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Technical Report

Tongue-Out Radiation Therapy for Patients With Head and Neck Cancer Facilitated a Rapid Recovery From Post-Radiation Therapy Dysgeusia by Lowering Oral Tongue Dose

Whoon Jong Kil, MD,[a,b,c,*] Ashley Stiffler, LPN,[a] Wyatt Smith, CMD,[a] and David Cousins, MD[a]

[a]*Department of Radiation Oncology, University of Pittsburgh Medical Center, Williamsport, Pennsylvania;* [b]*Department of Radiation Oncology, University of Pittsburgh School of Medicine, Pittsburgh; and* [c]*Department of Radiation Oncology, Walter Reed National Military Medical Center, Bethesda, Maryland*

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Purpose: To report the rapid recovery of treatment-related dysgeusia after tongue-out radiation therapy (TORT) for head and neck cancer (HNC).

Methods and Materials: We retrospectively reviewed 14 patients with HNC who completed TORT with 70 Gy for definitive or salvage and 60 to 66 Gy for adjuvant treatment with or without concurrent chemotherapy. Patient-reported quality of taste was evaluated before, at the end of TORT therapy, and periodically 1, 3, and 6 months after TORT therapy using the University of Washington Quality of Life questionnaire version 4, question 9, including options for no-, mild-, and severe dysgeusia and ageusia. Oral cavity (OC) and oral tongue (OT) were contoured following guidelines. A portion of the anteriorly displaced OT outside the mouth was separately contoured as OT_{OUT}. Statistical analysis was conducted with the χ^2 and t test. A probability level of $P < .05$ was considered significant.

Results: In 14 TORT plans, the average volume of OC and OT was 105.8 ± 25.3 and 67.6 ± 20.7 cm^3, respectively. OT_{OUT} comprised 20% (13.4 ± 9.1 cm^3) of the entire OT volume. Average mean dose (D_{MEAN}) to OC, OT, and OT_{OUT} was 25.2 ± 6.9, 26.4 ± 6.8, and 13.3 ± 2.9 Gy, respectively. Before TORT, no-to-mild versus equal or higher than severe dysgeusia (≥ severe dysgeusia) was 86% (n = 12) versus 14% (n = 2) of patients, respectively; 14% (n = 2) versus 86% (n =12) at the end of TORT ($P < .01$); 57% (n = 8) versus 43% (n = 6) at 1-month post-TORT ($P < .01$); 79% (n = 11) versus 21% (n = 3) at 3-month post-TORT ($P = .23$) and 93% (n = 13) versus 7% (n = 1) at 6-month post-TORT ($P = .18$).

Conclusion: TORT displaced OT anteriorly, lowered D_{MEAN} to OT, especially to $OT_{OUT,}$ and facilitated rapid regaining of sense of taste at 1-month post-TORT. Patient-reported quality of taste returned to the baseline at 3-month and 6-month post-TORT. Further randomized study to verify clinical advantages with TORT for HNC is warranted.

Introduction

Altered taste (dysgeusia) occurs in most patients during radiation therapy (RT) for head and neck cancer (HNC) and continues in a substantial number of patients even after completion of treatment.[1-5] Persisting post-RT

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*Corresponding author: Whoon Jong Kil, MD; Email: whoonkil@gmail.com

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dysgeusia causes negative effects on patients' overall nutritional status, recovery from cancer treatments, and quality of life.[5-7] Among other competing factors, radiation doses to taste buds have shown an association with the severity of RT-related dysgeusia.[8,9] Because taste buds are mainly located on the tongue within the oral cavity (OC), limiting the dose to the entire tongue and/or OC during RT for HNC has been recommended for mitigating RT-related dysgeusia.[1-3,5]

The entire tongue is located inside the mouth during traditional RT for HNC. However, substantial portions of oral tongue (OT) can be anteriorly displaced outside the mouth and away from RT targets when patients maintain the tongue-out position. Consequently, tongue-out position during RT (TORT) for HNC has shown significantly decreased radiation doses to OT by 25% to 40% and OC by 30% to those with non-TORT.[10-12] Thus, there is increasing interest in clinical studies aimed at determining whether such dosimetric advantages from TORT for HNC also translate into mitigating post-RT dysgeusia.

