Case Series of Hybrid Brachytherapy followed by Intensity Modulated Radiation Therapy (HyBIRT) Technique for the Definitive Management of Tongue Squamous Cell Carcinoma (TSCC)

Muhamad Yusri Musa
Advanced Medical & Dental Institute, Universiti Sains Malaysia

Gokula Kumar Appalanaido (✉ gokula@usm.my)
Advanced Medical & Dental Institute, Universiti Sains Malaysia

Ewe Seng Ch'ng
Advanced Medical & Dental Institute, Universiti Sains Malaysia

Syadwa Abdul Shukor
National University Cancer Institute

Eu Chong Soon
Hospital Universiti Sains Malaysia

Siti Noor Fazliah Mohd Noor
Advanced Medical & Dental Institute, Universiti Sains Malaysia

Ahmad Naqiuddin Azahari
Advanced Medical & Dental Institute, Universiti Sains Malaysia

Siti Hajariah Kamaruddin
Advanced Medical & Dental Institute, Universiti Sains Malaysia

Nor Hafizah Ishak
Advanced Medical & Dental Institute, Universiti Sains Malaysia

Mohd Zahri Abdul Aziz
Advanced Medical & Dental Institute, Universiti Sains Malaysia

Jasmin Jalil
Advanced Medical & Dental Institute, Universiti Sains Malaysia

Research Article

**Keywords:** Tongue cancer, interstitial brachytherapy, external beam radiotherapy, Intensity Modulated Radiation Therapy, HyBIRT

**Posted Date:** July 25th, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1886453/v1

**License:** ☭  This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Introduction

The Hybrid Brachytherapy followed by Intensity Modulated Radiation Therapy (HyBIRT) technique reverses the commonly used sequence by delivering high dose rate interstitial brachytherapy (HDRIBT) first followed by IMRT in the management of tongue squamous cell carcinomas (TSCC).

Materials and methods

Eleven patients treated with 20Gy in 5 fractions HDRIBT to TSCC followed by definitive IMRT to 69.96Gy to the involved nodes; 61.71Gy to the high risk volume and 56.1Gy to the low risk volume over 33 fractions in a single institution were analyzed retrospectively.

Results

All 11 patients achieved clinical complete response (cCR) and 9 patients with available radiological imaging achieved radiological complete response (rCR) at the primary site. One year locoregional progression-free survival was 90% (95% CI: 73.2% – 100%) and 18-month disease-free survival (DFS) for 8 patients who achieved rCR was 66.7% (95% CI: 30% – 100%). Median times to cCR and rCR at the primary site were 3.91 months and 4.34 months, respectively. Seven out of 8 patients with nodal disease achieved rCR of the nodes with a median time for rCR of 4.58 months. Two patients had persistent ulcer at 8 months and 11 months of follow-up.

Discussion

HyBIRT technique has the advantage of easy tumor identification during HDRIBT applicator insertion, ability to maneuver the subsequent IMRT plan and reduced the overall treatment time (OTT) while delivering tumoricidal dose to gross disease. Studies with larger sample size are needed to further confirm the efficacy of this organ sparing technique.

Introduction

While upfront surgery is considered the standard of care for patients with early and some selected locally advanced non-metastatic tongue squamous cell carcinoma (TSCC), the local control (LC) rate of organ sparing approach that incorporates interstitial brachytherapy (IBT) is not inferior [1]– [6]. External beam radiotherapy (EBRT) as single modality in definitive setting for oral tongue squamous cell carcinomas (TSCC) showed poor outcomes in many studies and only with the incorporation of IBT to EBRT and/or neck dissection, the LC rate and overall survival (OS) matched the surgical series [1]– [3], [5], [7]–[9]. The likely explanation for this phenomenon is that insufficient dose of radiation was delivered to the local tumor in the tongue due to daily variation of tongue position and variation in the surrounding structures leading to EBRT dose uncertainties. The EBRT technique used in these combined EBRT and IBT studies are either 2-dimensional radiotherapy (2D-RT) or 3-dimensional conformal radiotherapy (3D-CRT).

