CT-guided ^{125}I brachytherapy in the treatment of distant metastases in the oral cavity and maxillofacial region

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Abstract

PURPOSE: We aimed to evaluate the feasibility and clinical effectiveness of CT-guided ^{125}I brachytherapy for distant oral and maxillofacial metastases. *MATERIALS AND METHODS:* We retrospectively analyzed 65 patients with 84 distant oral and maxillofacial metastases. Thirty-one patients with 38 lesions received ^{125}I brachytherapy (group A) and 34 with 46 lesions received external beam radiotherapy (EBRT; group B). *RESULTS:* Median follow-up time was 16 months. The 3-, 6-, 12-, 18-, and 24-month local control rates for group A were 83.9%, 75.9%, 66.7%, 38.4%, and 25.0%, respectively; for group B they were 76.5%, 62.5%, 43.8%, 25.0%, and 0.0%, respectively (P < .05); the median local tumor progression-free survival times were 14 and 9 months, respectively. Group A had a better local tumor progression-free survival (LTPFS) relative to group B (P < .001; HR, 6.961 [95%CI, 2.109, 9.356]). Cox proportional hazards regression analysis indicated that ^{125}I brachytherapy, tumor size, and primary pathological type were the independent factors affecting LTPFS. Additionally, ^{125}I brachytherapy showed better performance in relieving patient clinical symptoms relative to EBRT (P < .05). Group A also had fewer complications than group B, especially regarding grade 3/4 complications according to Radiation Therapy Oncology Group grading criteria. Mean overall survival times in groups A and B were 17.1 and 14.8 months, respectively. *CONCLUSION:* CT-guided ^{125}I brachytherapy is feasible and safe for distant oral and maxillofacial metastases; it achieved a better local control rate, longer LTPFS and fewer complications without compromising overall survival compared with EBRT.

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Introduction

Distant metastasis to the oral and maxillofacial region is rare and represents 1% of all malignancies in this region. The most common primary in males are lung cancer (approximately 33%), followed by kidney cancer and malignant melanoma; in females they are breast cancer tumors (approximately 25%), followed by malignant tumors in the reproductive organs, lung, and kidney [1]. Most patients with oral and maxillofacial metastases usually have end-stage disease; the overall prognosis of such patients is poor, and the overall survival time from the appearance of metastases is 6–52 months [2]. Patient quality of life (QoL) is very poor and often accompanied with obvious clinical symptoms such as local swelling, pain, paresthesia, dysphagia, and trismus [3].

Usually, patients have received a series of previous comprehensive treatments, including surgery, systemic chemotherapy and local radiotherapy, to control the primary tumors and metastasis in other parts of the body [4]. Therefore, the patient's general condition is poor, the effectiveness of radical surgery for improving the prognosis and QoL is limited, perioperative morbidity and mortality are high, and the majority of patients still die from metastasis to another organ in 1–2 years after

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surgery [5,6]. Most reports consider that improving local control and patient QoL are the main goals at this stage [7]. There is no denying that radiotherapy plays an important role in the treatment of oral and maxillofacial metastases; numerous studies have also confirmed the effectiveness of radiotherapy in the relief of clinical symptoms and improvement in QoL [8]. However, these patients were in the end-stage concerning tumor staging and grading, and were in poor general health condition, especially those with metastasis close to the cardinal organs (such as the pharynx, eyes, and oral cavity); these organs usually have a poor tolerance to high doses of radiation [9]. Curative radiation doses often lead to severe side effects. Even though the latest technology is used, such as sophisticated 3-dimensional computerized planning systems, multileaf beam collimators or altered fractionation schedules, the detrimental side effects of radiotherapy cannot be avoided. This exacerbates the psychological burden of patients, and reduces patient cooperation and treatment efficacy [10]. Some patients may even die of severe complications such as radiation encephalopathy. Consequently, the physician has to reduce the radiation dose because there are too many complications associated with radiotherapy. These palliative radiotherapy regimens lead to a decline in local control and a higher incidence of residual tumors and recurrence; this seriously affects patient QoL [11].

In recent years, a new modality, ^{125}I brachytherapy, has been accepted as a useful and minimally invasive interventional modality, because it achieves higher local tumor control and fewer complications [12,13]. Many studies have evaluated ^{125}I brachytherapy have a good curative effect in pancreatic cancer, liver cancer, lung cancer, prostate cancer, and gynecological and brain malignancies [14]. The ^{125}I seed is a miniature radioactive source; it continuously delivers low doses of x-rays and γ-rays, and the radiation dose decreases rapidly with increasing distance from the source [15]. This characteristic makes it possible for CT-guided ^{125}I brachytherapy to completely cover the therapeutic target area avoiding damage to the adjacent normal tissues [16,17]. However, to date our study is the first

to report on the treatment of distant metastases to the oral and maxillofacial regions using the ^{125}I brachytherapy modality. The purpose of our study was to evaluate the effectiveness and safety of CT-guided ^{125}I brachytherapy for distant oral and maxillofacial metastases [18].

Materials and Methods

Study Population

This retrospective study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All patients in the study were fully informed of the potential risks and voluntarily signed informed consent forms.

