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Original Article

Oncology Section

Evaluation of Late Toxicities in Postoperative Cases of Oral Cavity Cancer Treated by Intensity-Modulated Radiotherapy (IMRT): A Retrospective Cohort Study

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ABSTRACT

Introduction: Surgical intervention serves as the primary treatment modality for operable oral cavity cancer. However, patients with locally advanced disease or unfavourable prognostic factors often require adjuvant Radiotherapy (RT) with or without concurrent Chemotherapy (CT). Advanced radiation techniques, such as Intensity-Modulated Radiotherapy (IMRT), have shown potential in minimising radiation-related toxicities while ensuring effective tumour control.

Aim: To assess common late toxicities, namely xerostomia, dysphagia, and hoarseness, in patients with postoperative Squamous Cell Carcinoma (SCC) of the oral cavity, who received adjuvant RT or concurrent Chemo-Radiotherapy (CRT) utilising IMRT with a Simultaneous Integrated Boost (SIB) approach.

Materials and Methods: A retrospective cohort study was conducted in the Department of Radiotherapy at IMS, BHU, Varanasi, Uttar Pradesh, India, from June 2018 to December 2021. Study was done using the medical records of 62 patients with SCC of the oral cavity and received adjuvant radiation by the IMRT technique with or without concurrent CT. Late toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 28.0, and a logistic regression model was used to establish the association between Organ-At-Risk (OAR) doses and the development of late toxicities.

Results: The median age of the study participants was 45 years (range: 25-68), and 95.2% (n=59) of the patients were male. A total of 62 patients (59 male, 3 female) were included. The median follow-up duration was 21.5 months. At two years, the cumulative incidence of xerostomia, dysphagia, and hoarseness was 28.5% (n=8), 21.4% (n=6), and 28.5% (n=8), respectively. Logistic regression showed that both the D mean of >26 Gy to the contralateral parotid (HR=4.32; 95% CI, 1.03-18.05; p=0.045) and the D mean of >26 Gy to the contralateral Submandibular Gland (SMG) (HR=6.41; 95% CI, 1.48-27.81; p=0.013) were significantly associated with the incidence of xerostomia. The D mean of >47 Gy to the pharyngeal constrictors (HR=17.89; 95% CI, 3.15-101.62; p=0.001) and the D mean of >50 Gy to the larynx (HR=5.77; 95% CI, 1.82-18.24; p=0.003) had a significantly high risk of dysphagia and hoarseness, respectively.

Conclusion: Adjuvant IMRT resulted in acceptable rates of late toxicities in oral cancer. Doses to the contralateral parotid and SMGs, pharyngeal constrictors, and larynx had a significant impact on late xerostomia, dysphagia, and hoarseness, respectively.

Keywords: Intensity-modulated radiotherapy, Oral cavity, Toxicity

INTRODUCTION

The incidence of oral cavity and lip cancers worldwide is 2% in males and 1.8% in females [1,2]. Surgery is the mainstay of treatment for operable oral cavity cancer. However, for patients with locally advanced disease (stage III, IV) and/or poor prognostic factors in the postoperative Histopathology Report (HPR), such as a close margin (<5 mm), lymphovascular invasion, or perineural invasion, RT is recommended. CT is added to RT if a positive margin and/or Extranodal Extension (ENE) is evident in the postoperative HPR [3-6]. RT, while addressing microscopic tumour cells at the postoperative site, also affects nearby OARs such as the oral mucosa, salivary glands, larynx, and Pharyngeal Constrictor Muscles (PCM). Radiation to these normal structures not only causes acute reactions but also leads to late toxicities that persist even beyond six months after completing treatment. However, with the evolution of advanced radiation techniques like IMRT/Volumetric Arc Therapy (VMAT), it is possible to decrease radiation doses to OARs, thereby reducing toxicities, while still providing adequate doses to target volumes. Compared to Three-Dimensional Conformal Radiation Therapy (3-DCRT), IMRT is associated with a decreased incidence and severity of xerostomia, with similar loco-regional control and overall survival [7-9]. IMRT has also been shown to be associated with a shorter duration of dysphagia and a lower rate of feeding tube placement compared to 3-DCRT [10]. IMRT with SIB allows irradiation of different target volumes to different desired dose levels and appears to have better conformity compared to sequential IMRT [11,12]. Xerostomia, dysphagia, and hoarseness are troublesome late toxicities of RT. The aim of the study was to evaluate these late toxicities in patients with postoperative SCC of the oral cavity who received adjuvant RT or concurrent CRT using advanced IMRT with SIB.