LC rate in surgical series depends on adequate resection margin and this corresponds to the amount of tongue tissue that needs to be excised [10], [11]. On the other hand, functional outcome depends on the residual tongue tissue that is left behind following excision. Hence, for larger tongue lesions and those involving floor of mouth, IBT offers an alternative modality of organ preservation with reasonably good functional outcomes [10]– [14]. Published tongue brachytherapy
series used uniform sequence of EBRT followed by either low-dose-rate (LDR) or high-dose-rate interstitial brachytherapy (HDRIBT) to the residual TSCC, with a significant number of patients being subjected to salvage neck dissection after the EBRT for persistent disease in the neck [15] – [18]. Recent series in the definitive EBRT setting showed 3- to 10-year regional nodal control rates in the range of 77.1 - 78% for head and neck squamous cell carcinomas (HNSCC) without planned neck dissection [9], [19]. IBT on the other hand gives a good LC rate of 80 – 100% at 2 years for T1-T3 disease, and 94% at 5 years to the primary site in TSCC [5], [6]. Hence the combination of IBT and EBRT is a double prong approach to achieve complete response of the local disease in the tongue and at the same time to have a good regional control in the neck without planned or salvage neck dissection.

While HDRIBT for TSCC can be delivered before or after EBRT, most of the published series used HDRIBT in the latter. Due to the technical issues associated with the sequence of EBRT followed by HDRIBT that will be detailed later, at ***** institute we reversed the common sequence by performing upfront definitive or adjuvant HDRIBT followed by Intensity modulated radiation therapy (IMRT) with or without concurrent chemotherapy to the neck and primary tumor/surgical bed since 2019. In this manuscript, we report our first eleven patients who were successfully treated with upfront HDRIBT to the TSCC followed by definitive chemoradiotherapy with IMRT technique.

With six patients being recurrence free and having a good functional outcome at 1 year, this reversed order of using adaptive IMRT to the earlier IBT dose distribution is a technique worth considering in the organ-sparing approach for patients with TSCC. To our best knowledge and after extensive literature search, this is the first publication of its kind that described this method of Hybrid Brachytherapy followed by adoptive Intensity Modulated Radiation Therapy (HyBIRT). The rationale for such a sequencing of upfront brachytherapy followed by chemo-IMRT is presented in this manuscript.

**Methods And Materials**

1. **Patient characteristics**

All TSCC patients referred for tongue brachytherapy are seen in combined clinic consisting of head and neck surgeon and radiation oncologist. Tumor dimension mapping, brachytherapy technical assessment and number of applicators needed is estimated.

Inclusion criteria:

1. Tumor limited to anterior 2/3 tongue.
2. Unable to undergo surgery for various reason.
3. ECOG PS 0-2
4. Histologically confirmed squamous cell carcinoma

Exclusion criteria:

1. Tumor involving the posterior 1/3 tongue, cortical bone involvement.
2. Radiologically confirmed metastatic disease (M1)
3. Contraindication for nasal intubation
4. ECOG PS 3-4
A total of 11 patients fulfilled the criteria above, gave informed consent and underwent the procedure after detailed explanation of the technique, the likely toxicity, possible outcome and the risk and benefits.

2. Implantation technique:

All patients had dental evaluation and customized mandible protector made from certified orthodontic resin (Linguobite©) is constructed at least 3 days before the procedure. Applicators were inserted in the operating room using aseptic technique and performed under general anaesthesia with nasal intubation. nucletron single side 6 French buttoned Comfort Cath Brachytherapy applicators (Nucletron, Veenendaal, the Netherlands) were inserted via submental region with buttons on the dorsum of the tongue and applicators fixed at the submental region. The applicators were placed at 1.5 cm equidistance covering the clinically visible or palpable tumor whilst ensuring that furthest applicators in the surrounding tissue was within 5mm from the tumor edge (Figure 1). Total number of applicators used range from 5 – 11.

