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Pattern of locoregional failure in postoperative cases of locally advanced carcinoma of buccal mucosa treated with unilateral versus bilateral neck radiation: lesson learned from a basic practice setup

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Abstract

Background: Carcinoma of buccal mucosa forms a sizeable percentage of the diagnosed oral cavity cancers in India. There is limited data on elective treatment of the contralateral neck for well-lateralized carcinoma with no involved nodes in the contralateral neck. We conducted this study to compare locoregional control in patients treated with unilateral vs. bilateral neck irradiation.

Materials and methods: 48 patients with carcinoma of buccal mucosa were selected. Patients were divided into unilateral and bilateral arms based on radiation treatment of the ipsilateral or bilateral neck. All patients received adjuvant radiation with Cobalt 60 unit.

Patient-specific and follow-up data were collected from records and dosimetric data from TPS. Chi-square and unpaired t-test was used to compare data between arms and Kaplan Meier plot; Cox regression was used for survival analysis.

Results: After a median follow-up of 23 months, 15 (31.3%) patients had developed disease recurrence, 8 and 7 in the unilateral and bilateral arms, respectively ($p = 0.591$). There was no contralateral neck failure during the follow-up period. The 2-year disease-free survival was 68.2% and 72.2% in the unilateral and bilateral arms, respectively. Among risk factors for disease recurrence, Depth of Invasion, delay in starting radiation and PTV coverage were significant contributing factors. Cox multivariate regression suggested DOI and delay in starting radiation to be significant prognostic factors for DFS.

Conclusion: Bilateral neck radiation does not provide any advantage over ipsilateral neck radiation for properly selected well lateralized buccal mucosal squamous cell carcinoma. Ipsilateral neck radiation facilitates better sparing of organs at risk.

Key words: buccal mucosa; oral cavity; contralateral neck radiation; PORT; adjuvant radiotherapy

Introduction

Cancer of the lip and oral cavity is a major contributor to the cancer burden in India. It accounts for approximately 377,713 cases and 177,757 deaths annually [1]. India contributes a major portion to the global oral cavity cancer burden accounting for 135,929 cases and 75,290 deaths annually [1]. Overall, it is the second most common cancer and most commonly occurring cancer among males in India. The high incidence of oral cavity cancer is probably due to the high prevalence of tobacco use in this region [2, 3].

Carcinoma of the buccal mucosa forms most cases among the diagnosed oral cavity cancers in India [4], most presenting with locally advanced disease. The standard treatment of carcinoma buccal mucosa is surgery followed by adjuvant therapy [5, 6]. The indications of adjuvant radiotherapy are positive margins, extranodal extension, lymphovascular invasion, perineural invasion, two and more involved nodes, and T3 and T4 disease [5, 7, 8]. In contrast, positive resection margins and extranodal extension are indications of concurrent chemoradiotherapy [9]. The postoperative radiation target volume is formed by the preoperative tumor extent, the surgical bed, and the draining neck nodal regions [10].

Elective treatment of the ipsilateral neck is recommended in well lateralized oral cavity/buccal mucosa cancers [11]. For well-lateralized carcinoma with no suspected nodes in the contralateral neck by clinical/radiological examination, there is no consensus guideline for the management of the contralateral neck. The contralateral neck is less frequently addressed given increased patient morbidity and less incidence of contralateral neck metastasis [12]. Some prefer treating the ipsilateral neck only, while others treat the contralateral neck as well by including it in the low-risk volume (PTV44/PTV54).

Our institution delivers both ipsilateral and bilateral neck radiotherapy based on the physician's preference. Though 3-dimensional conformal radiotherapy (3DCRT) and Intensity Modulated Radiotherapy (IMRT) are used to treat postoperative oral cancer patients in our institution, during the study period, a substantial chunk of patients was treated by cobalt 60 with Computed Tomography (CT) based planning employing rectangular fields. We undertook this study to compare the recurrences in the neck in these two groups of patients receiving these two volumes of radiation treatment for local recurrence and disease-free survival. We also wanted to compare risk factors that may contribute to disease recurrence.