From June 2006 to July 2014, we recruited 65 patients diagnosed with oral and maxillofacial metastasis; the site of the primary cancer and pathological type are detailed in Table 1. Most of the patients had already experienced systemic and comprehensive treatment to control local and systemic lesions; all patients were in relatively stable condition but had more prominent clinical symptoms related to the oral and maxillofacial regions. In all patients enrolled, 31 patients could not tolerate or were unwilling to undergo surgery and EBRT because of poor general condition and the location of the metastasis. These 31 patients received ^{125}I brachytherapy (group A) after they were fully informed of the risks associated with ^{125}I brachytherapy; 34 patients underwent EBRT (group B). Patient characteristics are detailed in Table 2.

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) patients with histologically proven oral and maxillofacial metastases; (2) 3 oral and maxillofacial lesions with each lesions having a diameter 5 cm; (3) patient age between 18 and 70 years; (4) East Coast Oncology group (ECOG) performance status value ≤2; (5) life expectancy of 3 months; (6) platelet count ≥10.0 × 109/L, and a blood coagulation function within normal ranges.

Table 1. Site of primary tumor and pathological type

	Group A (n = 31)					Group B (n = 34)					
	Number	T_{1-2}	T_{3-4}	N_0	N_{1-3}	Number	T_{1-2}	T_{3-4}	N_0	N_{1-3}	P
Lung cancer	8 (25.8%)	3	5	2	6	11 (32.4%)	5	6	2	9	.960
Squamous cell	4					6					
Adenocarcinoma	4					4					
Adenosquamous	0					1					
Renal cancer	6 (19.3%)	2	4	1	5	3 (8.8%)	2	1	0	3	.619
Clear cell	4					2					
Papillary cell	1					1					
Chromophobe cell	1					0					
Melanoma	5 (16.1%)	0	5	2	3	3 (8.8%)	1	2	0	3	.214
Breslow I	1					0					
Breslow II	1					2					
Breslow III	3					1					
Prostatic cancer	3 (9.7%)	1	2	0	3	5 (14.7%)	1	4	1	4	.753
Adenocarcinoma	3					5					
Breast cancer	4 (12.9%)	3	1	0	4	6 (17.6%)	4	2	1	5	.759
Noinvasive cancer	1					1					
Invasive cancer	3					5					
Ovarian cancer	2 (6.5%)	0	2	0	2	1 (2.9%)	0	1	0	1	.800
Serous carcinoma	1					1					
Mucinous carcinoma	1					0					
Liver cancer	2 (6.5%)	0	2	0	2	3 (8.8%)	0	3	0	3	.738
Hepatocellular carcinoma	2					3					
Colorectal	1 (3.2%)	0	1	0	1	2 (5.9%)	1	1	0	2	.593
Adenocarcinoma	1					2					

Note: According to the American Joint Committee on Cancer (AJCC), T_{1-2}, T_{3-4} refers to the conditions of the primary tumor, N_0, N_{1-3}, refers to the regional lymph node involvement.

Table 2. Patients' characteristics

Characteristics	Group A (n = 31)	Group B (n = 34)	P
Age			.678
Average ± SD[1]	56.6 ± 11.7	59.2 ± 12.6	
≥60	13 (41.9%)	16 (47.1%)	
<60	18 (58.1%)	18 (52.9%)	
Sex			.478
Male	20 (64.5%)	19 (55.9%)	
Female	11 (35.5%)	15 (44.1%)	
ECOG PS			.441
0	17 (54.8%)	23 (67.6%)	
1	12 (38.7%)	7 (20.6%)	
2	2 (6.5%)	4 (11.8%)	
Lesion diameter			.531
Mean diameter ± SD	3.72 ± 0.88	3.63 ± 0.69	
<3 cm	14 (45.2%)	18 (52.9%)	
3–5 cm	17 (54.8%)	16 (47.1%)	
Oral and maxillofacial site			.848
Oral cavity	4 (12.9%)	7 (20.6%)	
Soft tissue of facial area	8 (25.8%)	6 (17.6%)	
Lower jaw	9 (41.9%)	11 (32.4%)	
Upper jaw	4 (29.0%)	5 (14.7%)	
Other	6 (19.4%)	5 (14.7%)	
Number of lesion			.264
1	24 (77.4%)	22 (64.7%)	
2	7 (22.6%)	12 (35.3%)	
Number of other invaded organ[2]			.564
1	9 (29.0%)	7 (20.6%)	
2	6 (19.4%)	10 (29.4%)	
≥3	16 (51.6%)	17 (50.0%)	
History of treatment[3]			.791
Surgery	25 (80.6%)	23 (67.6%)	
Radiotherapy	18 (58.1%)	24 (70.6%)	
Chemotherapy	29 (93.5%)	27 (79.4%)	
Minimally invasive treatment	14 (45.2%)	18 (52.9%)	
Other[4]	6 (19.4%)	9 (26.8%)	

Notes: SD[1] = standard deviation. Number of other invaded Organ[2] = metastasis in other parts of the body, that not include the oral and maxillofacial region. History of treatment[3] = treatment modality that the patient has undergone. Other[4] = including immunobiological therapy, molecular targeting treatment and Chinese medicine treatment.