3. Treatment planning, dose-prescription, and treatment delivery

a. Brachytherapy

Contrast-enhanced tumor was contoured as gross tumor volume (GTV-P). The guiding tubes/applicators were identified and reconstructed using the Oncentra Masterplan V 5.0 (Nucletron BV, Veenendaal, the Netherlands) brachytherapy Treatment Planning System (TPS) (Figure 2A) with inverse planning capability. A dose of 4Gy in 5 fractions, treating twice daily was prescribed to cover the entire GTV-P while ensuring that 90% of GTV-P (D90) receive at least 25Gy in 5 daily fractions. The dose to the target was modulated by maneuvering the ‘dwell time’ and ‘dwell position’ to ensure the target coverage while limiting the dose to the mandible. The high dose region within GTV, defined as 200% of the prescribed dose was limited to less than 20% where possible without compromising the target coverage. The treatment plan was executed with Ir-192 remote afterloader HDR brachytherapy system. Applicators were removed immediately after completing the 5 fractions of brachytherapy.

b. Adoptive IMRT

IMRT was started within a week of completing the HDRIBT. Following applicators removal, patient was immobilized and CT simulated again with intravenous contrast from vertex to carina as per the standard IMRT protocol in the department. Treatment planning was performed with the Monaco TPS version 5.1 (Elekta CMS, Maryland Heights, MO, USA). The earlier CT-based HDRIBT dosimetric plan was fused and the area of 25Gy isodose volume in the HDRIBT was contoured. The OARs were contoured as per standard head and neck IMRT protocol while the involved nodes were contoured as the GTV-N (Figure 2B). Additional margins were applied to the GTV-N to create the clinical target volume (CTV$_{GTV-N}$) and planning target volume (PTV$_{GTV-N}$) that is prescribed a dose of 69.96Gy in 33 fractions. The high risk (CTV$_{HR}$ and PTV$_{HR}$) and low risk (CTV$_{LR}$ and PTV$_{LR}$) nodal volumes were also created based on the RTOG head and neck contouring atlas and prescribed a dose of 61.71Gy and 56.1Gy in 33 fractions respectively. The high risk areas include the ipsilateral level I and level II nodal region, the involved nodal region, 1 echelon below the involved nodal region, ipsilateral floor of the mouth, gingiva and as well as gingivo-buccal sulcus. The brachytherapy prescription isodose volume which corresponds to the pre-brachytherapy GTV-P (20Gy in 5 fractions) and ipsilateral hemi-tongue received 59.4Gy in 33 fractions. The remaining ipsilateral or contralateral nodal region, the entire tongue and uninvolved floor of mouth received elective dose of 56.1Gy in 33 fractions. A hard constraint of 63Gy was applied to the corresponding 25Gy HDRIBT isodose volume during the IMRT inverse planning process. In 4 patients, the high-risk volume was also extended to the contralateral tongue based on the
pre-brachytherapy GTV-P in MRI images with a margin. The cumulative 2Gy per fraction equivalent dose (EqD2) for alpha beta value of 10 (a/b = 10) for both HDRIBT and IMRT was ensured to be >85Gy to the D90 of primary tumor (GTV-P).

All but one patient received 6 cycles of single agent weekly Cisplatinum 40mg/m² concurrent with the IMRT.

4. Follow-up and statistical analysis

Patients were first reviewed at 2 weeks after completion of HyBIRT technique followed by monthly follow up for the first year. Patients were evaluated for recurrence both clinically and radiographically using CT or PET CT when indicated. Progression free survival (PFS), disease free survival (DFS) and response rate were calculated from the date of IBT. The statistical analysis about were calculated according to the Kaplan-Meier method. Statistical analyses were performed using STATA ver.9.0 software.

Results

Patient characteristics

Eleven patients consisting of 5 males and 6 females with TSCC were treated with HyBIRT technique in our institution from January 2019 till January 2021. The mean age was 49 years old (range 20-71). All tumors were histologically confirmed; all of them squamous cell carcinoma. The overall treatment time (OTT) defined as duration from the first fraction of brachytherapy until the last fraction of the IMRT range from 56 – 63 days for 10 out of 11 patients. For one patient, the OTT dragged to 74 days as he suddenly developed from post-covid19 related organizing pneumoniae after completing the 5 fractions of brachytherapy. Patient and disease characteristics, overall treatment time and indication for HyBIRT technique is presented in table 1. Patient refusing surgery, unfit for radical surgery and limited availability of operation theatre time during Covid-19 pandemic are the indications for HyBIRT.

