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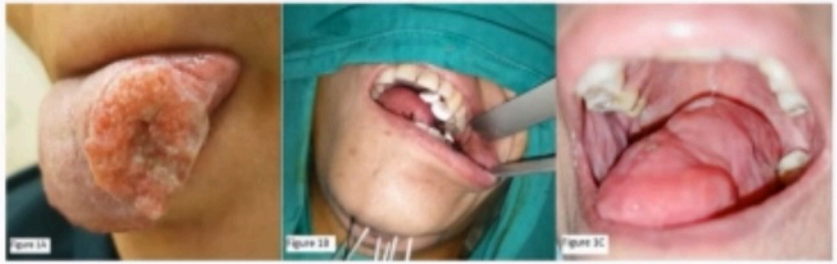
OC-0631

Upfront HDRIBT followed by IMRT for the Definitive Treatment of Tongue SCC



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Study protocol

Inclusion criteria	Exclusion criteria
- Tumor with epicentre at anterior 2/3 tongue. - Unable to undergo surgery for various reason/s. - ECOG PS 0-2. - Histologically confirmed SCC.	- Tumor with cortical bone involvement. - Technically not possible to approach the posterior tongue for applicator insertion. - Radiologically confirmed metastatic disease (M1) - Contraindication for nasal intubation.

Follow-up schedule

	Weeks(w), months(m) after IMRT
Clinical assessment - **Local control** - **Neck control** - **Toxicity scoring**	- 0 w, 2w, 6w, 3m, 4m, 5m, then 2 monthly x 2 years
Imaging: **MRI head & neck**	- 3m and then 3 monthly until CR (primary & neck). - Repeat CT-Scan, MRI or Pet-CT if clinically indicated thereafter

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20 patients who underwent definitive upfront high dose rate interstitial brachytherapy (HDRIBT) followed by adoptive IMRT + chemotherapy from January 2019 till August 2022 were prospectively followed up.

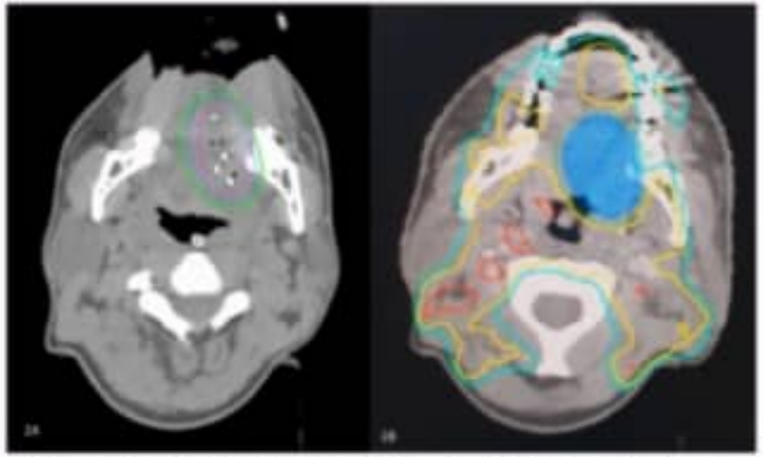

Figure 2A: HDR Brachytherapy plan showing the 20Gy isodose line (green), 25Gy isodose line (blue) and gross tumor volume; GTV (purple). Figure 2B: IMRT image set showing 25Gy isodose line (shaded blue), 20Gy isodose line (green) from brachytherapy plan that is co-registered with IMRT plan, 59.4 Gy isodose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

Treatment regimen:

- HDRIBT 20Gy in 5F to GTV-P, ensuring 90% of GTV-P receive 25Gy in 5F
- IMRT (33 fractions) within 10 days with weekly Cisplatin 40mg/m2 x 6 cycles
  - Dose:
    - 69.96-72.6Gy (gross disease/node),
    - 61.71Gy high risk region,
    - 56.1y to low risk volume and
    - 59.4Gy to the pre-treated HDRIBT field
  - EqD2 GTV-P (tongue) >85Gy
  - Hard constraint 63Gy to 25Gy HDRIBT volume/isodose line.

This study received institutional human ethics approval to be conducted at Advanced Medical & Dental Institute, Universiti Sains Malaysia (JEPeM Code : USM/JEPeM/21080564)

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TABLE 1: Patient and disease characteristics, overall treatment time and indication for brachytherapy

		(n/%)
Age	median	52-yrs
	range	20 – 71 yrs
Sex	male	(9/45%)
	female	(11/55%)
Smoker	Yes	(4/20%)
	No	(16/80%)
Co-morbid (n=9)	DM, HPT, CS	(1/5%)
	HPT	(3/15%)
	DM, HPT, BA	(1/5%)
	HPT, Gout	(1/5%)
	Sciosphrenia	(1/5%)
	DM, HPT	(2/10%)
HPE	WD SCC	(8/40%)
	MD SCC	(12/60%)
OTT (n=19)	56 – 60 d	(11/57.8%)
	61 – 65 d	(7/36.8%)
	74d	(1/5.4%)

