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ORIGINAL ARTICLE

Efficacy of brachytherapy concomitant with chemotherapy with docetaxel, cisplatin, and 5-fluorouracil in unresectable head and neck squamous cell carcinoma

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Summary

Purpose: *Brachytherapy is a form of targeted radiation therapy and has shown good short-term efficacy in clinical practice. The purpose of this clinical trial was to determine the feasibility and safety of radioactive iodine 125 seeds implantation concomitantly with chemotherapy with docetaxel, cisplatin, 5-fluorouracil (TPF) in patients with head and neck squamous cell carcinoma (HNSCC).*

Methods: *A total of 23 previously untreated patients with histologically documented advanced unresectable HNSCC underwent percutaneous interstitial implantation of radioactive iodine 125 seeds, and simultaneously received 3 cycles of chemotherapy every 21 days (75 mg/m^2 docetaxel D1, 75 mg/m^2 cisplatin D1, and 750 mg/m^2 5-fluorouracil D2-5). The treatment efficacy was evaluated based on tumor size and clinical symptoms of the patients.*

Results: *The overall response rate was 78.3%. No acute complications and treatment-related radiation damages occurred. Two-year progression-free survival (PFS) 60.9% and overall survival (OS) 52.2% were achieved. Four patients (17.4%) died of cardiovascular causes and local disease recurrence.*

Conclusion: *Brachytherapy based on iodine 125 seeds implantation given concomitantly with chemotherapy is a mildly invasive, effective and safe therapeutic approach for advanced HNSCC.*

Key words: *brachytherapy, concurrent chemoradiotherapy, head and neck, squamous cell carcinoma*

Introduction

The incidence of head and neck cancer has increased and now is the sixth malignant tumor worldwide [1,2]. HNSCC is the main histologic subtype of this disease, accounting for > 90% of all cases [3]. For patients in early-stage HNSCC, the principal treatment is surgery [4]. However, most of HNSCC patients suffer of loco-regionally advanced disease untreatable by surgery. Unfortunately, the prognosis of patients with nonsurgical disease is dismal [5-7]. With increasing rates of HNSCC incidence and mortality, chemoradiotherapy seems to be one of the important treatments methods.

Concomitant platinum-based chemoradiotherapy (CRT) is a standard treatment for unresectable, resectable but non-surgically treated, and postoperative high-risk patients with locally advanced HNSCC [8]. In a randomized phase II study, a sequential concurrent CRT has been shown to improve the survival rate when compared with simple radiotherapy [9]. Although successful outcomes have been achieved with CRT, external beam radiotherapy can cause severe damage to the normal tissues and/or their functions which limits its wide-scale application in clinical practice [10].

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Brachytherapy is another kind of radiotherapy that may be of relevance in the treatment of patients with HNSCC. Many clinical trials conducted over the past decade highlighted the feasibility of brachytherapy for the treatment of head and neck cancer. In our preliminary experiments, implantation of radioactive iodine 125 seeds was effective in preventing the recurrence and metastasis of oral and maxillofacial malignancy and improving the quality of life [11].

In addition, a retrospective study to assess the efficacy and morbidity of percutaneous interstitial implantation of radioactive iodine 125 seeds under computed tomography (CT)/ultrasonography guidance in 25 patients with HNSCC was conducted in China. This radiation technique showed that the 1- and 2-year local tumor control rates were 48.7% and 39.9%, respectively. The survival rate at 48 months was 28.3% (median:11). No blood vessel damage and neuropathy appeared [12].

However, brachytherapy administered concomitantly with TPF chemotherapy has not yet been reported but offers a potentially different approach using a microtrauma operative option. In this study, we determined the feasibility and safety of radioactive iodine 125 seeds implantation concomitantly with TPF chemotherapy for unresectable HNSCC. The primary endpoint of this study was the response rate, survival benefits and adverse events involved.

Methods

Patients

From November 2009 to February 2012, 23 patients were recruited. All patients in our study had confirmed stage III-IVb HNSCC of the tongue, buccal mucosa, palate, mouth floor, and parotid on the basis of the TNM staging criteria established by the International Union Against Cancer. The main inclusion criteria were: patients with unresectable lesions, or those who refused to receive external beam radiotherapy and surgery, histopathological diagnosis confirmed by surgical biopsy, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3, no distant metastases, minimum 18 years old, an expected survival time of at least 6 months, white blood cells no less than 3×10^9/L, platelet count at least 100×10^9/L, hemoglobin at least 9 g/L, and signed informed consent form prior to study entry. The ethics committee of our hospital approved the entire study protocol.