Exclusion criteria were: (1) primary or recurrent malignancy in the head and neck; (2) serious skin fester or infection around the lesions; (3) a serious bleeding tendency, and coagulation function disorder; (4) severe liver, kidney, heart, lung, and brain function insufficiency.

Treatment

^{125}I brachytherapy. The ^{125}I seed (Atom High Tech, Beijing, China) was formed by outsourcing the shell materials consisting of a titanium pipe with a diameter of 0.8 mm, length of 4.5 mm and wall thickness of 0.05 mm; the ^{125}I isotope was attached to the inner silver column (diameter, 0.5 mm; length, 3 mm). The main characteristics of ^{125}I seed were: initial radioactive activity, 0.8 mCi; average energy, 27–32 KeV; half-life, 59.6 days; and effective radiation radius, 1.7 cm.

CT images acquired in <1 week preoperatively were imported into the treatment planning system (TPS; RT-RSI: Beijing Atom and HighTechnique Industries Inc., Beijing, China). As shown in Figure 1, a clinical oncologist and a professional physicist together verified the outline of clinical target volume (CTV) and planning target volume (PTV); PTV refers to the boundary of the CTV scaled out by 1 cm. We calculated the number of ^{125}I seeds needed, activity and total radioactive dose activity using the TPS, regarding the dose required to reach the prescribed dose, namely the matching peripheral dose. Then we developed a dose-volume histogram, observed dose distribution, and adjusted the guide pin to achieve an optimal dose distribution in the PTV. The dose delivered to the planning target

volume should reach 95% of the prescribed dose, namely Vl00 >95%. The prescribed dose in this study was averaged at 120 Gy (100–140 Gy) according to the American Brachytherapy Society for prostate cancer and previous studies from our center.

Patients were usually located in a supine position. We drew the puncture path on the images after the CT scan at a thickness of 5 mm according to the TPS. After local infiltration anesthesia with 5–10 ml of 1% lidocaine, an 18-G spinal needle composed of an inner core needle and a needle cannula forming the outer layer (Yunke Pharmaceutical Limited Liability Company, Chengdu, China) was introduced into the tumor and the direction of the needle adjusted under CT guidance. Eventually, all of the needles reached to the farthest boundary of tumor while ensuring the distance between each seed needle was about 1 cm. The needle core was pulled out and applied using an ^{125}I seed implantation gun (Yunke Pharmaceuticals Limited Liability Company, Chengdu, China) to transport the ^{125}I seeds into the tumor through the outer needle cannula. One seed was released with withdrawal every 0.5 cm; a distance of about 1 cm was maintained from the skin and vital organs such as the oral mucosa, throat, nerves and other tissues. A CT scan was performed to confirm the precise release of the ^{125}I seeds and then the spinal needle was pulled out and the final CT image was imported into TPS to carry out dose verification.

EBRT. Group B were treated by physicians with 10 years' experience in radiotherapy; the radiotherapy modalities used were mainly three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). The radiotherapy physician delineated the gross tumor volume (GTV) and CTV using the Monaco TPS system (version 5.0) according to recent CT or magnetic resonance imaging (MRI) images. The GTV of lesions was visualized on CT or MRI. The CTV was the GTV with an additional 1- to 1.5-cm margin. The PTV was developed by extending the margin by an additional 3 mm relative to the CTV to allow for setup variability and internal motion.

The organs at risk (OAR) included the facial nerve, pharynx, oral mucosa, parotid glands, submandibular gland, temporomandibular joints and mandible. The dose constraints of the OAR were prescribed with a relatively low dose (50–60 Gy). The prescribed doses were 60–70 Gy to the GTV (2 Gy or 1.8 Gy per daily fraction, 5 days per week).

Follow-up and Evaluation Criteria

In accordance with our follow-up protocol, enhanced CT or MRI images were obtained for the evaluation of curative effect at the first month after treatment and then every 3 months.

Local control (LC) was defined as the proportion of patients with a complete response and partial response. The European Organization for Research and Treatment of Cancer-Quality of Life-Head and Neck Questionnaire (EORTC QLQ H&N35) was used to evaluate patient QoL; we statistically analyzed every patient's score and converted it into a standardized score ranging from 0 to 100. The two groups of patients were required to complete the EORTC QLQH&N35 before treatment and at 0, 3, 6, and 12 months after treatment. Complications in the two groups were evaluated according to the Radiation Therapy Oncology Group (RTOG) grading criterion.