Materials and methods

Patient selection

Postoperative cases of carcinoma of buccal mucosa who were referred to our radiation oncology department between 2016 and 2018 and had received postoperative radiotherapy (PORT) were taken for the study if they fit the inclusion and exclusion criteria. Age 18–65 years, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–2, well lateralized primary tumor with no nodes in the contralateral neck on clinical and radiological examination (by CT scan/PET CT scan), biopsy-proven SCC (squamous cell carcinoma), locally advanced pathological stage IV (either by pT4aN0-N2b, or pT1-3N2a/N2b) by AJCC 8th staging and at least one indication for PORT were the inclusion criteria for the study. Patients with histology other than SCC, who received neoadjuvant chemotherapy, bilateral neck dissection, and less than 12 months of follow-up with a clinically controlled disease were excluded from the study. Ethical clearance was obtained from the institutional ethics committee for the study.

1060 cases of head and neck cancer were registered during the study period, among which 180 were carcinoma buccal mucosa. After screening with the inclusion and exclusion criteria, 48 patients were selected for the study (Fig. 1).

Treatment details

All patients received radiation with Theratron 780C cobalt 60 Unit. Patients were immobilized with four clamp thermoplastic masks, using an appropriate headrest and base plate. Shoulder retraction was employed where bilateral treatment was given. Lead wires marked the postoperative scar. CT scans were taken with 3mm cuts at 3mm intervals from the vertex up to the carina, without any intravenous contrast (using PHILIPS Brilliance big bore CT simulator, Philips, Amsterdam, Netherlands). Treatment planning was done using Varian Eclipse TPS (Treatment planning system) (Varian Medical Systems, Palo Alto, California), licensed for Theratron 780c. The treatment target was the postoperative tumor bed, surgical bed, and either ipsilateral or bilateral neck, depending on the treatment arm. Patients receiving treatment to the tumor bed and ipsilateral neck were treated with either a single field or a wedge pair with matched neck field. Patients receiving treatment to the bilateral neck were treated with a parallel opposed field weighted accordingly (Fig. 2). For N0 neck, the radiation fields included levels Ia, Ib, II, and III. For patients with N+ disease, the whole of the neck from level I to V was included in the elective nodal volumes. The organs at risk (OARs) were the spinal cord, eyeballs, and contralateral parotid.

All patients were followed up three times monthly for two years and six times monthly after that. Follow-up was done by clinical examination. A routine Contrast-Enhanced Computed Tomography (CECT) and chest x-ray were done six months and 1 year post-treatment. Suspected recurrence was diagnosed by radiological examination with tissue biopsy, wherever applicable.

Data collection and statistical analysis

Patient particulars, tumor characteristics, treatment particulars, and follow-up data were collected in a structured questionnaire from patient records. Dosimetric data was collected from the Treatment Planning System (TPS). Dosimetric data collected was PTV V95% (Volume of Planning Target Volume receiving at least 95% of the prescribed dose), bilateral parotid mean dose, Spinal cord, and both eyeballs Dmax (Maximum point dose received by the volume). Data were tabulated and analyzed using SPSS version 23.

Patients were classified into two arms, a unilateral field arm and a bilateral field arm:

— unilateral field arm — patients who received radiation to the preoperative tumor bed, surgical bed, and ipsilateral neck;
— bilateral field arm — patients who received radiation to the preoperative tumor bed, surgical bed, and bilateral neck.

Patient and tumor particulars and treatment details were compared between the two arms using the chi-square test and fisher's exact test. The means of the dosimetric data were compared using an unpaired t-test. Disease-free survival (DFS) was used as an indicator for survival analysis. For our study, DFS was calculated as the time between completion of adjuvant treatment and occurrence of first disease failure (locoregional or distant). Patients with recurrence and locoregionally controlled disease were compared for risk factors, and the chi-square test was used as a test for significance. Survival analysis was done using Kaplan Meier and compared using the log-rank test. Cox multivariate regression was used to assess the impact of risk factors on survival.

Results

Among the 48 patients taken for the study, 26 were treated with unilateral radiation field, and 22 were treated with bilateral radiation field. The patient and tumor characteristics are described in Table 1. Patient characteristics are equally distributed between the treatment arms, except for addiction history. The unilateral treatment arm had more patients with no addiction history (38.5 % vs. 13.6%, p-0.05, chi-squared test). All patients had AJCC 8^{th} pathological stage IV A disease. 9 patients had positive margins, 3 had bone involvement, 8 had DOI >10mm, and 3 had a pathological node-negative disease. No extracapsular extension (ECE) was reported in our sample.

