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Evaluation of the Local Control Rate and Late Toxicity of High-Dose-Rate Interstitial Brachytherapy in Tongue Squamous Cell Carcinoma

Iman Amiri, Maryam Feli, Ali Bagheri, Hojattollah Shahbazian and Fatemeh Mohammadian*

Department of Radiotherapy, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

*** Corresponding author**
Fatemeh Mohammadian, MD
Department of Radiotherapy, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
Tel: +98 61 3373 8317
Fax: +98 61 3373 8330
Email: Drfmrt90@gmail.com

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Abstract

Background: Tongue Squamous Cell Carcinoma (TSCC) is one of the most consequential oral Squamous Cell Carcinomas (SCC) worldwide.

Methods: This retrospective cross-sectional study was conducted on 29 TSCC patients treated with High Dose Rate Brachytherapy (HDR-BT) with or without External Beam Radiotherapy (EBRT) between 2017-2020. Patients without distant metastasis at the time of treatment and at least one year after completion of brachytherapy were included.

Results: One-year Overall Survival (OS), Disease-Free Survival (DFS), and Local Control Rate (LCR) were 82.8, 79.3, and 100%, respectively. 6 patients (20.7%) had distant metastasis, of which 5 (17.2%) died. Local recurrence was not observed in any patients, and only one (3.4%) regional recurrence occurred. The most common late toxicity of HDR-BT was dry mouth (79.2%) and dysarthria (66.7%). There were no severe and life-threatening complications (grades 3 and 4) during one year. Also, 79.2% of the patients had good functional performance. One-year OS, the significant difference between the two groups of HDR-BT with and without EBRT (p=0.055).

Conclusion: Our findings indicated that the HDR-BT increases the OS of TSCC patients more than EBRT without developing grade 3-4 AEs and metastasis. We showed that the mean 3.2 ±0.7 *Gy* of HDR-BT has more OS compared to EBRT.

Keywords: Brachytherapy, Squamous cell carcinoma, Tongue cancer

Introduction

Tongue Squamous Cell Carcinomas (TSCC) are among the essential oral Squamous Cell Carcinomas (SCC) worldwide (1). Previous literature has shown that TSCC is more frequent in men and increases in older than 50 (2). However, recent epidemiological studies demonstrated a shifting trend in TSCC in women younger than 45 years (3). There is no data regarding the causes of more tumor incidence in young people compared to old people; however, in the recent investigation, it was found that the rate of TSCC in younger patients is less likely to result in gene mutations than in the older (4). It is worth noting that despite the association between tobacco consumption and TSCC incidence, in the younger population, by reducing tobacco consumption, TSCC decreases were not observed (4).

More benefits such as shorter hospitalization, more accurate therapy plan, and non-exposure of personnel to the radiation cause replacing Low Dose Rate Brachytherapy (LDR-BT) with High Dose Rate interstitial Brachytherapy (HDR-BT) (5,6). TSCC is a painful, invasive oral cavity tumor with challenging treatment strategies due to a lack of data about managing the rate of recurrence and risk factors. Nevertheless, it was found that HDR-BT following surgery in patients with an unfavorable prognosis is accompanied by a better outcome than sole surgery (7). Surgery has valuable consequences, but less favorable cosmetic results and injury to the normal tissue around the tumor is less satisfying to patients. Although HDR-BT is preferred over LDR-BT, there is a variable response to treatment following brachytherapy (8,9).

One of the main concerns is developing Adverse Events (AEs) following HDR-BT (10,11). Identifying the best treatment strategy by HDR-BT results in the most effective clinical outcome with reduced AEs (12). Additionally, HDR-BT with accurate localization radiation into the tumor without disrupting normal tissue takes the attention of researchers. The current survey investigates late AEs and LCR in TCCS patients with or without External Beam Radiotherapy (EBRT).

Materials and Methods

Study population

In the present study, patients with TSCC referred to the oncology department in Golestan Hospital were included. Selecting the patients was based on the inclusion criteria: patients with treated TSCC by HDR-BT, passing minimum 1-year follow-up, and patients without distant metastasis. The main target of the present survey was evaluating recurrence and AEs following BT; hence, patients with distant metastasis and treated relapsed patinates were excluded. Also, patients with incomplete data were considered as exclusion criteria.