In this report, we presented for the first time patient-reported quality of taste after TORT for HNC, which lowered radiation doses to OT and OC, leading to a rapid recovery from post-RT dysgeusia compared with other published non-TORT techniques for HNC.

Methods and Materials

Data for this report were collected by retrospectively reviewing medical records of 14 patients who received TORT with or without concurrent chemotherapy for HNC and documented patient-reported quality of taste using the University of Washington Quality of Life questionnaire version 4 (UWQoL) on each clinic visit before and after TORT. Patients with prior RT or chemotherapy, those without a UWQoL document, or follow-up visits in less than 6 months after TORT were not included. An institutional review board waived a board review on this report. Patients' characteristics are listed in Table 1. Primary tumors were in the oropharynx (n = 6), hypopharynx (n = 2), epiglottis (n = 3), retromolar trigon (n = 2), and parotid gland (n = 1). Patients with OT primary, tumor extending into OT, and/or severe trismus were excluded from TORT.

For TORT, the immobilization mask was customized to create a pouch around the patient's mouth (white arrow in Fig. 1B) for a reproducible tongue-out position following published guidance.[10-12] Then, all patients underwent a computed tomography (CT) simulation scan (CT-sim) using the customized immobilization mask and tongue-out position (Fig. 1B). High-risk clinical target volume (CTV_{High}) was defined as the primary tumor or tumor bed with/without neck nodes + 5 to 10 mm. Intermediate-risk CTV (CTV_{Int}) comprised CTV_{High} and the area at risk for microscopic disease. Low-risk CTV (CTV_{Low}) included elective nodal stations. Planning target volume (PTV) was CTV + 3 mm. The volumetric modulated arc therapy technique was used for planning TORT. Radiation prescription was 70, 63, and 56 Gy in 35 fractions to PTV_{High}, PTV_{Int}, and PTV_{Low}, respectively, for definitive and salvage treatment, and 60 to 66 Gy and 54 Gy in 30 to 33 fractions to PTV_{High} and PTV_{Low}, respectively, for adjuvant treatment.

Among normal organs at risk (OARs), we manually contoured the entire tongue, including the extrinsic and intrinsic muscles and the floor of the mouth. Then, the entire tongue was divided into the OT and base of tongue (BOT) by drawing a vertical line from the posterior hard palate to the hyoid. For dosimetric comparison, a portion of anteriorly displaced OT, extending outside the mouth with TORT, was retrospectively contoured as OT_{OUT}, separating from the part of OT remaining inside the mouth (OT_{IN}).

The eclipse RT planning system (version 15.6, Varian Medical System) was used with a Varian Edge linear accelerator using 6-MV photons. Planning objectives required PTV coverage of 95% to 110%. Radiation dose constraints for normal OARs followed published recommendations.

To compare patient-reported quality of taste before versus at the end of TORT and periodically 1, 3, and 6 months after TORT, respectively, we used UWQoL question 9, which includes the options of "patient can taste food normally" (no dysgeusia), "patient can taste most foods normally" (mild dysgeusia), "patient can taste some food" (severe dysgeusia), and "patient cannot taste any food" (ageusia). Comparison of patient-reported quality of taste was conducted using the χ^2 test. The student's t test was used to compare the radiation dose to OARs. A probability level of $P < .05$ was considered significant.

Results

Oral anatomy changes from TORT

The individual CT portion of the positron emission tomography scan was used as a non-TORT scan (Fig. 1A) to compare changes in oral anatomy in CT-sim for TORT (Fig. 1B). Average volume of OC, BOT, and OT in TORT plans was 105.8 ± 25.3, 14 ± 5.6, and 67.6 ± 20.7 cm^3, respectively. Compared with non-TORT, TORT facilitated slightly opening patients' mouths and displaced the entire tongue more anteriorly, resulting in an increased distance from the posterior pharyngeal wall to BOT by 1.4 ± 0 .7 cm (94% increase) and relocated 20% (13.4 ± 9.1 cm^3) of OT to be outside the mouth (OT_{OUT}: green star and green arrow in Fig. 1B).