Statistical Analysis

Statistical analysis was performed using statistical software (SPSS 20.0). All statistical tests were bilateral; there was considered to be a
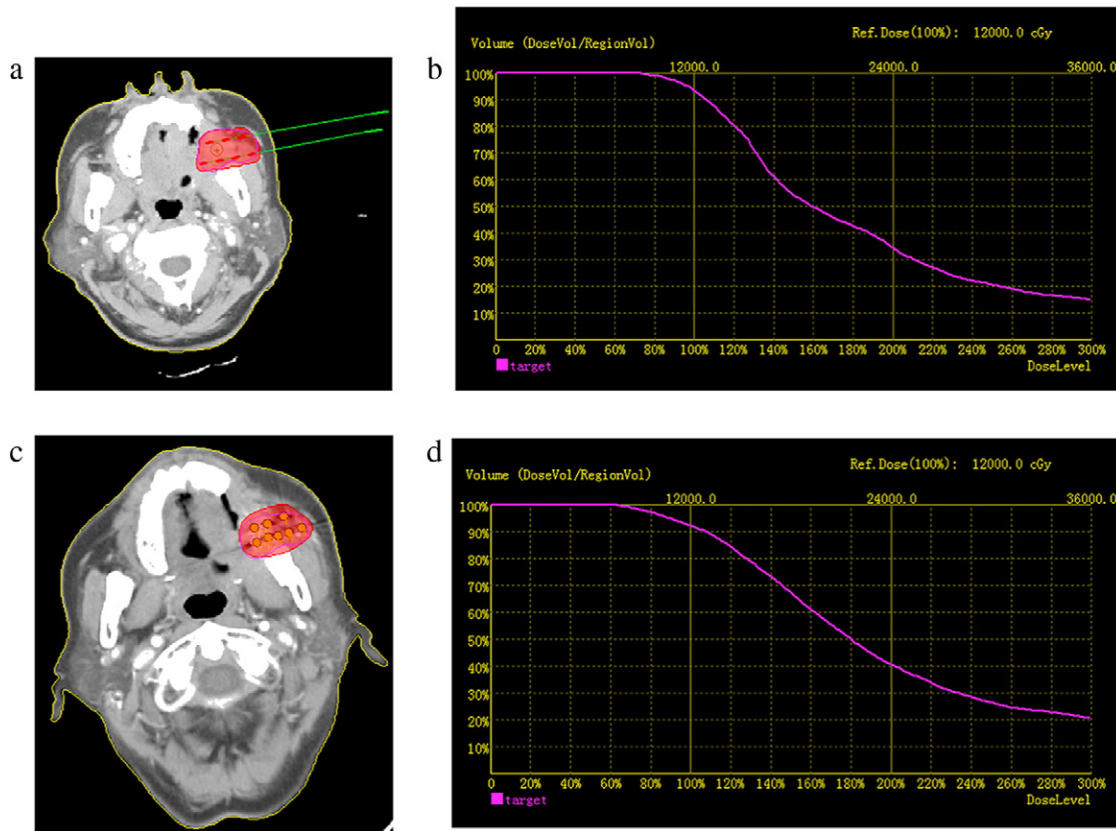
Figure 1. (a) Red lines represent the tumor's contour, the purple area is covered by 90% prescribed dose. (b) Preoperative dose volume histograms (DVH), target = tumor, we set the prescribed dose (PD) of 120 Gy. A total of 90% of the tumor target (D90 = 127.3 Gy) received 127.3 Gy, and 93.4% of the tumor target received 100% of the prescribed dose (V100 = 93.4%). (c) Postoperative distribution of seeds. d. Postoperative DVH, D90 = 129.3 Gy, V100 = 92.2%, postoperative dose distribution coincided with preoperative.

significant difference when the $P < .05$. Kaplan–Meier analysis and the log-rank test were used to compare OS and LTPFS in the two groups. We also built stratified Cox proportional hazard models and used the forward stepwise procedure to investigate the potential factors related to LTPFS and OS. Cox proportional hazards regression analysis was used to calculate the covariate entered into the model, hazard ratios and the confidence intervals (CI).

Results

A total of 31 patients with 38 lesions received ^{125}I brachytherapy procedures under CT guidance by radiologists with 10 years' experience. All patients underwent postoperative dose verification using the TPS. The median number of ^{125}I seeds used was 31 (range,

9–43). In group B, the median radiotherapy dose was 55 Gy (range, 45–70) Gy, the median radiotherapy treatment time was 30 (range, 25–35) days, and the median follow-up time in the two groups was 18 (range, 3–44) months.

Local Control and LTPFS

As shown in Table 3 the 3-, 6-, 12-, 18-, and 24-month LC rates for group A were 83.9%, 75.9%, 66.7%, 38.4%, and 25.0%, respectively, and for group B were 76.5%, 62.5%, 43.8%, 25.0, and 0.0%, respectively ($P < .05$).

The median LTPFS times in groups A and group B were 14 and 9 months, respectively. Kaplan–Meier curves for LTPFS are presented in Figure 2. Cox proportional hazards regression analysis revealed that

Table 3. Clinical efficacy of ^{125}I brachytherapy and external beam radiotherapy

| | Local control efficacy (%) | | | | | | | | | | |
| | Group A | | | | | Group B | | | | | |
Follow-up period	CR	PR	SD	PD	LC	CR	PR	SD	PD	LC	P
3 m	17	9	4	1	26/31 (83.9%)	7	19	5	3	26/34 (76.5%)	.030
6 m	14	8	5	2	22/29 (75.9%)	5	10	2	7	15/24 (62.5%)	.037
12 m	9	3	4	2	12/18 (66.7%)	2	5	2	7	7/16 (43.8%)	.032
18 m	4	1	7	1	5/13 (38.4%)	0	2	2	4	2/8 (25.0%)	.023
24 m	2	0	5	1	2/8 (25.0%)	0	0	1	4	0/5 (0.0%)	.032