The treatment details are tabulated in Table 2. Wide local excision (WLE) with mandibulectomy was the most common surgical procedure. Modified radical neck dissection (MRND) was the most common type of neck dissection, followed by supra omohyoid neck dissection (SOND) and radical neck dissection (RND). Twelve patients had received concurrent chemotherapy. Fourteen patients had a delay in initiation of radiation therapy post-surgery for more than eight weeks.

The dosimetric parameters are detailed in Table 3. PTV V95% coverage was significantly less in the unilateral arm ($p = 0.035$). The contralateral parotid had a significantly lower mean dose in the unilateral arm ($p < 0.001$). The contralateral eyeball Dmax and the spinal cord Dmax were significantly lower in the unilateral arm ($p < 0.001$).

After a median follow-up of 23 months (minimum 13 months, maximum 37 months), 15 (31.3%) patients developed disease recurrence. There were 8 (30.76%) recurrences in the unilateral arm and 7 (31.81%) in the bilateral arm ($p = 0.591$, chi-square test). Among the 15 recurrences, 7 were in the tumor bed, 5 in the ipsilateral neck, and 3 in both the tumor bed and ipsilateral neck. The median time to recurrence was 9.5 months (range 5–16 months), with time to recurrence being 9.5 and 10 months in the unilateral and bilateral arms, respectively. No recurrence was observed in the contralateral neck during the follow-up period in either of the arms. There were 4 distant failures (lung metastases) during the follow-up period in patients already diagnosed with locoregional failure, thus having no impact on the analysis of DFS. Since the evaluation of distant failure was not part of the study protocol and did not impact the analysis of DFS, they were not included in further analysis. The median disease-free survival (DFS) was 22.5 and 21 months in the unilateral and bilateral arms, respectively. The 2-year disease-free survival (DFS) was 68.2% in the unilateral arm and 72.2% in the bilateral arm. The mean DFS was not significantly different between the two arms (Fig. 3) (Log-rank p-value = 0.959).

Analysis of risk factors contributing to overall recurrence

Among the risk factors for disease recurrence, Depth of Invasion (DOI), delay in starting radiation and low PTV coverage were significant contributing factors (Tab. 4). Patients with DOI of > 10 mm had significantly higher recurrence than DOI of 5–10 mm and ≤ 5 mm (75% *vs.* 21.7% *vs.* 23.5%, $p = 0.014$). Delay in starting radiation of more than 8 weeks significantly impacted the overall disease recurrence, with 57.1% showing recurrence in this group ($p = 0.045$, chi square test). Planning target volume coverage also had a significant impact on disease control. Patients with PTV V95% coverage of less than equal to 90% had significantly higher overall disease recurrence than patients with PTV V95% of more than 90% (50% *vs.* 15.4%, $p = 0.011$). Patients with locoregionally controlled disease had significantly higher PTV V95% than patients with local recurrence ($p < 0.001$). Patients with positive margins had a recurrence in 55.6% of cases versus25.6% with negative margins; however, the association was not significant.

Analysis of risk factors contributing to regional recurrence

All 8 patients with regional failure had N2 nodal disease; however, it was not significant. Patients with a delay in starting radiation of more than 8 weeks had more regional recurrence

in the ipsilateral neck than patients who had their radiation therapy initiated at or before 8 weeks (35.7% vs. 8.8%, p- 0.037, chi-square).

Univariate and multivariate analysis of risk factors and survival

Univariate analysis suggests patients with DOI> 10mm, delay in starting radiotherapy of more than 8 weeks and PTV V95% of less than or equal to 90% had significantly lower median DFS (log-rank test) (**supplementary table 5**). Patients with DOI > 10 mm had a median DFS of 11 months compared to patients with DOI of ≤ 10 mm with a DFS of 22.5 months (p = 0.004, log-rank test). Patients with a delay in starting radiation of more than 8 weeks had a lower median DFS of 15.5 months (p = 0.026, log-rank test). Patients with PTV V95% of more than 90% had 5.5 months improvement in median DFS (p-0.015, log-rank test).Cox multivariate regression analysis also suggested DOI, and delay in starting radiation as significant risk factors (**Supplementary Table 6**).

In terms of regional recurrence, DOI > 10 mm (≤ 10 mm *vs.* >10 mm: 22.5 and 11 months; p = 0.05, log-rank test) and RT delay beyond 8 weeks (≤ 8 weeks vs. > 8 weeks: 24 and 15.5 months; p = 0.024, log-rank test) were potential risk factors for decreased regional recurrence-free survival.