MATERIALS AND METHODS

A retrospective cohort study was conducted in the Department of Radiotherapy at IMS, BHU, Varanasi, Uttar Pradesh, India, from June 2018 to December 2021. The study was conducted after obtaining approval from the Institute's Ethical Committee (Reference no- Dean/2022/EC/3310). Sixty-two patients were identified after applying suitable inclusion and exclusion criteria.

Inclusion criteria: Postoperative cases of SCC of the oral cavity who underwent R0/R1 resection, received adjuvant radiation by IMRT technique with or without concurrent CT, had an Eastern

Cooperative Oncology Group (ECOG) performance status of 0-2, and normal haematological, renal, and liver function tests were included in the study.

Exclusion criteria: Patients with two primary cancers/recurrent disease or a history of prior CT and/or RT were excluded from the study.

Study Procedure

Pre-RT diagnostic evaluation consisted of a complete physical examination, complete blood tests, chest X-ray, Computed Tomography scan (CT-scan), and/or Magnetic Resonance Imaging (MRI) of the head and neck region. In case of a suspicious lesion on the chest X-ray, a CT scan of the thorax was performed. Group staging was done according to AJCC 8th edition [13]. Based on the postoperative histopathological report, patients were planned for either adjuvant RT alone or with concurrent CT. Dental prophylaxis was performed in all patients before the start of RT. The patients were immobilised in the supine position with a four-clamp thermoplastic mask attached to a carbon fibre base plate. An appropriate head support was used for each patient. Contrast-enhanced planning CT images were obtained in the treatment position at a 3 mm interval from the vertex to the carina. Segmentation was done slice by slice on CT images. Clinical Target Volume High-Risk (CTV-HR) was defined as the regions of the resected primary tumour bed and pathologically positive lymph node stations in the neck (HR CTV-N). CTV Intermediate Risk (CTV-IR) was defined as lymph nodal stations adjacent to HR CTV-N, and CTV Low-Risk (CTV-LR) was defined as nodal stations that were adjacent to CTV HR-N or CTV IR-N and/or prophylactic treatment of contralateral neck node stations. The contralateral neck was addressed when the primary disease was reaching or crossing the midline, in the case of multiple positive ipsilateral neck nodes, single/multiple ipsilateral LNs with ENE. All the CTVs were modified by cropping from bone, cartilage, and air. The CTVs were subsequently expanded by 5 mm to generate the respective Planning Target Volumes (PTV). Doses prescribed to PTV-HR, PTV-IR, and PTV-LR were 60-66 Gy, 54-60 Gy, and 50-54 Gy, respectively, in 30-33 fractions, a single fraction in a day, 5 fractions per week. In the case of pathologically N0 disease or node-positive disease with negative ENE, only two volumes were created (PTV-HR and PTV-LR). All the patients were treated by IMRT with SIB.

The OARs were contoured according to the consensus guidelines by Brouwer CL et al., [14]. The contoured OARs included bilateral parotid glands, oral cavity, PCM, contralateral SMG, larynx, spinal cord, PRV cord, and brainstem. The dose constraints used were as follows: brainstem Dmax <54 Gy, spinal cord Dmax <45 Gy, PRV cord Dmax <50 Gy, each parotid gland Dmean <26 Gy or D_{50} <30 Gy, larynx Dmean <45 Gy, PCM Dmean <45 Gy, temporal lobe Dmax <60 Gy, and cochlea Dmax <54 Gy and Dmean <45 Gy.

All treatment plans were generated in the treatment planning system, and treatment was delivered using a 6 MV linear accelerator. Concurrent cisplatin with a dose of 35-40 mg/m^2 weekly was prescribed to all patients with positive margins and/or ENE. For toxicity assessment, patients were followed weekly during treatment, monthly from treatment completion up to three months, and 2-3 monthly thereafter. Late toxicities were defined in terms of xerostomia, dysphagia, and hoarseness of voice seen after six months of treatment completion. Toxicity scoring was done using the National Cancer Institute CTCAE v4.03 [15].