Clinical Outcomes

a. Locoregional progression-free survival and disease-free survival

1 out of 11 patients had progression disease during follow up and died of disease. The 12-month locoregional progression-free survival was 90% (95% CI: 73.2%-100%) (Figure 3A). 8 patients achieved radiological complete response (cCR) at primary site and nodes after treatment. These 8 patients were followed up for disease-free survival and one of them developed distant metastasis. The 18-month disease-free survival for these 8 patients was 66.7% (95% CI: 30%-100%) (Figure 3B).

b. Response Rate

All 11 patients achieved clinical complete response (cCR) at the primary site. The median time to cCR for the primary site was 3.91 months. 9 of 11 patients were available for radiological evaluation for rCR. All 9 patients achieved rCR at the the primary site. The median time to rCR for the primary site was 4.34 months (Figure 3c). 8 patients had nodal disease at presentation and 7 of them attained rCR at nodes. 1 patient had progressive disease at the node and died of disease. The median time to rCR for nodes was 4.58 months (Figure 3d).

Toxicity

All patients complete the scheduled treatment of HDR-IBT and IMRT. The most common CTCAE 5.0 grade 2 or more early toxicity is mucositis oral, dry mouth, dysphagia and altered taste. In 7 out of 8 patients, these early toxicities resolved to grade 1 by 6 months after treatment completion. However, grade 1 dry mouth and dysarthria which developed much later.
after completing the IMRT tend to persist even at 2 years of follow up. A 71-years old patient unfortunately died immediately after completing IMRT due to uncorrected dehydration that caused cerebral oedema and irreversible brain injury. This patient had complete clinical response of the TSCC at the primary site on the last follow-up. Two patients had persistent ulcer at 8 months and 11 months of follow-up, with one of them needing secondary suturing. Both these patients also had multiple biopsies and radiological assessment to rule out recurrence while on follow-up for the non-healing ulcer which turned out negative for malignancy. Treatment related toxicity which was recorded based on the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 scoring on each follow-up is summarized in table 2.

**Discussion:**

For resectable TSCC, upfront surgery with or without adjuvant radiotherapy is considered the standard of care in many centres especially for the mobile tongue since the historical outcomes with definitive EBRT alone had been poor [20], [21]. Organ preservation approach using the IBT with or without EBRT has shown comparable or better LC rate than many of the published surgical series [5], [6], [22], [23]. Functional outcomes are also better with organ preserving approach compared to surgery [10], [13], [14]. At current there is a trend towards addressing the neck either by surgery and/or EBRT in most patients with TSCC as the rate of lymph node metastasis is high even in clinically N0 [12], [24]–[27]. Given the high control rate in the neck when optimal radiation dose is delivered, there is a strong reason to consider definitive IMRT to neck in addition to IBT as a double prong approach to control the primary TSCC and the involved neck nodes [9], [19].

The tongue IBT program in our center was initially started with definite HDRIBT, followed by planned neck dissection and further EBRT to the neck for patients with high risk of recurrence (e.g. N2 disease and extra capsular extension of the lymph nodes in the surgical specimen). A few patients were also treated with upfront EBRT to primary TSCC and neck followed by neck dissection in-case of persistent node/s and HDRIBT boost to the residual tumor in the tongue. There were many issues encountered with this complex sequencing and thus we indigenously developed a hybrid technique of upfront HDRIBT, followed by adoptive IMRT to the earlier brachytherapy dose distribution. Using this approach since early 2019, we managed to ensure that definitive dose of radiation is given to the gross tumor volume (GTV-P) at the primary site in tongue and to regional nodes in the neck (GTV-N). The benefits of this reserved order of IBT first before EBRT (the HyBIRT technique) is summarized in Table 3.