Table 1 Baseline patients' characteristics

S. No.	Age	Diagnosis (stage)	Histology (p16 status)	Treatments			Tobacco history (pack-year)
				TORT (Gy)		ST	
1	38	Hypopharynx	SQ	Definitive	70	Cisplatin	12
		(cT1N3M0)	(−)				
2	47	Tonsil	SQ	Definitive	70	Cisplatin	20
		(cT3N3M0)	(+)				
3	80	Retromolar Trigon	SQ	Post-op	66	No	50
		(pT4a2b)	(n/a)				
4	69	Epiglottis	SQ	Definitive	70	No	50
		(cT1N1M0)	(n/a)				
5	77	Epiglottis	SQ	Definitive	70	Cisplatin	47
		(cT2N1M0)	(−)				
6	82	Parotid	AD	Salvage	70	No	45
		(rT2N0M0)	(n/a)				
7	62	BOT	SQ	Definitive	70	Cisplatin	0
		(cT2N1M0)	(+)				
8	48	Tonsil	SQ	Post-op	60	No	25
		(pT1N1)	(+)				
9	69	Hypopharynx	SQ	Definitive	70	Cisplatin	40
		(cT2N2M0)	(+)				
10	59	Tonsil	SQ	Definitive	70	Cisplatin	40
		(cT4N3M0)	(−)				
11	68	Retromolar Trigon	SQ	Salvage	70	Carbo/Taxol	40
		(rT2N3M0)	(−)				
12	60	Epiglottis	SQ	Definitive	70	Cisplatin	22
		(cT3N2M0)	(−)				
13	71	Tonsil	SQ	Definitive	70	Cisplatin	2.5
		(cT1N1M0)	(+)				
14	72	Tonsil	SQ	Definitive	70	No	0
		cT1N2M0	(+)				

Abbreviations: "+"= p16 positive; "−" = p16 negative; AD = adenocarcinoma; Carb = weekly carboplatin; Cisplatin = weekly cisplatin; cTxNxMx = clinical stage; n/a = unavailable; Post-Op = postoperative; pTxNx = pathologic stage; rTxNxMx = recurrent stage; SQ = squamous cell carcinoma; Stage = American Joint Committee on Cancer stage, 8th Edition; ST = standard therapy; TORT = tongue-out radiation therapy.

Radiation dose to intraoral structures from TORT

In TORT plans, average mean dose (D_{MEAN}) to OC, BOT, and OT was 25.2 ± 6.9, 48.4 ± 17, and 26.4 ± 6.8 Gy, respectively, and average volume receiving ≥ 30 Gy (V30) was 31.6% ± 19.4%, 82.9% ± 29.6%, and 30.4% ± 19.1%, respectively. OT_{OUT} received significantly less radiation than OT_{IN} (yellow dotted line and arrow in Fig. 1B). D_{MEAN} to OT_{OUT} and OT_{IN} was 13.3 ± 2.9 and 29.5 ± 7.9 Gy, respectively; V30 was 0.2% ± 0.8% and 37.5% ± 22.1%, respectively (all $P < .05$) (Table 2).

All patients reproduced and maintained OT_{OUT} position well, as verified by daily cone beam CT scans and real-time video monitoring during daily TORT, following published guidelines.[10-12]

Patient-reported quality of taste after TORT

Changes in patient-reported quality of taste are shown in Table 3 and Fig. 1C. Before TORT, no-to-mild dysgeusia and ≥ severe dysgeusia were 86% (n = 12) and 14% (n = 2) of patients, respectively. Compared with before TORT, patient-reported quality of