STATISTICAL ANALYSIS

The data analysis was performed using SPSS version 28.0. Categorical data were presented as frequencies and percentages. All continuous data were described using either the median and range or the mean and standard deviation, depending on the distribution. The late toxicities were reported as cumulative incidence. The correlation between the Dmean of salivary glands and the risk of late xerostomia was assessed using logistic regression. Similarly, logistic regression analysis was used to examine the correlation between the risk of developing late dysphagia and the Dmean of pharyngeal constrictors and larynx, as well as, between the risk of hoarseness and the Dmax of the larynx. The risk was expressed as Hazard Ratio (HR) with a 95% Confidence Interval (CI). A p-value cutoff of <0.05 was considered statistically significant.

RESULTS

The median age was 45 years (range: 25-68), and 95.2% (n=59) of the patients were male. The most common site was the buccal mucosa, accounting for 41.9% (n=26) of all cases. Sixty-six percent (n=41) of patients had stage IV disease. Patient and tumour-related characteristics shown in [Table/Fig-1].

Parameters	n (%)
Gender	
Male	59 (95.2)
Female	3 (4.8)
Age (years)	
≤40	22 (35.5)
41-60	29 (46.8)
>60	11 (17.7)
Median	45
Range	25-68
Subsite	
Tongue	20 (32.2)
Buccal mucosa	26 (41.9)
Upper alveolus	8 (12.9)
Lower alveolus	6 (9.7)
Lip	1 (1.6)
	1 (1.6)
cT stage	
1	4 (6.5)
2	15 (24.1)
3	13 (21)
4a	30 (48.4)
cN stage	
0	18 (29.0)
1	18 (29.0)
2a	5 (8.1)
2b	13 (21)
2c	7 (11.3)
3b	1 (1.6)
Clinical group stage	
I	1 (1.6)
II	7 (11.3)
III	13 (21.0)
IV	41 (66.1)
Pathological group stage	
I	1 (1.6)
II	7 (11.3)
III	21 (33.9)
IV	33 (53.2)
Grade	
I	21 (33.9)
II	27 (43.5)
III	9 (14.5)
Unknown	5 (8.1)

Extranodal extension	
Present	15 (24.2)
Absent	46 (74.2)
Unknown	1 (1.6)
Margin status	
Positive	9 (14.5)
1-5 mm	14 (22.5)
>5 mm	39 (63.0)
Depth of invasion	
<5 mm	7 (11.3)
5-10 mm	13 (21.0)
>10 mm	25 (40.3)
Unknown	17 (27.4)

[Table/Fig-1]: Patient and tumour characteristics.

Positive margins were found in 14.5% (n=9) of patients, while 24.2% (n=15) had ENE. Lymphovascular invasion was present in 19.3% (n=12) of patients, and perineural invasion was seen in 32.2% (n=20) of all patients. Neoadjuvant chemotherapy was administered in 21% (n=13) of patients. All patients received adjuvant radiotherapy. The CRT was delivered to 38.7% (n=24) of patients due to positive margin and/or ENE status. These patients received a radiation dose of 64-66 Gy/30-33 fractions. The median duration of radiotherapy was 45 days (range: 40-127). The majority of patients were able to complete treatment within 10 days of the planned treatment duration. Treatment details are described in [Table/Fig-2].

Parameters	n (%)
Neoadjuvant chemotherapy	
Yes	13 (21.0)
No	49 (79.0)
Concurrent chemotherapy	
Yes	24 (38.7)
No	38 (61.3)
IMRT type	
SIB	51 (82.2)
Sequential	11 (17.8)
EBRT dose (HR)	
66 Gy	21 (33.9)
60 Gy	38 (61.3)
64 Gy	3 (4.8)
RT duration (days)	
Median	45
Range	40-127
Within 10 days of planned duration	54 (87.1)
More than 10 days of planned treatment duration	8 (12.9)

[Table/Fig-2]: Treatment characteristics.
IMRT: Intensity-modulated radiotherapy; EBRT: External beam radiation therapy; RT: Radiotherapy

Late toxicity and doses to OARs: Grade 2 dysphagia developed in 5% (n=3) of patients, while hoarseness of voice was observed in 32.2% (n=20). All patients with hoarseness had grade 1 severity. The radiation doses to the normal organs were evaluated in all patients. The mean Dmean/Dmax received by the OARs is described in [Table/Fig-3].