<table>
<thead>
<tr>
<th><strong>Table 3</strong></th>
<th>Comparison between the HyBIRT approach and EBRT-first sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HyBIRT (HDRIBT followed by IMRT)</strong></td>
<td><strong>EBRT followed by HDRIBT</strong></td>
</tr>
<tr>
<td>Patients more receptive to the subsequent IMRT after HDRIBT induced tumor shrinkage.</td>
<td>Patients traumatized by EBRT toxicity may refuse further HDRIBT boost.</td>
</tr>
<tr>
<td>Easier to identify the GTV and tumor induration during the IBT applicator insertion.</td>
<td>Risk of “geographical miss” in HDRIBT.</td>
</tr>
<tr>
<td>IMRT isodose coverage can be “molded” to the earlier HDRIBT dose distribution.</td>
<td>Limited capability of HDRIBT to “mold” the dose distribution to conform the preceding EBRT.</td>
</tr>
<tr>
<td>Better sparring of parotid glands with the use of IMRT.</td>
<td>Limited capacity HDRIBT to compensate for IMRT dose non-uniformity within the target hence 3D-CRT technique is used.</td>
</tr>
<tr>
<td>Tumoricidal dose of radiation is delivered to the involved neck node/s and high area with IMRT.</td>
<td>EBRT dose is limited to 40Gy – 54Gy in 20–27 to prevent overdose to subsequent HDRIBT overlap region.</td>
</tr>
<tr>
<td>May wait up to 6 months before subjecting the patient to salvage neck dissection.</td>
<td>Immediate salvage surgery for persistent neck node/s after sub-optimal dose of EBRT.</td>
</tr>
<tr>
<td>IMRT started immediately after the HDRIBT, reducing the risk of tumor repopulation.</td>
<td>Planned or salvage neck dissection after EBRT will prolong the OTT.</td>
</tr>
</tbody>
</table>
With the immediate improvement in local symptoms associated with tumor shrinkage after HDRIBT, patients’ are more receptive to the subsequent IMRT. Furthermore, the peak of acute toxicity after the short course of 5 daily fractions of HDRIBT has not set in when EBRT is commenced. An inflamed oral and nasal mucosa after EBRT may also increase the risk of traumatic injury during nasal intubation. HyBIRT technique compresses the overall treatment time (OTT) to 8 weeks compared to 12–13 weeks for most published studies. This reduced OTT is likely to have a positive impact on avoiding tumor repopulation.

A common issue encountered by the brachytherapist performing IBT for tongue is the difficulty in identifying the target volumes intra-operatively [28]. Ideally, applicators should be placed at equidistance, with the most distal applicators located at the posterior, medial and anterior edges of tumor. After a gap of 4 weeks of completing EBRT or awaiting the wound healing after neck dissection, there is a high chance that the primary tumor may have shrunk significantly or in clinical complete resolution making clinical identification of the target volume difficult. These areas may still contain microscopic subclinical disease and hence the “geographical miss” with HDRIBT. Placing applicators upfront as in the HyBIRT technique increases the confidence levels of the brachytherapist in achieving good target coverage and avoiding the “geographical miss”.

With the advent of IMRT, tumoricidal dose of radiation can be delivered to the gross tumor while minimizing the dose to organs at risk, and hence improving LC or LRC rates. By performing the IBT upfront and superimposing the IBT plan with the subsequent IMRT plan, we managed to control and limit the dose to overlap areas with IMRT dose painting method in the treatment planning process while ensuring good coverage especially to the ipsilateral level Ia and Ib which are the most frequently involved node/s in TSCC [24]. In contrast, “molding” the HDRIBT dose distribution in a reverse of this process with EBRT first is limited to dwell time and dwell position of the source and the optimal placement of the brachytherapy applicators.

Another issue noted in the published upfront EBRT series is the need for planned neck dissection which is usually done before IBT because of the lower dose of EBRT in the range of 40Gy – 50Gy used to address the neck. Since these doses are known to be sub-optimal in addressing the gross disease, patients with residual or new neck nodes after EBRT are subjected to neck dissection. However, a significant proportion of the post-operative surgical specimen showed complete tumor resolution in the nodes which indirectly points to the fact that many patients were subjected to unnecessary surgery [3]. Recent studies have shown that complete tumor resolution after radiotherapy can take up to 6 months and this approach of watchful waiting can only be implemented if optimal doses are delivered to the nodes [29]. On top of improving the tumor control probability (TCP) with IMRT dose escalation, there is also better sparing of the normal structures such as parotids and mandible with the HyBIRT technique employing both IBT and adoptive IMRT [30].