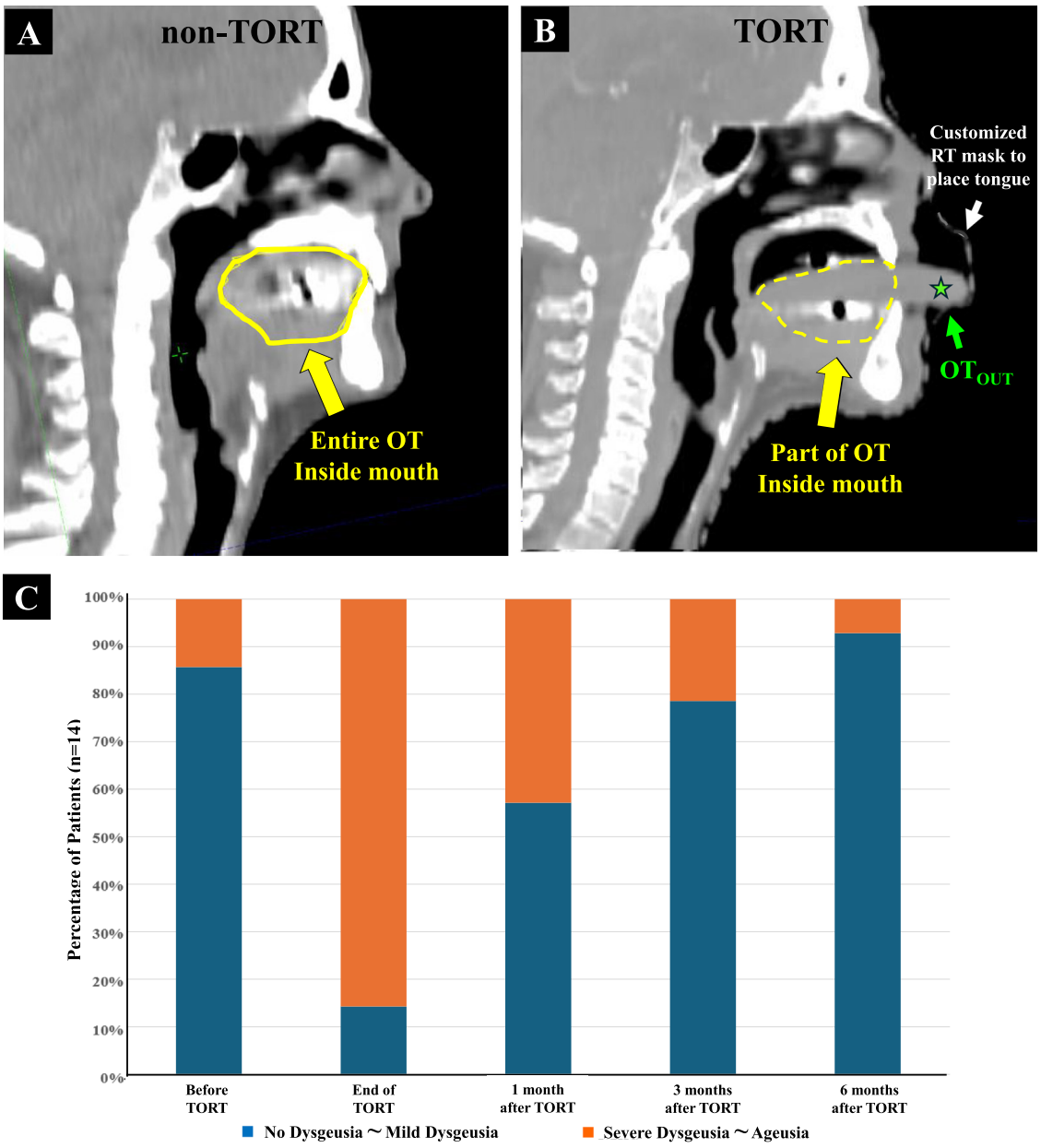

Figure 1 (A) Sagittal view of a computed tomography (CT) portion of a positron emission tomography scan in a head and neck cancer patient. A yellow solid line and arrow indicate the entire oral tongue (OT) inside the mouth. (B) Sagittal view of CT-simulation scan for planning tongue-out radiation therapy (TORT). A yellow dotted line and arrow indicate a part of OT inside the mouth. A green star and arrow indicate OT outside the mouth (OT_{OUT}). (C) Status of patient-reported dysgeusia before and after TORT using the University of Washington Quality of Life questionnaire version 4, question 9. No dysgeusia = patient can taste food normally. Mild dysgeusia = patient can taste most foods normally. Severe dysgeusia = patient can taste some foods. Ageusia = the patient cannot taste any food. The blue bar indicates no-to-mild dysgeusia. The orange bar indicates severe dysgeusia-to-ageusia.