		(n/%)
Tumor characteristics	LD (mean)	4.8cm
	FOM+	(13/65%)
	>1cmm ML	(4/20%)
	<1cm ML	(8/40%)
	ML +	(8/40%)
	Post 1/3+	(17/85%)
TNM7 T-stage	T1	(1/5%)
	T2	(3/15%)
	T3	(4/20%)
	T4a	(12/60%)
TNM7 N-stage	N0	(3/15%)
	N1	(3/15%)
	N2	(14/70%)
Brachytherapy indication	Ref. surg	(14/70%)
	Covid-19	(2/10%)
	CS	(1/5%)
	Surg. unfit	(3/15%)
ECOG - PS	ECOG 1	(20/100%)

DM; Diabetes Mellitus, HPT; Hypertension, CS; Cervical spondylosis, BA; Bronchial Asthma, HPE; Histopathology, OTT; overall treatment time, WD; Well differentiated, MD; Moderately differentiated, SCC; Squamous cell carcinoma, FOM; floor of mouth, d; days, LD; largest dimension, ML; mid-line of tongue, +; involvement, Post 1/3; posterior 1/3 of tongue, T; primary tumor, N; nodal, Ref. surg; refused surgery, Covid-19; Corona virus 19 pandemic related healthcare resource issues, Surg. Unfit; unfit for surgery, ECOG; European Cooperative Oncology Group Performance Status.

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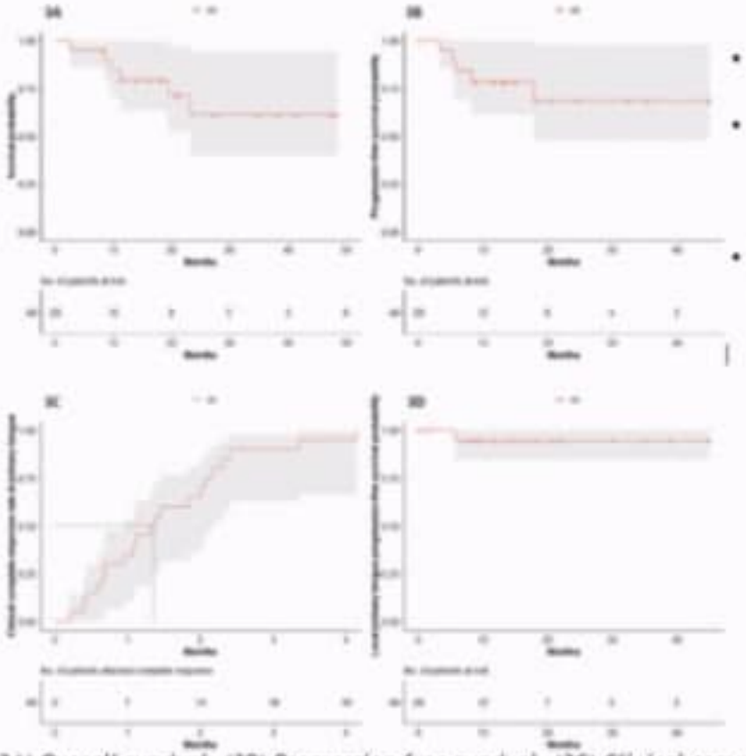
Results



- Average follow-up : 22 months(m)
- 17 pts was node positive at presentation:
  - 13 achieved radiological (r) CR by 8m. 2 pts had PD.
  - Median time for nodal rCR is 3.5m (95% CI 2.5, --)
- One patient presented to different centre with severe tongue bleed and died **(assumed local/tongue recurrence).**
  - Other 19 patients achieved clinical (c) CR at primary site
  - Median time to cCR at primary is 1.3m (95% CI 0.95,2.2)

	1-year (95% CI)	3-year (95% CI)
OS	79% (63%,100%)	61% (40%,94%)
DFS	94% (84%,100%)	73% (50%,100%)
PFS	78% (61%,100%)	68% (48%,98%)
LC (tongue)	94% (84%,100%)	94% (84%,100%)
LRPFS (nodal)	88% (73%,100%)	88% (73%,100%)

(3A) Overall survival. (3B) Progression free survival. (3C) Clinical complete response rate at the primary site. (3D) Primary site progression free survival in months (m)

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Discussion - Toxicity (n=20)

Common Terminology Criteria for Adverse Events (CTCAE) 5.0 scoring from end of IMRT						
	M(%)	X(%)	D(%)	A(%)	P(%)	n
w 7	G2(50), ≥G3(50)	G1(5), G2(70), G3(25)	G1(10), G2(55), ≥G3(35)	G1(50), G2(10)	G1(25)	20
12m	G1(47), G2(13), ≥G3(13)	G1(80), G2(20)	G1(53), G2(20)	G1(20), G2(7)	G2(20),G3(7)	15
24m	G1(57), G2(14)	G1(86)	G1(14), G2(29)	G1(43)	G1(14), G3(14)	7
M:mucositis oral, X:dry mouth, D:dysphagia, P:periodontal disease, A:dysarthria,G:grade, w:week, m:month.						