Discussion

Carcinoma of the buccal mucosa is the most commonly involved site of the oral cavity in India, probably due to the widespread use of various forms of oral tobacco, with many cases presenting with locally advanced disease [3, 13]. Adjuvant radiotherapy is indicated for most of these cases and also in cases with intermediate (LVI, PNI) and high risk factors in histopathology specimen (positive margins, ECE) [5, 7–9]. Management of the neck is of utmost importance in the oral cavity and buccal mucosa carcinoma. Even for clinically negative neck, about 25% of patients may have occult nodal metastasis, and 3% may have contralateral nodal metastasis [14, 15]. Elective treatment of the ipsilateral neck in well-lateralized carcinoma of the buccal mucosa is standard; however, recommendations are limited for managing the contralateral neck. Studies have been published for oral cavity carcinoma treating both ipsilateral and bilateral neck; however, comparative data is sparse.

Studies irradiating only the ipsilateral neck in carcinoma oral cavity have reported a contralateral neck nodal failure of 3.4–6% [10, 16, 17]. Among them, Rath et al. had 100% of carcinoma buccal mucosa, and Vergeer et al. had 62% cases with buccal mucosa primary [10,

17]. With 37.9% of patients with stage IV disease, Rath et al. reported a 2-year locoregional control and DFS of 80.9% and 77.4%, respectively [10]. Our study reported a lower 2-year DFS of 68.2% in the unilateral arm, possibly due to all patients being stage IVA disease. Our study also had 25% of patients treated with concurrent chemoradiation. No contralateral nodal failure was reported in the follow-up period.

Studies have reported results of bilateral neck irradiation in oral cavity cancer with 75–100% cases of diagnosed carcinoma of buccal mucosa [18–20]. Contralateral neck treatment rate was 40.8–57%, with 2 of them reporting 5 year DFS of 69–79% and locoregional control of 65–78% [18, 19]. Lai et al. reported contralateral neck failure of 5%. Chien et al., with all patients in stage IV, reported a 3-year DFS of 52.8% and a 3-year contralateral nodal recurrence rate of 15.7% [20].

Only a known study of buccal mucosa comparing unilateral and bilateral neck radiation showed no difference in locoregional control between unilateral and bilateral neck radiation [6]. In the study, 59.3% of patients had stage IV disease, and 82.8% were treated with unilateral radiotherapy. In contrast, all patients in our study had pathological stage IVA disease, and 54% of patients were treated with unilateral radiotherapy. The 5-year DFS for stage IV patients was 60% in the study mentioned above, with a contralateral neck failure of 2.1%.

The role of adjuvant radiotherapy or concurrent chemoradiotherapy in postoperative head and neck carcinoma is primarily based on risk factors described in RTOG 9501 and EORTC 22931 [5, 8, 9]. Carcinoma of the oral cavity constitutes only 30% and 24% in each arm of Cooper et al. and 26% in Bernier et al. [5, 8]. However, the same risk factors derived from the Bernier and Cooper study are accepted globally for treating buccal mucosa cancers. Various studies of oral cavity carcinoma and buccal mucosa have reported risk factors for poor disease control. OCAT study treated postoperative locally advanced oral cavity cancers with adjuvant concurrent chemoradiation, accelerated radiation, and standard fractionation radiotherapy. They reported no benefit with concurrent chemoradiation over other arms [21].

Among the risk factors for locoregional recurrence evaluated in our study, depth of invasion (DOI), delay in starting radiation beyond 8 weeks and PTV V95% coverage of less than or equal to 90% were significant. However, only DOI and delay in starting radiation were significant factors for poor DFS in multivariate analysis. All patients with regional failure had pathological N2 disease. Delay in starting radiation beyond 8 weeks also led to poor regional

recurrence-free survival. Risk factors for locoregional control reported in studies are skin invasion, N classification, ECE, positive and close margins, tumor thickness > 10 mm, high grade, positive nodes, and delay in starting radiation beyond 30 days [19, 22, 23]. Rath et al. suggested the nodal stage as a significant risk factor for locoregional control and DFS [10].