Note: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
LC, based on the Response Evaluation Criteria in Solid Tumors (RECIST), LC defined as the proportion of patients with complete response and partial response.
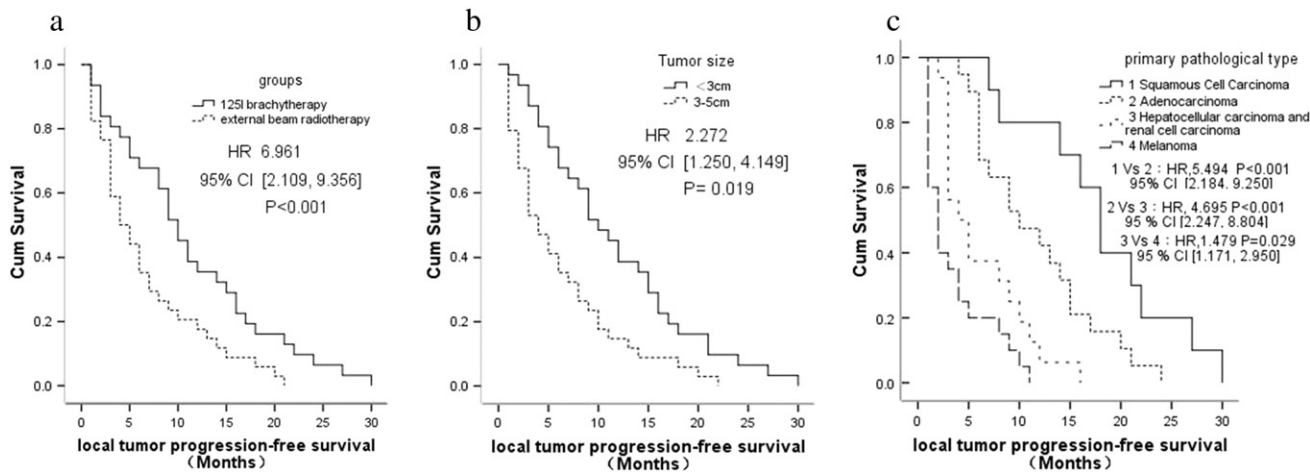
Figure 2. (a) Local tumor progression-free survival in group A and group B. (b) Local tumor progression-free survival in patients with different sizes.(c) Local tumor progression-free survival with different primary pathological type.

group A had better LTPFS (*P* < .001; HR, 6.961 [95%CI, 2.109, 9.356]) and ^{125}I brachytherapy was an independent factor related to LTPFS. As shown in Table 4, tumor sizes and primary pathological type were also independent factors affecting the LTPFS.

Relief of Clinical Symptoms

In this study, the major clinical symptoms in the oral and maxillofacial regions were pain (84.6%), swelling (100%), paresthesia (55.4%), bleeding (18.5%), trismus (30.8%) and dysphagia (16.9%). As summarized in Table 5, the remission rate of clinical symptoms in group A was significantly superior to that in group B.

QoL

As summarized in Table 6, before treatment, the QoL scores were 71.34 ± 21.13 and 69.87 ± 23.98 (*P* = .681). At 3, 6 and 12 months after treatment, the scores for group A had significantly improved 9.21, 15.20, and 18.55, respectively and reached 62.13, 56.14, and 52.79, respectively. However, in group B the scores had not obviously improved relative to group A and had even deteriorated; at 0, 3, and 6 months after treatment they degenerated 6.02, 6.28, and 1.48, respectively and reached 75.89, 76.15, and 71.35, respectively. Only at 12 months after

treatment had the QoL scores for group B mildly improved 5.66 to 64.21. Statistical analysis also indicated that group A had better performance regarding the improvement in QoL score than group B (*P* < .001).

Complications in Groups A and B

No serious complications occurred during the process of ^{125}I brachytherapy. Major complications in the two groups during the follow-up period are detailed in Table 7. The results indicated that patients in group A had significantly fewer complications than those in group B. There were no complications of grade 5 in two groups; 61.8% (21/34) of patients in group B experienced complications of grade 3/4, while only 12.9% (4/31) of patients experienced complications of grade 3/4 in group A. Seed migration occurred in 3/31 (9.7%) of patients without any severe complications during the follow-up period.

OS

The mean OS in groups A and B was 17.1 months and 14.8 months, respectively. The 1-, 2-, and 3-year OS rates were 54.8%, 25.8%, and 6.5%, respectively in group A and 47.6%, 14.7%, and 2.9%, respectively in group B. Kaplan–Meier survival curves are presented in Figure 3. The

Table 4. Results of Cox proportional hazards regression analysis for LTPFS and OS

Variable		OS			LTPFS		
		P	HR	95%CI	*P*	HR	95% CI
groups	A				<0.001	6.961	2.109, 9.356
	B						
Tumor size	3-5 cm				0.019	2.887	2.109, 4.215
	<3 cm						
Number of other invaded Organ							
	≥3	<0.001	9.524	2.516,17.548			
	2						
	1	0.023	2.783	1.227,4.584			
Primary pathological type							
	Squamous Cell Carcinoma				<0.001	5.494	2.184, 9.250
	Adenocarcinoma						
	Hepatocellular carcinoma and renal cell carcinoma				<0.001	4.695	2.247, 8.804
	Melanoma				0.029	1.479	1.171, 2.950

Note: OS = overall survival; LTPFS = local tumor progression-free survival; HR = hazard ratio; CI = confidence interval.