taste worsened at the end of TORT, with most patients (n = 12, 86%) experiencing ≥ dysgeusia, including 6 cases of ageusia. At 1 month after TORT, however, patients showed a recovery of senses of taste by reporting mild dysgeusia in more than half of patients (n = 8), and only 2 patients had ageusia remaining. Patient-reported quality of taste rapidly improved and returned to its pre-TORT state: no-to-mild dysgeusia 79% (n = 11) and severe dysgeusia 21% (n = 3) without ageusia at 3 months after TORT (P = .23); no-to-mild dysgeusia 93% (n = 13) and severe dysgeusia 7% (n = 1) at 6 months after TORT (P = .18).

Table 2 Radiation dose to intraoral structures from tongue-out radiation therapy

	Oral tongue with TORT		
Parameters	**Total**	**Inside mouth**	**Outside mouth**
Volume (μL)	67.6 ± 20.7 c	51.2 ± 19.9	13.4 ± 9.1
D_{MEAN} (Gy)	26.4 ± 6.8	29.5 ± 7.9	**13.3 ± 2.9**
D_{MAXv} (Gy)	61.3 ± 12.3 Gy	61.3 ± 12.3 Gy	**26.3 ± 11.3**
V30 (%)	30.4 ± 19.1	37.5% ± 22.1	**0.2 ± 0.8**
P value			*p<0.05*

Statistical analysis was conducted using the *t* test. A probability level of $P < .05$ was considered significant.
Abbreviations: D_{MAX} = maximum dose; D_{MEAN} = mean dose; V30 = volume receiving equal or greater than 30 Gy; TORT = tongue-out radiation therapy.
Numbers in bold in colume 4 are statistically lower compared to numbers in colume 2 and 3.

Table 3 Patient-reported quality of taste with tongue-out radiation therapy (TORT) for head and neck cancer (n = 14)

			Time after TORT		
Taste status (UWQoL)	**Before TORT**	**End of TORT**	**1 mo**	**3 mo**	**6 mo**
No dysgeusia, n (%)	11 (79)	0 (0)	0 (0)	7 (50)	8 (57)
Mild dysgeusia, n (%)	1 (7)	2 (14)	8 (57)	4 (29)	5 (36)
Severe dysgeusia, n (%)	2 (14)	6 (43)	4 (29)	3 (21)	1 (7)
Ageusia, n (%)	0 (0)	6 (43)	2 (14)	0 (0)	0 (0)
P value		*p<0.01*	*p<0.01*	*p=0.23*	*p=0.18*

Statistical analysis was conducted with the χ^2 test. A probability level of $P < .05$ was considered significant.
Abbreviations: Ageusia = patient cannot taste any food; Mild dysgeusia = patient can taste most foods normally; No dysgeusia = patient can taste food normally; Severe dysgeusia = patient can taste some foods; UWQoL = University of Washington Quality of Life questionnaire version 4, question 9.
Numbers in bold are statistically significant.

Discussion

Taste receptor cells are present in the taste buds, which are primarily located on the dorsal and lateral surfaces of the tongue and, to a lesser extent, on the surfaces of the OC, oropharynx, and larynx. With a half-life of approximately 15 days and availability to regenerate, these receptor cells transduce the stimuli of sweet, salt, sour, umami, and bitter. Multiple factors, such as aging, tobacco use, poor oral hygiene, certain medical conditions, medications/drugs, and damage to gustatory tissues, affect patients' capability of sensing tastes.[13] Among patients receiving RT, radiation dose response data showed that gustatory tissue damage occurred at ≥ 30 Gy.[8,9] In modern RT for HNC, a high OC dose (D_{MEAN} ≥ 40-50 Gy) was reportedly associated with dysgeusia in patients.[1-5] Thus, reducing the entire OC dose was suggested to promote early recovery from post-RT dysgeusia.