**Conclusion**

Historically the local control rate at the primary site for TSCC has been poor with definitive radiotherapy alone, most likely due to the insufficient dose received, unlike the involved neck nodes. HyBIRT technique reversed the commonly used sequence by giving HDRIBT first followed by definitive dose of IMRT to the primary site and the neck. The subsequent adoptive IMRT technique enabled the dose maneuvering according to the earlier HDRIBT isodose distribution. This technique showed a good outcome in our first 9 surviving patients in terms of disease control, toxicity profile and functional outcomes. Despite the limitation on follow-up period and relatively small sample size of this study, HyBIRT technique should be seriously considered as the preferred technique in the organ sparing approach for TSCC.

**References**


Tables 1 And 2
<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Smoker</th>
<th>Comorbidities</th>
<th>ECOG</th>
<th>HPE</th>
<th>Stage (TNM 7)</th>
<th>HyBIRT indication</th>
<th>OTT (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>No</td>
<td>DM, HPT, Cervical spondylosis</td>
<td>1</td>
<td>WD SCC</td>
<td>Lt mid-ant-lat, &lt;5mm from midline, involved FOM. [3 x 4]</td>
<td>T4aN2M0 (Stage IVA)</td>
<td>Cervical spondylosis</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>F</td>
<td>No</td>
<td>HPT</td>
<td>1</td>
<td>MD SCC</td>
<td>Rt mid-lat, &lt;5mm from midline. [3 x 3]</td>
<td>T2N2cM0 (Stage IVA)</td>
<td>Refused surgery</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>F</td>
<td>No</td>
<td>-</td>
<td>1</td>
<td>WD SCC</td>
<td>Lt mid-post-lat, touching midline, involved FOM. [3.5 x 4.3]</td>
<td>T4aN2M0 (Stage IVA)</td>
<td>refused surgery</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>M</td>
<td>Yes</td>
<td>-</td>
<td>1</td>
<td>MD SCC</td>
<td>Lt mid-post-lat, involved FOM. [3 x 4.5]</td>
<td>T4aN1M0 (Stage IVA)</td>
<td>refused surgery</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>F</td>
<td>No</td>
<td>DM, HPT, BA</td>
<td>1</td>
<td>MD SCC</td>
<td>Lt mid-lat, involved FOM. [1.5 x 3.5]</td>
<td>T4aN0M0 (Stage IVA)</td>
<td>unfit for surgery</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>F</td>
<td>No</td>
<td>-</td>
<td>1</td>
<td>MD SCC</td>
<td>Lt mid-ant-lat, touching midline, involved FOM. [3.5 x 4.2]</td>
<td>T4aN2bM0 (Stage IVA)</td>
<td>refused surgery</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>F</td>
<td>No</td>
<td>-</td>
<td>1</td>
<td>MD SCC</td>
<td>Lt mid-ant-lat, involved FOM. [3.5 x 4.0]</td>
<td>T4aN0M0 (Stage IVA)</td>
<td>refused surgery</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>M</td>
<td>Yes</td>
<td>HPT, Gout</td>
<td>1</td>
<td>MD SCC</td>
<td>Lt mid-ant-lat. &lt;5mm from midline, [2.0 x 4.3]</td>
<td>T3N0M0 (Stage III)</td>
<td>refused surgery</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>F</td>
<td>No</td>
<td>Scizophrenia</td>
<td>1</td>
<td>MD SCC</td>
<td>Rt mid-ant-Lat. &lt;5mm from midline, [2.2 x 4.5]</td>
<td>T3N2M0 (Stage IVA)</td>
<td>Covid-19 pandemic</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>M</td>
<td>No</td>
<td>-</td>
<td>1</td>
<td>WD SCC</td>
<td>Rt mid-post-lat. &lt;5mm from midline, involved FOM [5.2 x 2.2]</td>
<td>T4aN1M0 (Stage IVA)</td>
<td>refused surgery</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>M</td>
<td>No</td>
<td>DM, HPT</td>
<td>1</td>
<td>MD SCC</td>
<td>Lt mid-ant-lat, involved FOM. [2.5 x 4.1]</td>
<td>T4aN0M0 (Stage IVA)</td>
<td>Covid-19 pandemic</td>
</tr>
</tbody>
</table>