Table 5. Relief of clinical symptoms

Symptoms	Group A						Group B						P
	No	SI	PI	IC	AG	RR	NO	SI	PI	IC	AG	RR	
Pain	25	15	5	5	0	20/25 (80.0%)	30	6	14	8	2	20/30 (66.8%)	.026
Swelling	31	15	11	4	1	26/31 (83.9%)	34	9	12	11	4	21/34 (61.8%)	.014
Bleeding	5	4	1	0	0	5/5 (100.0%)	7	1	4	2	0	5/7 (71.4%)	.008
Paresthesia	17	7	3	5	2	10/17 (58.8%)	19	2	3	10	4	5/19 (26.3%)	<.001
Trismus	11	5	4	2	0	9/11 (81.8%)	9	1	2	4	2	3/9 (33.3%)	<.001
Dysphagia	5	3	1	1	0	4/5 (80.0%)	6	0	2	2	2	2/6 (33.3%)	<.001

Note: The relief of clinical symptoms after treatment were evaluated comprehensively according to a series of assessment criterion, such as imaging, physical examination, EORTC-QLQ H&N35,classification standard of maximal mouth opening, patients' subjective feeling, and so on. The relief of clinical symptoms was divided into significant improvement (SI), partial improvement (PI), indistinctive change(IC) and aggravation (AG). Remission rate of clinical symptoms was the proportion of SI and PI. The final evaluation results determined by the same two physicists, if the results of the two physicists were controversial, the patients' evaluation results must go through negotiation to reach an agreement.
No = number; RR = remission rate of clinical symptoms = (SR + PR)/No.

Table 6. Patients' mean EORTC-QLQ H&N35 scores of 35 items .

	Standard score of EORTC-QLQ H&N35 (mean score ± SD)				P
	Group A		Group B		
	Score	Difference	Score	Difference	
Before treatment	71.34 ± 21.13		69.87 ± 23.98		.681
0 month after treatment	72.13 ± 19.78	+0.79 ± 6.27	75.89 ± 20.65	+6.02 ± 9.12	.026
3 months after treatment	62.13 ± 21.14	−9.21 ± 8.21	76.15 ± 13.98	+6.28 ± 11.27	<.001
6 months after treatment	56.14 ± 13.23	−15.20 ± 17.34	71.35 ± 16.49	+1.48 ± 9.14	<.001
12 months after treatment	52.79 ± 20.92	−18.55 ± 13.51	64.21 ± 18.16	−5.66 ± 13.93	<.001

Note: The EORTC Quality of Life Head and Neck Module (EORTCQLQ-H&N35) is a questionnaire specific to head and neck cancer patients consisting of 35 items designed to assess health-related QoL. Given that all the scales assess symptoms, higher scores correspond to lower quality of life.
    Calculated every patient's score in each items and converted into standardized score ranged 0 to 100, adding score of 35 items and then using the sum score of 35 items divided 35.

log-rank (Mantel-Cox) test suggested no statistical difference (χ-3.190; P = .074) in the survival curves. Cox proportional hazards regression analysis revealed that the number of other invaded organs was the only independent factor affecting OS. (See Fig. 4.)

Discussion

Although 125I brachytherapy has been successfully applied in many solid tumors, our study is the first to use this modality in the treatment of oral and maxillofacial metastases [19]. It is significant because patients with oral and maxillofacial metastases can often feel the presence of these lesions and have obvious clinical symptoms in these regions [20,21]. Palliative radiotherapy can alleviate the clinical symptoms to some extent, but its side effects and complications are significant [22,23].

125I seeds emit continuous low doses of γ-rays, this can efficiently inhibit tumor cell proliferation, promote apoptosis and maximize the destruction of the tumor without damaging the normal surrounding tissue; this is because the energy of the γ-rays rapidly decays with increased distance [24]. Therefore, 125I brachytherapy with a higher LC rate and fewer complications is a good choice for patients with distant oral and maxillofacial metastasis.