Demographic information of the patients was collected. Also, a radiation specialist and assistant radiotherapist collected the results of the stage, type, size, and depth of tumor, type of treatment, AEs, recurrence, and metastasis. Magnetic Reassurance Irradiation (MRI) and CT-scan were used to evaluate metastasis. This study was performed after obtaining the permission from the Research Council and approval of the Medical Ethics Committee of Ahvaz University of Medical Sciences (IR.AJUMS.HGOLESTAN.REC.1400.177).

Treatment strategy

HDR-BT alone or alongside EBRT has been conducted for 1-2 weeks. EBRT with 3D conformal and 50 *Gy* (2 *Gy* per fraction) was performed (Figure 1).

Interstitial brachytherapy catheters are placed under general anesthesia in this center. First, the desired volume of the implant is determined by a two-handed examination and examination of the surgical scar. In the next step, 15-*cm* metal trocars are inserted to cover the surgical scar with a margin of one centimeter from the submandibular area to the distance. They enter 1-1.5 *cm* from each other. Then, blind-end plastic catheters with buttons are replaced by trocars in the craniocaudal direction, and plastic buttons finally fix these catheters in the submandibular area (Figure 2). The sole HDR BT in case of negative prognostic factors including; close or positive surgical margin, lymphovascular and/or perineural invasion was conducted.

Treatment efficacy

All the patients underwent CT simulation for a 3D brachytherapy plan. The radiation treatment plan was

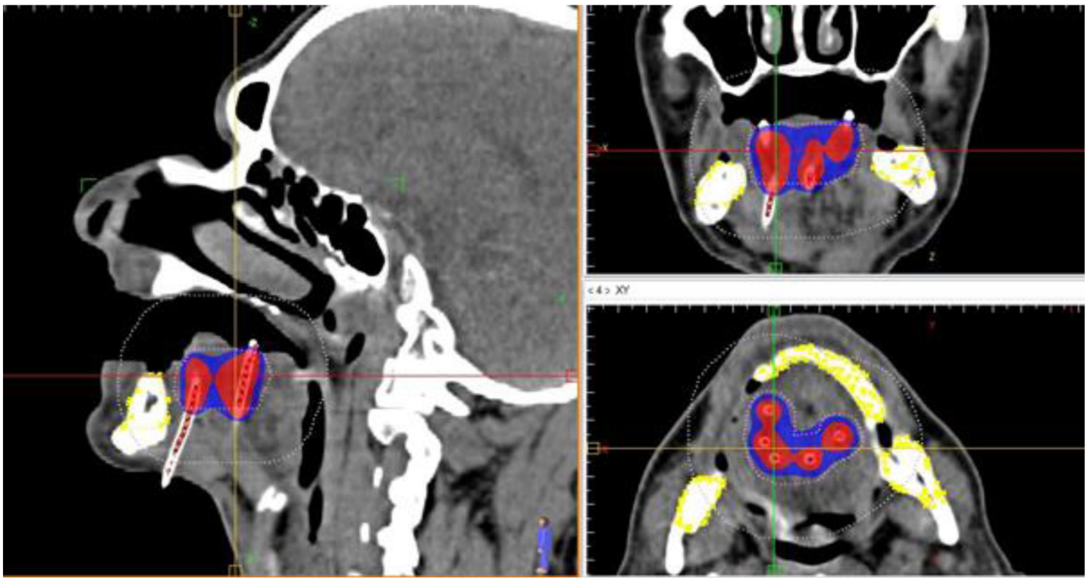

Figure 1. Blue isodose 100 and red isodose 150.

Figure 2. The used catheters.

evaluated by observing the three-dimensional dose distribution in the dose-volume histogram. Based on the dose-volume histogram information, the treatment plan was optimized to deliver the prescribed dose (minimum peripheral dose) to cover at least 95% of the clinical target volume (PTV). In contrast, the mandibular dose was kept as low as possible to minimize the risks of radio-osteosclerosis.