Historically, it was considered that specific regions of the tongue were responsible for sensing certain tastes, for example, the tip of the tongue for sweet, the anterior-lateral side for salt, the posterior-lateral side for sour, and the posterior for bitter. Recent data, however, suggests that taste receptor cells within a taste bud can transduce all 5 taste stimuli, allowing all areas of the tongue to sense different tastes almost equally.[14] As such, while respecting recommended dose constraints to the entire OC during RT planning, additional efforts to further reduce radiation dose to a certain portion of OT may further mitigate post-RT dysgeusia.

Notably, TORT for HNC created an OT_{OUT} comprising an average of 20% of the entire OT in our patients and reduced the dose to OT_{OUT} to less than 50% of the dose to OT_{IN} (D_{MEAN}, 13.3 ± 2.9 vs 29.5 ± 7.9 Gy, respectively, $P < .05$). TORT also lowered V30 and maximum dose (D_{MAX}) for OT_{OUT} to be 0.2% ± 0.8% and 26.3 ± 11.2 Gy, respectively. Thus, nearly the entire OT_{OUT} was able to avoid receiving ≥ 30 Gy (which is reportedly a gustatory tissue-damaging dose), whereas

one-third of OT_{IN} and OC still received ≥ 30 Gy (37.5% ± 22.1% and 31.6% ± 10.4%, respectively, Fig. 1B and Table 2). Such additional dose reduction to OT_{OUT} with TORT may prevent severe radiation-related damage to taste buds on the surface of OT_{OUT} and facilitate regaining senses of taste within a month after treatment, compared with non-TORT, which reportedly worsened patient-reported quality of taste score at 1 month post-treatment for HNC.[3] Furthermore, rapidly returning patient-reported quality of taste score to its baseline at 3 months after TORT is also promising because 25% to 27% of the patients reportedly maintained severe dysgeusia or taste loss at 12 months after non-TORT for HNC.[1-3]

Interestingly, a patient (case 8) with 25 pack-years of tobacco use and daily cigarette smoking (0.5-1 pack per day) reported severe dysgeusia at diagnosis of HNC. He quit smoking tobacco immediately before TORT and reported no dysgeusia at 6 months post-TORT (D_{MEAN} to OT_{OUT} and $OT_{IN,}$ 13.5 and 23.3 Gy, respectively). His case demonstrates how tobacco use can negatively affect patients' quality of taste and implies the importance of smoking cessation during and after HNC treatment to mitigate treatment-related dysgeusia.

Additionally, our patients often inform us that their sense of taste differs across different portions of the tongue during and after TORT for HNC. Thus, we are currently evaluating a potential association between the anatomic locations of the tongue and dysgeusia with TORT.

TORT provides the additional benefit of sparing minor salivary glands on the surface of the tongue and OC by lowering the dose to OT and OC. Patient-reported quality of saliva (UWQoL question 10) also showed a trend of rapid recovery after TORT, similar to dysgeusia status in our patients (data not shown), though more data are required because primary HNC location and target volumes in our patients may confound the effect of TORT.

Limitations to this report include the relatively small number of cases in heterogeneous diseases and treatments. We retrospectively reviewed only subjective patient-reported outcomes, which also limits a more detailed evaluation of other factors that may affect treatment-related dysgeusia and its recovery process. Further randomized study including a large number of patients to verify clinical advantages with TORT for HNC is warranted.

In conclusion, we reported for the first time patient-reported quality of taste after TORT for HNC. Anteriorly displaced OT with TORT reduced radiation dose to OT, especially to $OT_{OUT,}$ and is associated with rapid regaining of the sense of taste as early as 1 month after TORT. Patient-reported quality of taste returned to the baseline status at 3 months and 6 months after TORT for HNC.

Disclosures

None.

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