Table 2. Effect of different variables on weight loss

Variable	**Weight Loss Significant (>5% BW)**	**Weight Loss Not Significant (<5% BW)**	***P* Value**
Gender			
Male	5 (28%)	13 (72%)	*P= 0.766*
Female	3 (33%)	6 (67%)	
Primary site			
Larynx	4 (33%)	8 (67%)	*P= 0.706*
Hypopharynx	4 (27%)	11 (73%)	
NG tube			
NG tube	2 (22%)	7 (78%)	*P= 0.551*
No NG tube	6 (33%)	12 (67%)	
Chemotherapy			
Cisplatin	2 (12%)	15 (88%)	*P=* ***0.008***
Carboplatin	6 (60%)	4 (40%)	
Stage			
Stage III	6(32%)	13(68%)	*P = 0.732*
Stage IV	2(25%)	6(75%)	
Age			
<60 years	4(31%)	9(69%)	*P= 0.901*
≥60 years	4(29%)	10(71%)	
GTV volume			
<32cc	4(24%)	13(76%)	*P= 0.365*
≥32cc	4(40%)	6(60%)	

cc: Cubic centimetre; NG: Naso-gastric; BW: Baseline weight

Table 3. Haematological and acute toxicities recorded during the course of the treatment

Hematological Toxicity (n=27)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Anaemia	20(74%)	6(22%)	1(4%)	0	0
Thrombocytopenia	25(93%)	2(7%)	0	0	0
Leucopenia	10(37%)	8(30%)	4(15%)	5(19%)	0
Neutropenia	15(56%)	5(19%)	5(19%)	1(4%)	1(4%)
Acute Toxicity (n=27)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Acute dermatitis	0	13(48%)	12(44%)	2(7%)	0
Acute oral mucositis	3(11%)	13(48%)	10(37%)	1(4%)	0
Acute xerostomia	1(4%)	21(78%)	5(19%)	-	0
Acute dysphagia	0	11(41%)	8(30%)	8(30%)	0
Late Toxicity (n = 16)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Late xerostomia	12(75%)	4(25%)	0	0	0
Late dysphagia	11(69%)	2(12.5%)	1(6%)	2(12.5%)	0
Late SC fibrosis	15(94%)	1(6%)	0	0	0

SC: Subcutaneous

Table 4. Effect of different variables on Acute Xerostomia and Dysphagia

Variable	**Grade 1 Xerostomia**	**Grade 2 Xerostomia**	***P* Value**	**Grade 1 Dysphagia**	**Grade 2 Dysphagia**	***P* Value**
Age						
<60 years	10(77%)	3(23%)	*P = 0.867*	6(46%)	7(54%)	*P = 0.581*
≥60 years	12(86%)	2(17%)		5(36%)	9(64%)	
Gender						
Male	14(78%)	4(22%)	*P =0.484*	7(39%)	11(61%)	*P =0.946*
Female	8(89%)	1(11%)		3(38%)	5(62%)	
Primary Site						
Larynx	11(92%)	1(8%)	*P =0.223*	5(42%)	7(58%)	*P =0.930*
Hypopharynx	11(73%)	4(27%)		6(40%)	9(60%)	
Stage						
Stage III	16(84%)	3(16%)	*P = 0.574*	6(32%)	13(68%)	*P = 0.135*
Stage IV	6(75%)	2(25%)		5(62%)	3(38%)	
Chemotherapy						
Cisplatin	15(83%)	3(17%)	*P = 0.726*	7(39%)	11(61%)	*P = 0.782*
Carboplatin	7(78%)	2(22%)		4(44%)	5(56%)	

Table 5. Relationship between toxicity and radiation therapy dose to organ at risk

At treatment completion	**(n=27)**			
Organ	**MEAN DOSE**	**GRADE 1 XEROSTOMIA**	**GRADE 2 XEROSTOMIA**	**p VALUE**
Parotid Gland	<26Gy	7(100%)	0	*p = 0.100*
	≥26Gy	14(70%)	6(30%)	
Submandibular gland	<39Gy	19(83%)	4(17%)	*p = 0.718*
	≥39Gy	3(75%)	1(25%)	
	MEAN DOSE	**< GRADE 1 DYSPHAGIA**	**>GRADE 2 DYSPHAGIA**	
Superior constrictor	<55Gy	6(43%)	8(57%)	*p = 0.816*
	≥55Gy	5(38%)	8(62%)	
Mid constrictor	<55Gy	1(50%)	1(50%)	*p = 0.869*
	≥55Gy	11(44%)	14(56%)	
6 months post treatment	**(n=16)**			
	MEAN DOSE	**GRADE 0 XEROSTOMIA**	**GRADE 1 XEROSTOMIA**	
Parotid gland	<26Gy	3(60%)	2(40%)	*p = 0.350*
	≥26Gy	9(82%)	2(18%)	
Submandibular gland	<39Gy	10(71%)	4(29%)	*p = 0.383*
	≥39Gy	2(100%)	0	
	MEAN DOSE	**< GRADE 1 DYSPHAGIA**	**>GRADE 2 DYSPHAGIA**	
Superior constrictor	<55Gy	10(%)	2(%)	*p = 0.712*
	≥55Gy	3(%)	1(%)	
Mid constrictor	<55Gy	2(100%)	0	*p = 0.468*
	≥55Gy	11(79%)	3(21%)	

Gy: Grays