Treatment safety

The treatment team evaluated all the patients who had completed at least one year of brachytherapy in terms of delayed complications of brachytherapy, including oral mucositis, oral pain, dry mouth, trismus, osteonecrosis of the jaw, taste disorder, hypoglossal nerve disorder, dysphagia, dysarthria, soft tissue necrosis, and fistula of the oral cavity were evaluated. The severity of complications was determined and recorded based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 scale from 1 to 5.

Also, the patients' nutritional status (normality of diet) and verbal (understandability of speech) were evaluated using the FACT-HN scale, a self-report questionnaire to check the patients' quality of life with head and neck cancer. This scale assesses the functional status of patients as good, average, or wrong. This study used the practical dimension of this questionnaire.

All patients were examined clinically and by imaging regarding local recurrence, regional recurrence, distant metastasis, and secondary cancer in the oral cavity. Local Control Rate (LCR) and Disease-Free Survival (DFS), and Overall Survival (OS) were evaluated within one year after brachytherapy.

Statistical analysis

Descriptive statistics, including mean and Standard Deviation (SD), were utilized to describe the fracture resistance values. The normality of data distribution was assessed using Shapiro-Wilk and Kolmogorov Smirnov tests. Data analysis was performed using Kruskal-Wallis and post hoc tests. Fisher exact tests were utilized to check the relationship or independence of the grouped quantities from each other, and the qualitative data were analyzed using the Chi-square test. The significant level was considered as $p < 0.05$. The collected data were analyzed with IBM.SPSS statistics software 24.0 Version.

Results

Study population

Twenty-nine patients were selected, including 19 (65.5%) women and 10 (34.5%) men. The mean age was 50.3±12.8 years. Twenty-six patients (89.7%) underwent primary surgery, and 24 (82.8%) had lateral neck dissection (Table 1).

Pathology results

Twelve participants (41.4%) were well differentiated and followed by 10 (34.5%) moderately differentiated and 3 (34.5%) poorly differentiated, respectively. 75.9% of the subjects were marginal-free. T1 (58.6%) and N0 (65.5%) were the more frequent subtypes. Lymphovascular and perineural invasions were detected in 27.6% and 24.1% of the patients. The mean tumor depth and DOI were 0.82 ±0.95 and 0.64 ±0.6 (Table 2).

Table 1. The demographic information of the patients

Variables	Report
Age, mean ± SD (year)	50.3 ±12.8
Gender (%)	
Male	10 (34.5)
Female	19 (65.5)
Surgery (%)	
Initial	26 (89.7)
Salvage	2 (6.9)
No	1 (3.4)
Reconstruction (%)	
Yes	23 (79.3)
No	6 (20.7)
Lateral neck dissection (%)	
Yes	24 (82.8)
No	5 (17.2)
Type of Lateral neck dissection (%)	
Unilateral	14 (58.3)
Bilateral	10 (41.7)

Table 2. Results of pathology evaluation of participants

Pathology parameters			Results
Differentiated (%)	Well-differentiated		12 (41.4)
	Moderately differentiated		10 (34.5)
	Poorly differentiated		3 (10.3)
	Indeterminate		4 (13.8)
Margin (%)	Free		22 (75.9)
	Closed		3 (10.3)
	Indeterminate		4 (13.8)
Tumor stage (%)	T	T1	17 (65.5)
		T2	9 (31)
		T3	2 (6.9)
		T4	1 (3.4)
	N	N0	19 (65.5)
		N1	6 (20.7)
		N2	4 (13.8)
	M0		29 (100)
Thickness (*cm*)	Indeterminate (%)		21 (72.4)
	Mean ± SD		0.82±0.95
DOI (*cm*)	Indeterminate (%)		18 (62.1)
	Mean ± SD		0.64 ± 0.6
LVI (%)	Yes		8 (27.6)
	No		14 (48.3)
	Indeterminate		7 (24.1)
PNI (%)	Yes		7 (24.1)
	No		4 (48.3)
	Indeterminate		8 (27.6)

LND: Lateral neck dissection; DOI: Depth of invasion; LVI: Lymphovascular invasion; PNI: Perineural invasion