Late toxicity was assessed in all patients (n=62) who had a minimum of six months of follow-up after treatment completion. The median follow-up for the entire cohort was 21.5 months (range: 9-51 months). Grade 1 and grade 2 late skin toxicity (fibrosis/induration) were observed in 75% and 10% of patients, respectively. At six months, 59.7% (n=37) of patients experienced xerostomia, with the majority having grade 1 severity. The incidence of grade 2 xerostomia was 11.3% (n=7), while no patients developed grade 3 toxicity. The cumulative incidence of xerostomia, dysphagia, and hoarseness at six months, one year, two years, and three years is described in [Table/Fig-4].

Organ at risk	Mean dose (Gy) of cohort N (SD)
Ipsilateral parotid, mean Dmean	49.45 (13.44)
Contralateral parotid, mean Dmean	23.48 (12.2)
Larynx, mean Dmean	44.59 (12.43)
Pharyngeal Constrictor Muscles (PCM), mean Dmean	44.16 (8.01)
Contrateral Submandibular Gland (SMG), mean Dmean	42.40 (17.41)
Spinal cord, Mean Dmax	37.08 (5.52)
PRV cord, mean Dmax	39.82 (7.17)
Brainstem, mean Dmax	31.80 (7.90)

[Table/Fig-3]: Doses to OARs.

Late toxicity	Cumulative incidence (any grade)	Grade 3	Grade 2	Grade 1
Xerostomia				
Six months	37/62	0	7	30
One year	22/51	0	4	18
Two years	8/28	0	0	8
Three years	3/16	0	0	3
Dysphagia				
Six months	15/62	0	3	12
One year	11/51	0	2	9
Two years	6/28	0	1	5
Three years	1/16	0	0	1
Hoarseness of voice				
Six months	20/62	0	0	20
One year	10/51	0	0	10
Two years	8/28	0	0	8
Three years	3/16	0	0	3

[Table/Fig-4]: Late toxicties.

On univariate analysis, a Dmean of >26 Gy to the contralateral parotid was significantly associated with a high risk of late xerostomia (HR=6.23; 95% CI, 1.58–24.49; p=0.009). Similarly, a Dmean of >26Gy to the contralateral SMG (HR=8.9; 95% CI, 2.15-36.84; p=0.003) showed a significant association with xerostomia. In multivariate analysis, both the Dmean to the contralateral parotid (HR=4.32; 95% CI, 1.03-18.05; p=0.045) and the contralateral SMG (HR=6.41; 95% CI, 1.48-27.81; p=0.013) were positively associated with the risk of xerostomia. The results of the univariate and multivariate analyses are presented in [Table/Fig-5].

	Univariate analysis				Multivariate analysis		
Factors	n	HR	95% CI	p-value	HR	95% CI	p-value
For xerostomia							
Dmean contralateral parotid							
≤26 Gy	42	6.23	1.58-24.49	0.009	4.32	1.03-18.05	0.045
>26 Gy	20						
Dmean contralateral Submandibular Gland (SMG)							
≤26 Gy	14	8.9	2.15-36.84	0.003	6.41	1.48-27.81	0.013
>26 Gy	48						
For dysphagia							
Dmean Pharyngeal Constrictor Muscle (PCM)							
≤47 Gy	39	24.05	4.64-124.53	0.001	17.89	3.15-101.62	0.001
>47 Gy	23						
Dmean larynx							
≤50 Gy	40	5.83	1.65-20.52	0.006	2.05	0.44-9.41	0.355
>50 Gy	22						

[Table/Fig-5]: Univariate and multivariate analyses of various factors.

At six months, grade 1 and grade 2 dysphagia were observed in 19.3% (n=12) and 4.8% (n=3) of patients, respectively. There were

no cases of grade 3 dysphagia. At one and two years, grade 2 dysphagia occurred in 3.2% (n=2) and 1.6% (n=1) of cases, respectively. Univariate analysis showed that late dysphagia was significantly associated with a Dmean of >47 Gy to the pharyngeal constrictors (HR=24.05; 95% CI, 4.64-124.53; p=0.000) and a Dmean of >50 Gy to the larynx (HR=5.83; 95% CI, 1.65-20.52; p=0.006). In multivariate analysis, only the dose to the pharyngeal constrictors was significantly associated with a high risk of dysphagia (HR=17.89; 95% CI, 3.15-101.62; p=0.001). Hoarseness of voice was present in 32.2% (n=20) of patients at 6 months, and all cases were grade 2. By the end of one year, hoarseness disappeared in half of the patients (n=10). Logistic regression analysis revealed a significant association between hoarseness and a mean dose of >50 Gy to the larynx (HR=5.77; 95% CI, 1.82-18.24; p=0.003).