2 patients had persistent tongue ulceration that needed secondary suturing, healed by 14 months.
- ? Keeping the HDRIBT dose low (20Gy in 5F) reduced the rates of ulceration.

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Discussion - Causes of death (n=6)

Causes of death in 6 patients										
	Stage (TNM 7)	Mid-line	FOM	Post 1/3	Age	P	N	Cause of death	Time	?P
1	T4aN2	yes	yes	yes	52	CR	PD	Progressive nodal disease	16m	x
2	T4aN0	<1cm	yes	no	71	CR	NL	Dehydration/cerebral oedema	1m	±
3	T4aN2	yes	yes	yes	52	CR	CR	Advanced metastasis	19m	x
4	T3N2	<1cm	yes	yes	60	CR	CR	Blocked tracheostomy tube, (schizophrenic)	9m	±
5	T4aN2	yes	yes	yes	55	CR	SD	Uncontrolled tongue bleed	6m	x
6	T4aN2	yes	yes	yes	51	PD	SD	Bleeding duodenal ulcer	1w	±

FOM:Floor of mouth, Post 1/3:posterior 1/3 of tongue, P:response at primary lesion (tongue), N:nodal assessment, Time:timeline of death from completion of chemoradiotherapy, m:months, w:weeks, ?P: preventable?

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Discussion - unplanned & preliminary analysis of patients with systemic staging

- We found very low distant failures / non-regional metastasis during this updated analysis
  - ? Lead time bias
  - ? Patient selection
  - Surveillance imaging are not part of our protocol but preliminary analysis for patients with systemic imaging post treatment as below

Nine patients with available systemic staging post treatment

	Stage	Imaging	D (m)	results
1	T2N2	Pet-CT	21	No DM
2	T4aN2	Pet-CT	13	Persistent neck node/s. No DM.
3	T4aN2	Pet-CT	5	DM. No pre-treatment systemic imaging.
4	T3N0	CT-TAP	14	No DM
5	T4aN1	Pet-CT	10	No DM
6	T4aN0	Pet-CT	4	No DM
7	T2N2	CT-TAP	4	No DM
8	T4aN2	Pet-CT	10	Persistent neck node/s. No DM
9	T2N2	Pet-CT	5	No DM

Stage; AJCC TNM7 staging, Pet-CT; positron emission topography with CT-fusion, CT; computed topography, TAP; thorax, abdomen & pelvis, D; interval duration from HDRIBT to latest Pet-CT, m; months, DM; distant metastasis.

Preliminary - only 1 out of 9 patients (with imaging) had DM post treatment.

- Need study protocol modification for scheduled surveillance scans for DM.

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Discussion - Advantages of upfront HDRIBT followed-by IMRT/chemo

HDRIBT followed by IMRT	EBRT followed by HDRIBT
Patients more receptive to the subsequent IMRT after HDRIBT induced tumor shrinkage.	Patients traumatized by EBRT toxicity may refuse further HDRIBT boost.
Easier to identify the GTV and tumor induration during the IBT applicator insertion.	Risk of "geographical miss" in HDRIBT.
IMRT isodose coverage can be "molded" to the earlier HDRIBT dose distribution.	Limited capability of HDRIBT to "mold" the dose to the preceding EBRT.
Better sparring of OAR's with the use of IMRT.	Generally, 3D-CRT technique is used.
Tumoricidal dose to the involved neck node/s and high risk areas with IMRT.	EBRT (3D-CRT) dose is limited to 40Gy - 54Gy in 20 - 27 to prevent overdose to subsequent HDRIBT overlap region. - Immediate salvage surgery for persistent neck node/s after sub-optimal dose of EBRT.
IMRT immediately after the HDRIBT (↓OTT).	Planned or salvage neck dissection before HDRIBT may prolong OTT.

Hybrid Brachytherapy followed-by IMRT - "HyBIRT"

Discussion

If not lead time bias, can the low DM rate be due to:

- Practice of injecting lidocaine into tongue tumor during HDRIBT applicator insertion *(Badwe e.al 2022. Effect of peritumoral infiltration of LA before surgery and survical in BC)*
- Reduced OTT and chemotherapy within 10 days of HDRIBT "clears" any microscopic dissemination during applicator insertion
- Short anesthesia reducing the risk of hypoxia and distant metastasis *(Rankin et.al 2016, Hypoxic control of metastasis)*
- IMRT/EBRT after HDRIBT sterilize the field/applicator tract and hence avoiding dermal lymphatic spread

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Conclusion and future direction

- Brachytherapy role in the treatment of tongue squamous cell carcinoma needs a re-look. It has the promising role of becoming modality of choice rather than being limited to patients who refused surgery.
  (With the good QOL and disease control → "will it be an injustice to subject patients to mutilating surgery"?)
- Low dose HDRIBT (20Gy) combined with full dose IMRT is tolerable and all our initiated patients completed the full treatment regimen.
- Longer follow-up and larger patient sample is needed to confirm the efficacy of this method (HyBIRT) that combine upfront HDRIBT followed by IMRT/chemo within a week.

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