Treatment Strategy

Adjuvant therapy was used in 79.3% of the patients, salvage (17.2%), and just in 1 (3.4%) patient with sole radiotherapy. Also, HDR-BT in 7 (24.1%) was conducted before EBRT, in 11 (37.9%) subjects after EBRT, and in 11 remaining patients, HDR-BT was done lonely (Table 3). The mean dose of EBRT in the tongue and neck were 47.4±2.4 *Gy* (44-50 *Gy*) and 52.2±6.6 *Gy* (45-65 *Gy*), respectively. 3.3±0.7 *Gy* per fraction (2-7 *Gy*/fraction total) was the mean HDR-BT with 28.01±10.9 *Gy* (10-45.5 *Gy*). The mean days of EBRT, HDR-BT, EBRT, and BT

Table 3. The used treatment strategies

Radiotherapy strategy		Report
Type of radiotherapy (%)	Definitive	1 (3.4)
	Adjuvant	23 (79.3)
	Salvage	5 (17.2)
Re-irradiation (%)	Yes	3 (10.3)
HDR-BT setting (%)	HDR-BT alone	11 (37.9)
	Boost BT before EBRT	7 (24.1)
	Boost BT after EBRT	11 (37.9)
EBRT dose (EQD210)	Tongue Median (IQR) Mean ± SD	 46 (45-50) 47.4 ± 2.4
	Neck Median (IQR) Mean ±SD	 50 (45-60) 52.2 ± 6.6
BT does/fx (Gy) Median (IQR) Mean ± SD		 3.3 (3-3.4) 3.3 ± 0.7
BT total dose (Gy) Median (IQR) Mean ± SD		 21 (21-40.8) 28 ± 10.9
Number of HDR-BT sessions, mean ± SD		7 ± 3.07
EBRT duration, day Mean ±SD		 35.3 ± 5.1
HDR-BT duration, day Mean ± SD		 6.2 ± 2
EBRT + HDR-BT duration, day Mean ± SD		 65.2 ±11.9
Used catheters Median (IQR) Mean ± SD		 8 (6-9) 7.8 ± 2.1 (5-14)
Chemotherapy strategy		
Type of treatment (%)	No chemotherapy	12 (41.4)
	Radiotherapy and chemotherapy concurrent	15 (51.7)
	Adjuvant	2 (6.9)

BT-Brachytherapy, High Dose Rate Brachytherapy-HDR-BT, Low Dose Rate brachytherapy-LDR-BT, External Beam Radiotherapy-EBRT.

were 34.5, 6, and 65.2 days, respectively. The mean catheter used for patients was 7.86±2.1 (5-14). 2 (6.9%) patients received adjuvant chemotherapy, 15 (51.7%) received chemotherapy concurrent with EBRT, and 12 (41.4%) remaining patients did not receive chemotherapy (Table 3).

Evaluating the treatment efficacy

CT simulation calculated the brachytherapy treatment plan using 3D reconstruction of target and peripheral structures (mandible). The information extracted from the dose-volume histogram, calculation of target coverage evaluation indices, and dose coverage in the Clinical Target Volume (CTV) is presented in Table 4. Based on the results, the ratio of non-uniformity of Dose distribution (DNR) in the target volume was 0.37 on average, and the average Compliance index (COIN) was 0.715. The dose parameter values received by the target organ and mandible during brachytherapy are presented in table 4.

Comparing the safety between groups

Late AEs: The more prevalent late AEs were dry mouth (79.2%) and dysarthria (66.7%). During one-year follow-up, Grade 3 (severe) and 4 (life-threatening) AEs were not observed (Figure 3) (Table 5).

Nutritional status and performance in a verbal test

The normality of diet and under-stability of speech in all the patients were evaluated based on FACT-HN and classified into good, intermedia, and bad subgroups. 19 (79.2%) precipitants had a good function, and 5 (20.8%) were intermediate (Table 6). The impaired function was not recognized.

One year following treatment, the rate of AEs was more frequent in the HDR-BT+EBRT group, but this difference was not significant. Also, the nutritional and verbal performance in the HDR-BT Group was better than HDR-BT+EBRT, but this was not significant, too (Table 7).