DISCUSSION

The present study aimed to evaluate the incidence and severity of late xerostomia, dysphagia, and hoarseness in patients with oral cavity cancer treated with adjuvant IMRT. At one year, we observed no cases of grade 3 xerostomia, with an incidence of grade 1 and grade 2 xerostomia at 29.0% (n=18) and 6.4% (n=4), respectively. Various studies have reported varying incidences of grade 1, grade 2, and grade 3 xerostomia at one year, ranging from 13.1% to 42%, 10% to 19.7%, and 0% to 1.6%, respectively [16-19]. When correlating xerostomia with the dose to the parotid, the authors found a significantly increased risk when the mean dose to the contralateral parotid exceeded 26 Gy. Mazzola R et al., also demonstrated that grade 1 or higher xerostomia was associated with a mean dose of ≥26 Gy to the contralateral parotid [17]. Similarly, in a retrospective study, Muzumder S et al., showed that a mean dose of ≥26 Gy to the parotids had a significantly higher risk of xerostomia [20]. The incidence of xerostomia in patients treated with IMRT and non-IMRT techniques was reported by Nutting CM et al., who found that grade 2 or worse xerostomia at 12 months was significantly lower in the IMRT group compared to the conventional RT group. They also reported significantly better recovery of saliva secretion in IMRT-treated patients [7]. Similarly, a randomised controlled trial by Gupta T et al., comparing 3DCRT with IMRT, reported significantly lesser grade 2 or worse acute salivary gland toxicity in IMRT-treated patients [8].

In the present study, similar to the parotid, the authors found that a mean dose of >26 Gy to the SMG was an independent risk factor for the incidence of xerostomia. A mean dose of >26 Gy to the gland was significantly associated with a higher risk of xerostomia in both univariate and multivariate analyses. Under stimulated conditions, 20-30% of saliva is produced by the SMGs, while in a non-stimulated state, the SMGs contribute up to 90% of salivary output [21,22]. Literature suggests that the dose to the SMGs should be minimised to avoid xerostomia [23]. The IMRT technique helps spare these critical structures responsible for saliva secretion and improves Quality of Life (QoL). In a prospective study by Lin A et al., it was reported that after parotid-sparing IMRT, xerostomia and QoL scores significantly improved during the first year of therapy. Each domain of QoL, including communication, eating, emotion, and pain, showed improvement [24].

The authors observed an incidence of dysphagia at one year and two years of 21.6% and 21.4%, respectively. A similar incidence of dysphagia, 27.3% at one year and 23.8% at two years, was reported by Muzumder S et al., [20]. Among all the patients who developed dysphagia, 80% (n=12) had grade 1 severity. Baudelet M et al., also reported a majority of patients with grade 1 dysphagia when evaluating the impact of IMRT on late toxicities in head and neck cancer patients [25]. In the present study, authors found a significant correlation between a mean dose of >47 Gy to the pharyngeal constrictors and late dysphagia. This observation is similar to the study by Muzumder S et al., which demonstrated a significant association with a mean dose of ≥45 Gy to the pharyngeal constrictors [20]. However, in a review by De Felice F et al., the incidence of late dysphagia was significantly associated with a mean dose of >63 Gy to the pharyngeal constrictors and >56 Gy to the larynx [26]. In the present study, mean dose of >50 Gy had a higher risk of dysphagia on univariate analysis. A mean dose of >50 Gy to the larynx was also associated with a higher risk of hoarseness. Literature also suggests that in order to decrease voice changes, the mean dose to the larynx should be kept ≤50 Gy [27].

Limitation(s)

The retrospective nature and small sample size are major limitations of the study. However, despite the small sample size, the study not only revealed the incidence of late toxicities in the Indian scenario but also identified significant dosimetric parameters of OARs related to these toxicities. A study including a larger number of patients and a longer duration of follow-up would provide additional information on late toxicities and the dosimetric parameters of OARs related to these toxicities.

CONCLUSION(S)

Adjuvant IMRT in patients with postoperative SCC of the oral cavity resulted in acceptable rates of late toxicities. Dose-volume associations showed that minimising mean doses to the contralateral parotid and SMGs, pharyngeal constrictors, and larynx would contribute to a reduced risk of late xerostomia, dysphagia, and hoarseness, respectively.

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