The risk of contralateral neck metastasis in well-lateralized buccal mucosa cancer with a clinically negative contralateral neck is relatively low. The incidence of contralateral nodal metastasis in oral cavity cancer varies from 0.9 to 36% [24]. Studies addressing this issue have tried discovering factors associated with contralateral neck metastasis [12, 20]. M Mair et al. stated that skin involvement and ipsilateral nodal metastasis are predictors of contralateral neck involvement in carcinoma buccal mucosa [12]. Rath et al. reported a 2-year contralateral nodal recurrence rate of 3.4%, the risk factors being positive nodal status and high nodal burden [10]. Vergeer et al. suggested the number of lymph node metastases as the only risk factor for contralateral nodal control [17]. Chein et al. reported contralateral lymph node recurrence rate in patients in stage IVA–B well lateralized oral cavity cancer of buccal mucosa, retromolar trigone, and gingiva, of which 50 (41.7%) were carcinoma of buccal mucosa [20]. 3-year contralateral neck failure was 15.7%, with positive nodal metastasis and PNI being a significant risk factor for contralateral failure. For early-stage well lateralized oral cavity carcinoma treated with ipsilateral neck radiation, Liu et al. reported no significant risk factors for contralateral nodal metastasis [16]. Our study did not report any contralateral nodal metastasis; thus, risk factors could not be identified.

Overall, our study reported good locoregional control with both unilateral and bilateral radiation treatment comparable to the abovementioned studies. It is probably the second study comparing unilateral and bilateral neck radiation of stage IVA postoperative buccal mucosa patients. The other study, however, had 82.8% of patients treated with unilateral radiation, and 59.3% had stage IV disease.

Our study had several limitations like small sample size, short follow-up duration, and treatment decisions being made at individual physicians' discretion rather than by study protocol. Since it is a retrospective cohort study, various data like complete toxicity profiles were unavailable apart from the obvious selection bias. Moreover, this study included patients treated with cobalt 60 using rectangular fields. However, this data on conventional treatment outcomes has enabled us to answer the question regarding the need for a contralateral neck unambiguously. Thus it may be inferred from our results that bilateral neck

radiation does not give an additional advantage over ipsilateral neck radiotherapy for locoregional control in a highly lateralized primary like buccal mucosa, even for advanced stages.

Conclusion

Bilateral neck radiation does not provide any advantage over ipsilateral neck radiation for properly selected well lateralized buccal mucosal squamous cell carcinoma, and thus, ipsilateral neck nodal irradiation is enough for such primaries. Moreover, ipsilateral neck radiation facilitates better sparing of organs at risk. Thus standard radiotherapy treatment plan for well lateralized buccal mucosa primaries should include ipsilateral tumor bed and neck only.

Conflict of interest

No conflict of interest.

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Table 1. Patient characteristics and tumor characteristics in the study population

	Unilateral field arm (n = 26)	**Bilateral field arm (n = 22)**	**p-value**
Mean age	52.6 years	50 years	
Sex			
Male	21 (80.8%)	20 (90.9%)	0.284
Female	5 (19.2%)	2 (9.1%)	
Addiction			
No addiction	10 (38.5%)	3 (13.6%)	***0.05***
Tobacco + alcohol	16 (61.5%)	19 (86.4%)	
ECOG PS			
0–1	25 (96.2%)	22 (100%)	0.542
2	1 (3.8%)	0 (0%)	
Histopathology			
Squamous cell carcinoma	100%	100%	
Differentiation			
Well-differentiated	11 (42.3%)	11 (50%)	0.404
Moderately differentiated	15(57.7%)	11 (50%)	
T stage			
T2	10 (38.5%)	12 (54.5%)	0.5
T3	10 (38.5%)	7 (31.8%)	
T4	6 (23.1%)	3 (13.6%)	
N stage			
N0	2 (7.7%)	1 (4.5%)	0.361
N1	2 (7.7%)	0 (0%)	
N2	22 (84.6%)	21 (94.5%)	

AJCC stage			
Stage IVA	26 (100%)	22 (100%)	
DOI [mm]			
≤ 5	9 (36.4%)	8 (36.4%)	0.87
> 5 – ≤ 10	12 (46.2%)	11 (50%)	
> 10	5 (19.2%)	3 (13.6%)	
Postoperative margins			
Positive	4 (15.4%)	5 (22.7%)	0.389
Negative	22 (84.6%)	17 (77.3%)	
Bone involvement			
Involved	1 (3.8%)	2 (9.1%)	0.436
Not involved	25 (96.2%)	20 (90.9%)	
Node dissected			
< 12 nodes	8 (30.8%)	9 (40.9%)	0.464
≥ 12 nodes	18 (69.2%)	13 (59.1%)	
Node positivity			
Node negative	2 (7.7%)	1 (4.5%)	0.257
≤ 5 nodes positive	23 (88.5%)	17 (77.3%)	
5 or more nodes positive	1 (3.8%)	4 (18.2%)	