A major finding of this study was that 125I brachytherapy can achieve better LC (P < .05) and longer LTPFS (HR, 6.961 [95% CI, 2.109, 9.356]). In comparing LC over different time periods, it was

Table 7. Complications in two groups

| RTOG	Group A				Group B				P
	0	1/2	3/4	3/4%	0	1/2	3/4	3/4%	
Myelosuppression	20	8	3	9.6%	19	10	5	14.7%	.484
Fever	20	8	3	9.6%	16	11	7	20.6%	.265
Local skin reaction[1]	18	11	2	6.4%	11	15	8	23.5%	.039
Oral mucosa reaction[2]	25	5	1	3.2%	15	14	5	14.7%	.028
Nerve damage[3]	26	5	0	0.0%	21	9	4	11.8%	.031
Alopecia	31	0	0	0.0%	25	8	1	2.9%	.031
Dry eye	28	3	0	0.0%	24	7	3	8.8%	.045
Keratitis	31	0	0	0.0%	28	6	0	0.0%	.015
Epistaxis	31	0	0	0.0%	27	5	2	5.9%	.028
Dysarthria	31	0	0	0.0%	29	4	1	2.9%	.028
Hearing loss	31	0	0	0.0%	25	6	3	8.8%	.015
Radioactive otitis media	31	0	0	0.0%	26	7	1	2.9%	.005
Radiation encephalopathy	31	0	0	0.0%	28	4	2	5.9%	.028
Osteoradionecrosis	31	0	0	0.0%	24	7	3	8.8%	.015

Note: [1]Local skin reaction, including allergies, rashes, hard nodules, scar. fibrosis. [2]Oral mucosa reaction, including oral ulcers, radioactive stomatitis, gingivitis, dry mouth. [3]Nerve damage, dominated by a series of clinical neurological symptoms, including facial paralysis, visual or hearing impairment, etc.
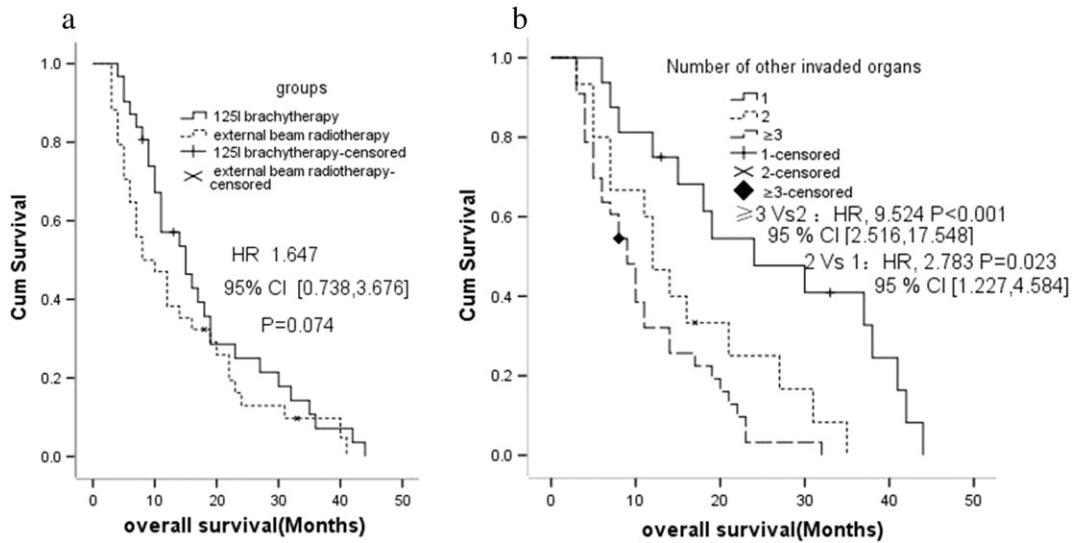
Figure 3. (a) Overall survival rate in group A and group B. (b) Overall survival rate in patients with different number of other invaded organs.

significantly higher using ^{125}I brachytherapy than EBRT, especially regarding the complete remission rate; in group A at 3, 6, 12, 18, and 24 months the complete remission rates were, 54.8% (17/31), 48.3% (14/29), 50.0% (9/18), 30.8% (4/13), and 25.0% (2/8), respectively, while in group B they were 20.6% (7/34), 20.8% (5/24), 12.5% (2/16), 0.0% (0/8), and 0.0% (0/5), respectively; group A also had better performance concerning LTPFS (median LTPFS 14 months vs 9 months). Cox proportional hazards regression analysis suggested that
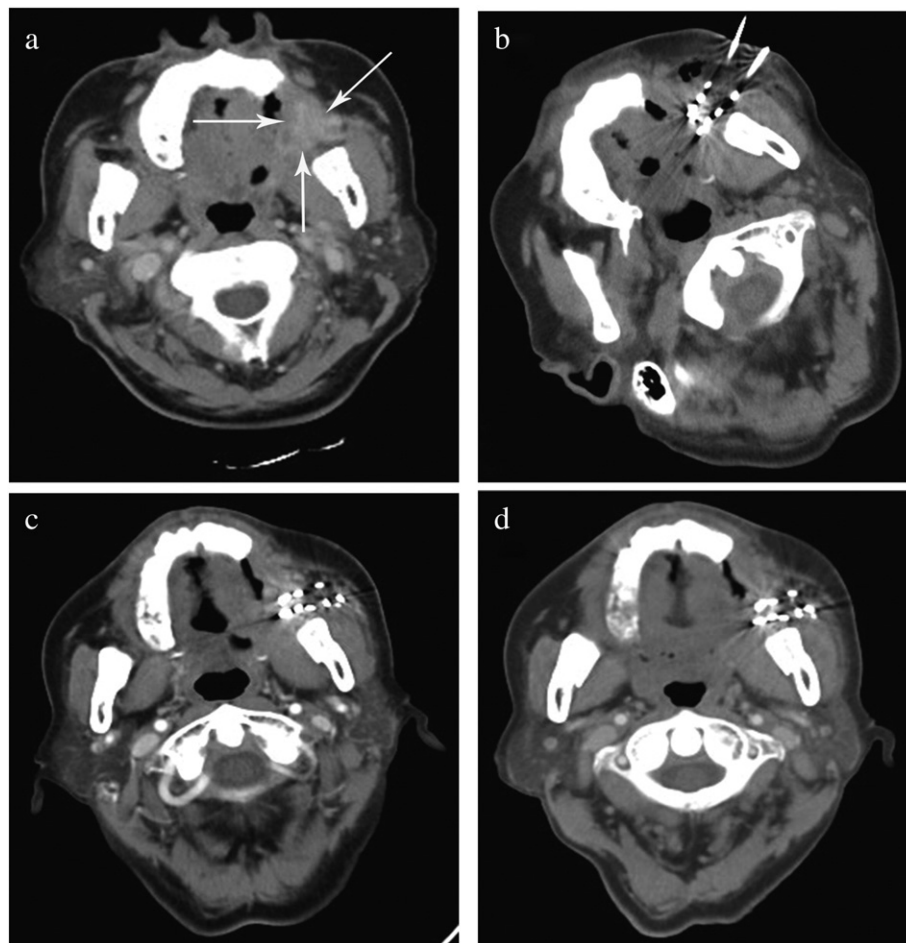
Figure 4. A 70-year-old male patient with facial metastasis proved with pathological diagnosis of prostatic cancer.(a) Preoperative CT scan; arrow represents the tumor's boundary.(b) Intraoperative CT scan. (c-d). 1 and 4 months after ^{125}I brachytherapy, the lesion apparently shrunk, enhanced CT show there is not activity.