Brachytherapy

Iodine 125 seeds implantation was designed by a computer-based treatment plan system (TPS) (Astro Technology Ltd., Beijing, China). The radioactive particle (JACO Pharmaceuticals Ltd, Ningbo, China) had an apparent activity per seed of 0.6 to 0.8 mCi, a half-life of 59.6 days and a matched peripheral dose (MPD) of 90 to 120 Gy. Before implantation, the tumor and its surrounding major organs/tissues were measured using enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans. Using the TPS, we calculated the required radiation dosage in the targeted area, the number of radiation sources, and the space distribution in order to make sure that the 90% of the targeted organ receives 90% of the prescribed dose.

Before the operation for the implantation, sedative drugs were administered to the patients. Under local or general anesthesia, body surface was positioned in accordance with the treatment plan by TPS. The space between the needles was approximately 1 cm each. Implantation was guided by CT, to ensure that all needles were met the following requirements: planning target volume (PTV) was the gross target volume (GTV) plus 0.5 cm margin, and mini doses to some important tissues and organs. Finally, a second CT or MRI scan were performed 1 week after the procedure and the CT images were introduced into the TPS. Location, amount, and distribution of the seeds were performed to verify and guarantee.

Chemotherapy

TPF was started on the 7th day after the operation. On the day before chemotherapy, dexamethasone (8 mg) was administered every morning for 3 consecutive days.

Docetaxel and cisplatin were administered intravenously on day 1 for 1 h at a dosage of 75 mg/m^2, followed by 5-fluorouracil 750 mg/m^2 as continuous infusion for days 2 to 5. The cycle was repeated every 21 days, and 3 cycles were given in total.

Evaluation of treatment

All the patients were followed from the date of iodine 125 seeds implantation. When treatment was completed, patients were evaluated for disease status by physical examination and CT or MRI scans every 3 moths until disease progression. The criteria for response were based on Response Evaluation Criteria in Solid Tumors (RECIST) [13].

Complete response (CR) was defined as the disappearance of all target and non-target lesions for at least 4 weeks. Partial response (PR) was defined as at least 30% decrease in the sum of the longest diameter of target lesions for at least 4 weeks. Progressive disease (PD) was defined as increase in the sum of the longest diameter of the measurable lesions by ≥20% or appearance of new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Adverse reactions consisted of the events caused by brachytherapy and chemotherapy. Acute radia-

tion-induced injuries were evaluated using the grading criteria developed by Radiation Treatment Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC). The hematologic, dermatologic, and systemic toxicities were evaluated according to the guidelines of National Cancer Institute Common Toxicity Criteria version 3.0 (CTC3.0) [14].

Statistics

The primary endpoint was local control, and secondary endpoints were PFS, OS, as well as short and long term toxicities. PFS was defined as the time from the start of brachytherapy to progressive disease or death from any cause. OS was measured from the start of brachytherapy until death from any cause. Measurement data were analyzed by the statistical software SPSS (version 13.0, SPSS). Survival curves were calculated using the Kaplan-Meier method with log rank test and survival rates were estimated with 95% confidence intervals. A p value of <0.05 indicated statistical significance.

Results

Twenty-three patients were enrolled in this trial during November 2009 to February 2012. None of the patients dropped out of the study, and all of them had an objective evaluation of tumor. Table 1 shows the patient characteristics. Fifteen men and 8 women were enrolled, with a median age of 59.3 years (range 41-77). Of 23 patients, 5 (21.7%) had stage III and 18 (78.3%) stage IV disease. The sites of disease are shown in Table 2, and included the tongue (42.1%), buccal mucosa (15.8%), parotid (10.5%), and floor of the mouth (31.6%).

After brachytherapy with concomitant chemotherapy, 8 patients (34.8%) achieved CR and 10 (43.5%) attained PR, for an overall response rate (ORR) of 78.3%. The disease control rate (DCR) which included also SD was 91.3%. Response rates across primary tumor sites are shown in Table 2 and included the tongue (ORR 77.8%, DCR 88.9%), buccal mucosa (ORR 80.0%, DCR 100%), parotid (ORR 100%, DCR 100%), and mouth floor (ORR 71.4%, DCR 85.7%). Finally, 2 patients developed new lesions with tumor progression in the first month after chemotherapy.

The median OS survival of all patients was 23.0 months (range 2-51). The OS after 1 year was 78.3% (95% CI 76.9-79.7) and 60.9% (95% CI 58.9-62.9%) after 2 years (Figure 1). Four of the patients died: 2 of tumor recurrence and 2 of cardiovascular disease. The PFS for the years 1 and 2 was 65.2% (95% CI 63.3-67.1) and 52.2 % (95% CI 50.1-54.3), respectively, with a median PFS of 21.1 months (Figure 2).