Comparing the clinical outcomes

OS through one year in the patients under HDR-BT was 82.8%, and DFS was 79.3%. Distant metastasis was identified in 6 (20.7%) subjects, 5 (17.2%) expired, and one had bone marrow metastasis. Finally, just 1 (3.4%) patient was recognized with regional relapse in the neck.

Our findings demonstrated that OS in the BT

Table 4. Dose-volume histogram information and dose coverage at the clinical target volume

Variables	Parameters	Median (IQR)
DNR (implant)		0.37 (0.31-0.4)
COIN		0.715 (0.682-0.767)
CTV/PTV		
Dose received by the target organ (Gy)	D 90 Vol%	3.12 (2.8-3.2)
	D 90 Vol% (dose is % of R_x)	96.1 (92-99)
The volume of the organ that received the prescribed dose (cm^3)	V 90% R_x	19.8 (15.5-26.4)
	V 90% R_x (% of total organ volume)	94.7 (91.6-96.7)
	V 100% R_x	16.6 (14-23.9)
	V 100% R_x (% of total organ volume)	86 (82.5-89)
	V 150% R_x	7.6 (4.5-8.9)
	V 150% R_x (% of total organ volume)	32.3 (28.6-35.9)
	V 200% R_x	3.04 (1.6-3.8)
	V 200% R_x (% of total organ volume)	12.3 (10.4-14.4)
Mandible		
Dose received by mandibular bone (Gy)	D 0.1 cm^3	2.1 (1.9-2.4)
	D 0.1 cm^3 (% of R_x)	70.3 (59.9-76)
	D 0.5 cm^3	1.98 (1.73-2)
	D 0.5 cm^3 (% of R_x)	59.9 (51-67.2)
	D 1 cm^3	1.7 (1.4-1.9)
	D 1 cm^3 (% of R_x)	54.8 (46.8-61.1)
	D 2 cm^3	1.52 (1.2-1.6)
	D 2 cm^3 (% of R_x)	50.5 (40.9-54.3)

DNR: Dose non-uniformity ratio; COIN: Conformal Index; PTV: planning target volume; CTV: clinical target volume.
D 90%: Dose received by 90% of the target organ volume; V200%: volume receiving 200% of the dose; V150%: volume receiving 150% of the dose; V100%: volume receiving 100% of the dose; D 0.1 cm^3: Dose received by 0.1 cm^3 of organ volume; D 0.5 cm^3: Dose received by 0.5 cm^3 of organ volume; D 1 cm^3: Dose received by 1 cm^3 of organ volume; D 2 cm^3: Dose received by 2 cm^3 of organ volume.

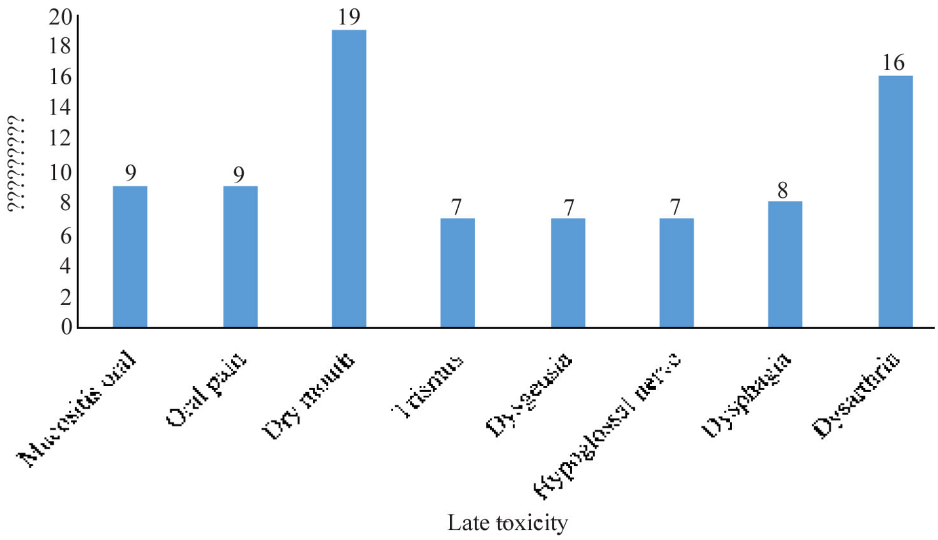

Figure 3. Prevalence of Adverse Events (AEs).