[125]I brachytherapy was an independent factor related to LTPFS. This is because ^{125}I seeds can deliver locally higher radiation doses; the prescribed dose for group A reached 100–140 Gy, while in group B it only reached 60–70 Gy. Additionally, in group B, most of the patients had to reduce their total radiation dose because they could not tolerate the acute radiotherapy-induced complications; thus, the total radiation dose in group B merely reached 45–70 Gy although the prescribed dose was 60–70 Gy. This resulted in a reduction in LC and LTPFS rates for patients in group B.

Another finding in our study was that ^{125}I brachytherapy had a huge advantage concerning the improvement of clinical symptoms and QoL. Higher clinical remission rates can significantly improve the clinical symptoms and QoL. There was no significant difference in the EORTC QLQH&N35 score before treatment, but this score significantly improved to 9.21, 15.20, and 18.55 at 3, 6, and 12 months, respectively after treatment in group A, while in group B there was unobviously improvement and the score even deteriorated; it was deteriorated 6.02, 6.28, and 1.48 at 0, 3, and 6 months, respectively after treatment. QoL has a close relationship with radiotherapy-induced acute complications; the late radiation-induced complications reduced the positive role of EBRT in improving clinical symptoms to some extent and resulted in a worse QoL. Even though the QoL score for group B improved mildly 5.66 at 12 months after treatment, treatment effectiveness was far lower than ^{125}I brachytherapy at 12 months after treatment.

Complications associated with radiotherapy are often more significant because of the unique oral and maxillofacial anatomy [25]. Schoot et al. reported that 70% of patients who undergo radiotherapy for head and neck cancer may experience RTOG complications of grade 3/4 [26]. In our study, 61.8% (21/34) of patients in group B experienced complications of grade 3/4, while only 12.9% (4/31) experienced these complications in group A. Although in group A 3/31 (9.7%) patients had seed migration, this did not cause severe complications. This was because the radiation dose of ^{125}I seeds decayed rapidly with increased distance; This had a significant effect regarding tumor cell killing while minimizing damage to the surrounding normal tissue [27]. Thiele et al. reported that in a study of metastases in the head and neck that the mean OS from manifestation of the metastasis was 14 months [28]; in our study the findings were similar where the mean OS in groups A and B were 17.1 and 14.8 months, respectively. Although Cox proportional hazards regression analysis suggested that ^{125}I brachytherapy is not an independent factor affecting OS, the aim of our study was to improve patient QoL and maxillofacial symptoms; Indeed, the therapeutic effectiveness of ^{125}I brachytherapy was comparable with EBRT regarding OS.

Our study had several limitations. First, it was a single-center retrospective study; as a result of low morbidity, only 65 patients could be enrolled. Second, although we strictly followed the TPS during ^{125}I implantation, there was still some deviation in the actual seed implantation as a result of patient positioning and movement, which will have affected the treatment effect to some extent.

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Sun Yat-sen University Cancer Center and met the basic standards of the Declaration of Helsinki. All patients in the study were fully informed the potential risks and voluntarily signed informed consent.

Consent for Publication

All authors read and approved the final manuscript.

Competing Interests

We declare that we have no conflict of interest.

Authors' Contributions

H. Y, Z. X, and Z. Z performed the study. Z. M and T. Z performed statistical analysis. G. C. performed data collection. F. Z. and F. G. conceived the study.

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