ECOG PS — Eastern Cooperative Oncology Group Performance Status; DOI — Depth of Invasion; AJCC — American Joint Committee on Cancer; T stage — Tumour stage; N stage — nodal stage

Table 2. Treatment details in the study population

	Unilateral field arm (n = 26)	**Bilateral field arm (n = 22)**	**p-value**
Primary surgery			
WLE	9 (34.6%)	8 (36.4%)	NA
WLE + mandibulectomy	15 (57.7%)	14 (63.6%)	
Others	2 (7.7%)	0 (%)	
Neck dissection			
RND	1 (3.8%)	1 (4.5%)	0.705
MRND	19 (73.1%)	18 (81.8%)	
SOND	6 (23.1%)	3 (13.6%)	
Total radiation dose [Gy]			
60	22 (84.6%)	18 (81.8%)	0.548
66	4 (15.4%)	4 (18.2%)	
Duration of treatment [weeks]			
Up to 6	21 (80.8%)	18 (81.8%)	NA
Up to 7	5 (19.2%)	3 (13.6%)	
More than 7	0	1(4.5%)	
Concurrent chemotherapy			
Yes	7 (26.9%)	5 (22.7%)	0.502
No	19 (73.1%)	17 (77.3%)	
Delay in initiating radiation post-surgery [weeks]			
2–4	6 (23.1%)	3 (13.6%)	0.118

> 4 – ≤ 8	10 (38.5%)	15 (68.2%)	
> 8	10 (38.5%)	4 (18.2%)	

WLE — wide local excision; RND — radical neck dissection; MRND — modified radical neck dissection; SOND — supra omohyoid neck dissection; NA — not applicable

Table 3. Dosimetry of the target and the organ at risks

	Unilateral arm	**Bilateral arm**	p-value(unpaired t-test)
PTV V95% (%)	89.19 ± 2.30	90.34 ± 1.27	**0.035**
Parotid mean [Gy]			
Ipsilateral	62.28 ± 1.69	42.58 ± 1.57	< **0.001**
Contralateral	13.20 ± 2.49	40.25 ± 3.35	< **0.001**
Spinal cord Dmax [Gy]	39.45 ± 6.76	48.37 ± 2.06	< **0.001**
Eye Dmax [Gy]			
Ipsilateral	40.22 ± 6.23	38.18 ± 3.31	0.17
Contralateral	16.56 ± 2.53	32.12 ± 3.37	< **0.001**

PTV V95% — volume of planning target volume receiving at least 95% dose; Dmax — maximum point dose

Table 4. Relation of disease recurrence with risk factors

Risk factors	**Recurrent disease (15)**	**Loco regionally controlled disease (33)**	**p-value**
Mean age	53.46 ± 10.17	50.54 ± 12.33	0.39
Age group			
≤ 40 years	3 (20%)	12 (80%)	0.215
> 40 years	12 (36.4%)	21 (63.6%)	
Sex			
Male	13 (31.7%)	28 (68.3%)	0.622
Female	2 (28.6%)	5 (78.4%)	
Addiction history			
Yes	12 (34.3%)	23(65.7%)	0.354
No	3 (23.1%)	10 (76.9%)	
T stage			
T1–T3 disease	12 (30.8%)	27 (69.2%)	0.585
T4 disease	3 (33.3%)	6(66.7%)	
N stage			
N0, N1	0	5 (100%)	0.139
N2	15 (34.9%)	28 (64.1%)	
Number of nodes positive			
Node negative	0	3 (100%)	0.456
Less than 5 nodes positive	13 (32.5%)	27 (67.5%)	