HyBIRT; Hybrid Brachytherapy followed by Intensity Modulated Radiation Therapy, ECOG; European Cooperative Oncology Group Performance Status, HPE; Histopathology, OTT; overall treatment time, DM; Diabetes Mellitus, HPT; Hypertension, BA; Bronchial Asthma, WD; Well differentiated, MD; Moderately differentiated, SCC; W; width, L; length, Squamous cell carcinoma, Lt; Left, Rt; Right, FOM; floor of mouth, Tongue divided into (ant: anterior 1/3, mid: middle 1/3, post: posterior 1/3), Lat; Lateral.
### Table 2: Common Terminology Criteria for Adverse Events (CTCAE) 5.0 scoring at significant timeline

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>M (%)</th>
<th>X (%)</th>
<th>D (%)</th>
<th>P (%)</th>
<th>U (n/%)</th>
<th>A (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of IMRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>w 7</td>
<td>≤ G2 (64)</td>
<td>≤ G2 (73)</td>
<td>≤ G2 (55)</td>
<td>≤ G2 (100)</td>
<td>≤ G2 (100)</td>
<td>G1 (9)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>≥ G3 (36)</td>
<td>≥ G3 (27)</td>
<td>≥ G3 (45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 m</td>
<td>≤ G2 (100)</td>
<td>≤ G2 (90)</td>
<td>≤ G2 (100)</td>
<td>G1 (100)</td>
<td>≤ G2 (100)</td>
<td>G1 (80)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>≥ G3 (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2 (20)</td>
<td></td>
</tr>
<tr>
<td>After IMRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 m</td>
<td>G1 (12)</td>
<td>≤ G2 (100)</td>
<td>G1 (50)</td>
<td>G1 (36)</td>
<td>≤ G2 (100)</td>
<td>G1 (88)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ G3 (10)</td>
<td></td>
<td></td>
<td></td>
<td>G2 (12)</td>
<td></td>
</tr>
<tr>
<td>12 m</td>
<td>G1 (100)</td>
<td>G1 (17)</td>
<td>G1 (17)</td>
<td>G1 (83)</td>
<td>G1 (100)</td>
<td>G1 (83)</td>
<td>6</td>
</tr>
<tr>
<td>18 m</td>
<td>G1 (100)</td>
<td></td>
<td>G1 (50)</td>
<td>G1 (100)</td>
<td>G1 (100)</td>
<td>G1 (100)</td>
<td>4</td>
</tr>
<tr>
<td>24 m</td>
<td>G1 (100)</td>
<td></td>
<td>G1 (50)</td>
<td>G1 (100)</td>
<td>G1 (100)</td>
<td>G1 (100)</td>
<td>2</td>
</tr>
</tbody>
</table>


---

### Figures

**Figure 1**

*Figure 1A: Tumor seen at the left border of tongue Figure 1B: Arrows showing brachytherapy applicator. Figure 1C: Complete resolution of tumor*
Figure 2

Figure 2A: HDR Brachytherapy plan showing the 20Gy isodose line (green), 25Gy isodose line (blue) and gross tumor volume; GTV (purple). Figure 2B: IMRT image set showing 25Gy isodose line (shaded blue), 20Gy isodose line (green) from brachytherapy plan that is co-registered with IMRT plan, 59.4 Gy isodose (blue), 61.71 Gy Isodose line (yellow) and 69.96 Gy isodose line (red)
**Figure 3**

Survival curves and response rates. (A) Locoregional progression-free survival. (B) Disease-free survival after radiological complete response. (C) Clinical and radiological complete response rate at the primary site. (D) Radiological complete response rate at the nodes.