Table 5. The severity of delayed complications in the patients based on the CTCAE Version 5 scale

Adverse event	Not detected (%)	Grade 1 (Mild) (%)	Grade 2 (Moderate) (%)
Oral mucositis	17 (70.8)	5 (20.8)	2 (8.3)
Mouth pain	15 (62.5)	7 (29.2)	2 (8.3)
Dry mouth	5 (20.8)	10 (41.7)	9 (37.5)
Trismus	17 (70.8)	5 (20.8)	2 (20.8)
Osteonecrosis of the jaw	24 (100)	0	0
Dysgeusia	17(70.8)	3 (12.5)	4 (16.7)
Hypoglossal nerve damage	17 (70.8)	6 (25)	1 (4.2)
Dysphagia	16 (66.7)	8 (33.3)	0
Speech impediment	8 (33.3)	15 (62.5)	1 (4.2)
Soft tissue necrosis of the head	24 (100)	0	0
Oral cutaneous fistula	24 (100)	0	0

CTCAE: Common Terminology Criteria for Adverse Events.

Table 6. Examining the nutritional and verbal performance of the patients based on the FACT-HN scale

Function	Good (%)	Intermediate (%)
Performance	19 (79.2)	5 (20.8)
Normalcy of diet	16 (66.7)	8 (33.3)
Understandability of speech	18 (75)	6 (25)

FACT-HN: Functional Assessment of Cancer Therapy-Head and Neck

Group was significantly higher than in BT+EBRT groups (100% vs. 72.2%) (p-value=0.05). However, significant differences were not found between groups when adjusted for DFS, distant metastasis, and local and regional recurrence (p-value >0.05) (Table 8). Just one locoregional (neck) patient was recognized in the BT+EBRT group. With further analysis, the significant differences were not found for favorable response with HDR alone when adjusted for disease stages (p-value >0.05) (Table 9).

Table 7. Comparing safety between two groups

Adverse event	HDR-BT (N=11)	HDR-BT+EBRT (N=18)	p-value
Oral mucositis (%)	4 (36.4)	3 (23.1)	0.225
Mouth pain (%)	4 (36.4)	5 (38.5)	0.234
Dry mouth (%)	7 (63.7)	12 (89.3)	0.175
Trismus (%)	2 (18.2)	5 (38.5)	0.305
Dysgeusia (%)	2 (18.2)	5 (38.5)	0.507
Hypoglossal nerve damage (%)	2 (18.2)	5 (38.5)	0.471
Dysphagia (%)	2 (18.2)	6 (46.2)	0.103
Speech impediment (%)	5 (45.5)	11 (87.6)	0.128
Performance, good (%)	10 (90.9)	9 (69.2)	0.13
Normalcy of diet (%)	9 (81.8)	7 (53.8)	0.179
Understandability of speech (%)	10 (90.9)	8 (61.5)	0.099

Table 8. Comparing HDR-BT and HDR+EBRT groups for clinical outcome

Variable	HDR-BT (N=11)	HDR-BT +EBRT (N=18)	p-value
OS*	11 (100)	13 (72.2)	0.055
DFS (month)	10 (90.9)	13 (72.2)	0.224
Recurrence (%)	0	1 (7.7)	0.336
Regional Recurrence (%)	0	1 (7.7)	0.398
Distance metastasis (%)	1 (9.1)	5 (27.8)	0.273

* Five-year survival rate

Table 9. Evaluating the stages of the disease on overall survival between groups

T Stage			Overall survival		p-value
			Expired (%)	Alive (%)	
T1	HDR. Group	With RT	0	6 (100)	0.204
		Without RT	2 (18.2)	9 (81.1)	
T2	HDR. Group	With RT	0	5 (100)	0.071
		Without RT	2 (50)	2 (50)	
T3	HDR. Group	With RT	1 (50)	1 (50)	-
T4	HDR. Group	Without RT	0	1 (100)	-

Evaluating Metastasis

Of 29 patients, six subjects had metastasis during 1-year follow-up. Further analyses were conducted to explore predisposing risk factors for metastases. The results have shown that the probability of metastasis in patients with the N0 stage is less (p-value=0.005) (Table 10).