5 or more nodes positive		2 (40%)	3 (60%)	
Differentiation				
Well-differentiated		7 (31.8%)	15 (68.2%)	0.938
Moderately differentiated		8 (30.8%)	18 (69.2%)	
DOI [mm]				
≤ 5		4 (23.5%)	13 (76.5%)	**0.014**
> 5 – ≤ 10		5 (21.7%)	18 (78.3%)	
> 10		6 (75%)	2 (25%)	
Margin status				
Positive		5 (55.6%)	4 (44.4%)	0.092
Negative		10 (25.6%)	29 (74.4%)	
Bone involvement				
Involved		2 (66.7%)	1 (33.3%)	0.227
Not involved		13 (28.9%)	32 (71.1%)	
Type of surgery				
WLE		5 (29.4%)	12 (70.6%)	0.838
WLE + mandibulectomy		9 (31%)	20 (69%)	
Others		1 (50%)	1 (50%)	
Delay in starting radiation [weeks]				
2–4		2 (22.2%)	7 (77.8%)	**0.045**
> 4 – ≤ 8		5 (20%)	20 (80%)	
> 8		8 (57.1 %)	6 (42.9%)	
Concurrent chemotherapy	Yes	6 (50%)	6 (50%)	0.106
	No	9 (25%)	27 (75%)	
PTV V95%				
≤ 90%		11 (50%)	11(50%)	0.011
> 90%		4 (15.4%)	22 (84.6%)	
Mean PTV V95%		*87.98 ± 2.49*	*90.57 ± 0.97*	***< 0.001***

DOI — depth of invasion; WLE — wide local excision; PTV V95% — volume of planning target volume receiving 95% of prescribed dose

Supplementary File

Table S1. Univariate analysis of risk factors for disease-free survival

Risk factors	**median DFS (in months)**	**p-value (log rank test)**
Sex		
Male	20	0.886
Female	24	
Addiction		
No	20	0.448
Yes	22	
T stage		
T1–3	24	0.980

T4	20	
N stage		
N0, N1	24.5	0.142
N2	20	
Number of nodes positive		
< 5 or node-negative	20	0.745
≥ 5	17	
DOI [mm]		
≤ 10	22.5	**0.004**
> 10	11	
Margin status		
Negative	22	0.212
Positive	15	
Bone involvement		
No	20	0.154
Yes	15	
RT delay [weeks]		
≤ 8	24	**0.026**
> 8	15.5	
Concurrent CT		
Yes	17.5	0.093
No	22	
PTV V95%		
≤ 90%	17	**0.015**
> 90%	22.5	

DOI — depth of invasion; RT delay — radiotherapy delay; DFS — disease-free survival; PTV V95% — volume of planning target volume receiving 95% of prescribed dose

Table S2. Cox multivariate proportional hazard ratio for analysis of disease-free survival

Covariates	**df**	**Hazard ratio**	**p-value**
RT delay (> 8 weeks *vs*. ≤ 8 weeks)	1	1.094	**0.05**
PTV V95% (≤ 90% *vs*. > 90%)	1	3.404	0.076
DOI (≤ 10 mm *vs.* >10 mm)	1	3.181	**0.024**

DOI — depth of invasion; df — degree of freedom; PTV V95% — volume of planning target volume receiving 95% of prescribed dose

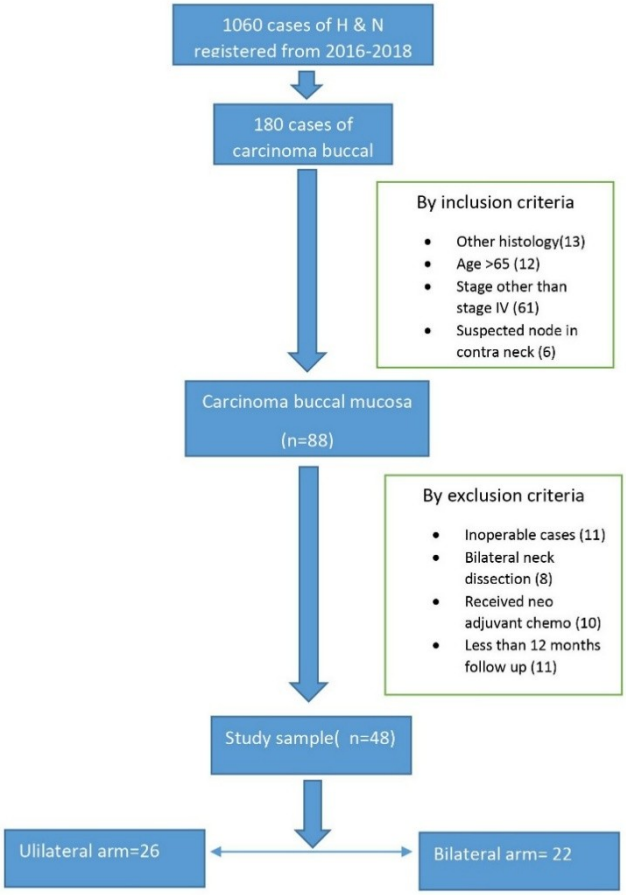

Figure 1. Diagram representing sample selection and distribution between the treatment arms

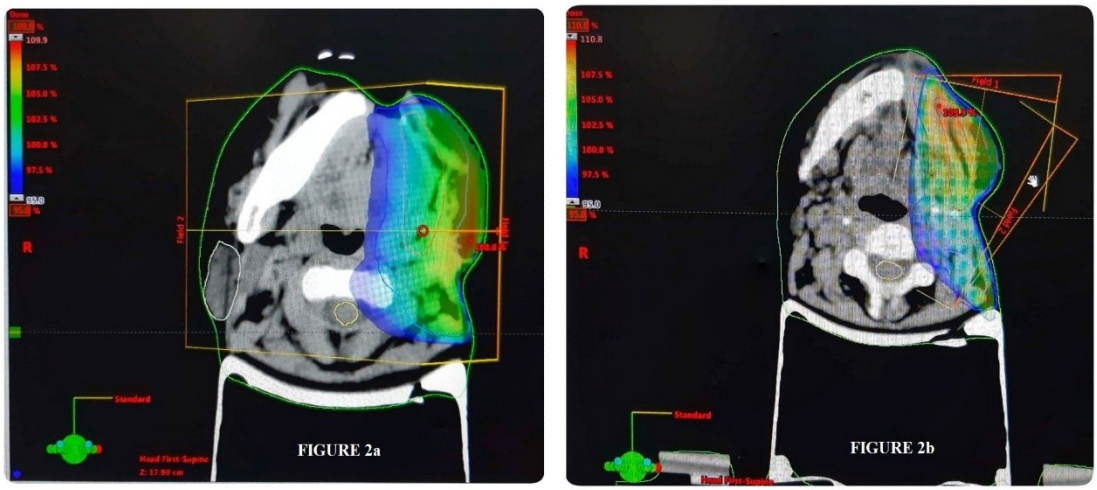

Figure 2. A. Treatment with weighted parallel opposed fields; **B.** Treatment with wedge pair for unilateral radiation

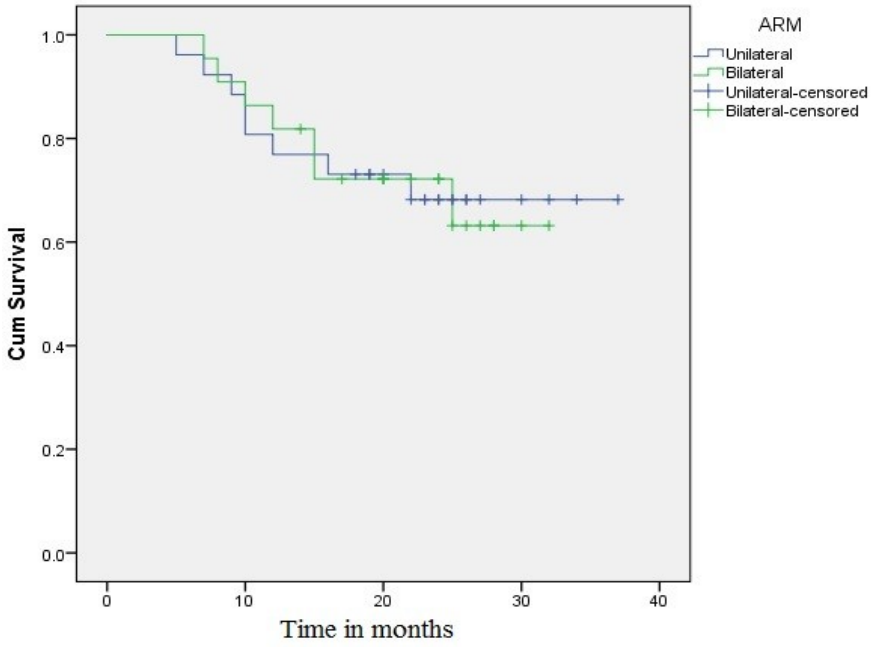

Figure 3. Kaplan Meier Curve showing disease-free survival between the treatment arms. Blue — unilateral arm; Green — bilateral arm