Discussion

The impact of initial treatment at diagnosis time on patient outcome and rate of response to therapy is irrefutable. This causes a proliferation of considerable studies to find the most effective clinical development in TSCC by investigating various aspects.

With the progression in surgical techniques, the use of BT was challenged due to AEs. However, with the improvement of BT strategy, it again attracted researchers' attention. Additionally, it was demonstrated that BT has various efficacy on initial to progressed TSCC stage (13). Hence, in the present survey, we tried to find valuable results in BT designing treatment protocols.

Compared to radiotherapy with radiopharmaceuticals, BT's body fluids (urine, saliva, sweat) are not radioactive; thus, even with similar efficacy, BT is preferable. BT by DNA damaging in the cancerous cell, induces cell apoptosis. Since the ability of DNA repair reduces cancer, it results in increased apoptosis in tumor cells.

Our data indicated that most TSCC patients were T1 and N1 stages. Also, treatment with HDR-BT showed favorable OS. In our findings, BT alone was accompanied by lower toxicity than BT+EBRT; however, this was insignificant. Since most of the studied population in the present survey had the same stages, insignificantly between BT and BT+EBRT groups for AEs-related treatment can be due to the low sample size. The same investigation by Ali *et al* demonstrated that therapy with HDR-BT is accompanied by limited toxicity additional to OS, DFS, and complete response (9).

In contrast, in the study of Mattei *et al*, grade 3-4

Table 10. Comparing metastatic and non-metastatic patients

Variables		Metastatic (N=6)	Non-metastatic (N=23)	p-value
Age, median (IQR)		50 (33-63)	48 (41-63)	0.483
Gender (%)				
Male		2 (33.3)	8 (34.8)	0.946
Female		4 (66.7)	15 (66.2)	
Salvage surgery (%)		0	2 (0.7)	0.673
Tumor stage, T (%)	T1	3 (50)	14 (60.9)	0.719
	T2	2 (33.3)	7 (30.4)	
	T3	1 (16.7)	1 (4.3)	
	T4	0	1 (4.3)	
Tumor stage, N (%)	N0	1 (16.7)	18 (78.3)	0.005
	N1	4 (66.7)	2 (8.7)	
	N2	1 (16.7)	3 (13)	
Tumor differentiated (%)	Well	1 (16.7)	11 (47.8)	0.174
	Moderate	2 (33.3)	8 (34.8)	
	Poorly	2 (33.3)	1 (4.3)	
Type of radiotherapy treatment (%)	Definitive	0	1 (4.3)	0.863
	Adjuvant	5 (83.3)	18 (78.3)	
	Salvage	1 (16.7)	4 (17.4)	
Length of EBRT, median (IQR)		36 (31.5-37.5)	34 (30.5-41)	0.934
Dose of EBRT, tongue, median (IQR)		46 (44.5-49)	50 (45-50)	0.525
Dose of EBRT, neck, median (IQR)		60 (52.5-60)	50 (45-55)	0.35
Length of HDR-BT, median (IQR)		6 (6-7)	5 (4-6)	0.107
Dose of HDR-BT in each section, median (IQR)		3.7 (3.1-6.25)	3 (3-3)	0.29
Total dose of HDR-BT, median (IQR)		21 (20.5-23.2)	21 (19.2-21)	0.756
Chemotherapy (%)	No	1 (16.7)	11 (47.8)	0.208
	Concurrent	5 (83.3)	10 (43.5)	
	Adjuvant	0	2 (8.7)	
DNR, median (IQR)		0.4 (0.3-0.47)	0.37 (0.32-0.4)	0.476
COIN, median (IQR)		0.7 (0.7-0.8)	0.7 (0.6-0.7)	0.043

High Dose Rate Brachytherapy-HDR-BT. Low Dose Rate brachytherapy-LDR-BT. External Beam Radiotherapy-EBRT

toxicity was observed even in LDR (14). Also, residual pain and dysesthesia were the most frequent late AEs (14), while dry mouth and dysarthria were prevalent in our data. On the other hand, the HDR-BT group had better nutritional status and performance in the verbal test than EBRT+BT. Santos *et al* have demonstrated HDR-BT in locally advanced tongue carcinomas with a median dose of 18-24 *Gy*, increased permit of local dose, improving response to treatment than alone EBRT (15). This is in accordance with the present survey that OS in HDR-BT was higher than HDR-BT plus EBRT; however, the median dose we used was 21-40 *Gy* BT in 3-13 fraction, while Santos *et al* used 18-24 *Gy* in 6-8 fractions (15). One of the most significant challenges in HDR-BT is the optimal dose. Unfortunately, there is no data about the most effective dose of HDR-BT. Concerning damage to the normal tissue around the tumor, dose determination is a lot of caution. In our investigation, we utilized 3.3±0.7 mean *Gy* of HDR-BT per fraction; at the same time, Cheung et al. indicated that by using inverse planning simulated annealing (IPSA), it is possible to increase the HDR-BT dose to 6 *Gy* without increasing AEs (16). IPSA and Hybrid Inverse Planning and Optimization (HIPO) are verified algorithms for improving the HDR-BT efficacy. IPSA and HIPO improve HDR-BT dose distribution and reduce damage to normal tissues (19), although more investigations are required to design the most effective HIPO and IPSA algorithms in the therapy plane of TSCC.

Dong *et al* evaluated the efficacy of iodine-125 interstitial BT without any adjuvant treatment on primary locally advanced adenoid cystic carcinoma of the base of the tongue. Their results revealed that the solely iodine-125 interstitial BT is accompanied by favorable OS and DFS (17). Also, they found that the OS following metastasis significantly decreases, in contrast with the present survey results[17] The study by Yoshimura et al. demonstrated HDR-BT by using Au-198 grains or Ir-192 pins; the 3- years LC and DFS of TSCC patients are more efficient than EBRT; also, this response rate of treatment was higher in cT1-2 grades (18). Additionally, they reported 6% of grades 3 and 4 of AEs, whereases we just recognized grades 1-2 AEs. According to the NCCN guideline, patients with superficial T1 can be treated just with BT, and surgery is conducted for infiltration of T1 and T2 lesions. In Iran, the aggressive treatment strategy for patients with superficial T1 includes surgery combined with BT, EBRT, or both. The only common denominator among all studies is the emphasis on combination treatments; chemotherapy, surgery, and BT had lower OS.

Clinically, neck is one of the main prognostic factors in oral SCC. Thus, the proper management of the neck has a vital role in SCC outcomes. The type of surgery could influence BT outcome. Patients who undergo modified neck dissection experience more expansive AEs-related surgery than selective neck dissection. Based on the evidence, most centers prefer modified neck dissection in the US and UK, whereas in the Netherlands, selective dissection is major surgery (19). This variation in treatment protocols influences the OS and DFS in TSCC. In this regard, all the possible influential factors should be considered in the interpretation efficacy of HDR-BT. For instance, it was demonstrated that BT following positive/narrow margins present post-primary surgical resection of oral TSCC, which are in the T1N0 stage, is more efficient and causes a reduction in mortality consequence of EBRT (20). In this regard, predictive factors have a potential efficacy in outcome improvement, such as depth of invasion. Depth of invasion with 96.8% accuracy was reported as a reliable predictive factor in choosing type of dissection in early carcinoma stages (21). It can be concluded that considerable factors influence the efficacy of the therapy strategy. Therefore, more outstanding efforts are needed to understand impactful agents before initialing the primary treatment.

Conclusion

Our findings showed that the HDR-BT increases the OS of TSCC patients more than EBRT without developing grade 3-4 AEs and metastasis. In the present, it was demonstrated that the mean 3.2±0.7 *Gy* of HDR-BT has more OS than EBRT, but the influence of promoting agents and auxiliary algorithms was not evaluated. In this line, it is highly recommended in further surveys that this plan considers alongside the supplemental therapies.

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Conflicts of Interest

The authors declare that they have no competing interests.

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