Table 3 provides the details of toxicities in all patients. Of 23 patients, 4 (17.4%) developed grade 3 and 4 toxicities. Although the most frequent toxicity caused by TPF was leucopenia (69.6%), grade 4 leucopenia was observed only in one patient. One

Table 1. Baseline patient, disease and RT characteristics

Characteristics	*N*	*%*
Sex		
Male	15	65.2
Female	8	34.8
Age, years		
Median	59.3	
Range	41-77	
ECOG performance status		
0	3	13.0
1	6	26.1
2	12	52.2
3	2	8.7
TNM stage		
III	5	21.7
IVa	15	65.2
IVb	3	13.0
Tumor stage		
T1	0	0.0
T2	4	17.4
T3	10	43.5
T4(a/b)	9 (7/2)	39.1(30.4/8.7)
Lymph node stage		
N0	5	21.7
N1	3	13.0
N2(a/b/c)	14 (4/6/4)	60.9 (17.4/26.1/17.4)
N3	1	4.3
Dosage (Gy)		
Median	106.7	
Range	90-120	

Table 2. Response in different disease sites

Site	*Patients N (%)*	*Response (N=23)*				*ORR %*	*DCR %*
		CR	*PR*	*SD*	*PD*		
Tongue	9 (39.1)	2	5	1	1	77.8	88.9
Buccal mucosa	5 (21.7)	3	1	1	0	80.0	100.0
Mouth floor	7 (30.4)	1	4	1	1	71.4	85.7
Parotid	2 (8.7)	2	0	0	0	100.0	100.0

For abbreviations, see text

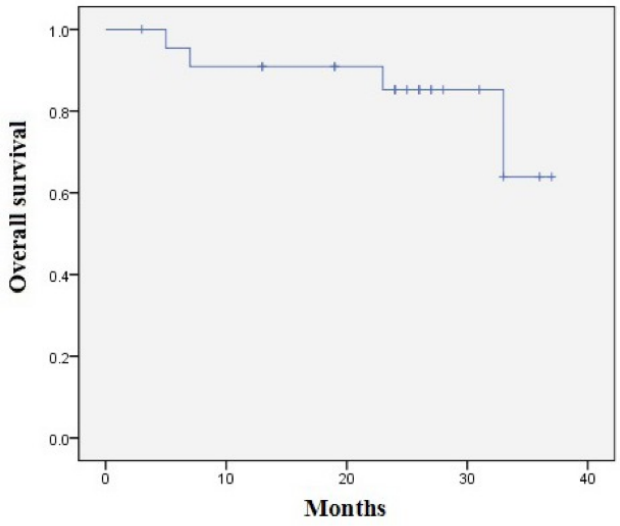

Figure 1. Overall survival after iodine 125 seeds implantation combined with TPF.

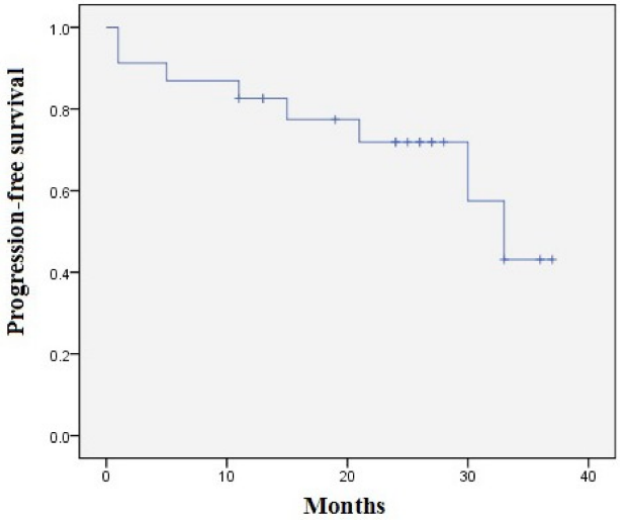

Figure 2. Progression-free survival after iodine 125 seeds implantation combined with TPF (median 21.1 months).

of the patients with PR suffered of grade 3 febrile neutropenia in the third cycle of chemotherapy. Granulocyte-colony stimulating factor (G-CSF) was administered until white blood cells and neutrophils returned to normal levels. Unfortunately, this patient died of cardiac failure caused by chronic cardio-pulmonary disease at the third month after chemotherapy. Gastrointestinal toxicities of grade 3 or higher were not seen in this study.

According to the RTOG/EORTC grading criteria, no adverse events of grade 3 or higher were found during this study (Table 4). Five patients (21.7%) with squamous cell carcinoma of the mouth floor and tongue suffered from dysphagia following iodine 125 seeds implantation which was improved after symptomatic treatment.

Table 3. Acute toxicity according to CTC criteria

Toxicity	*Grade 1-2*		*Grade 3-4*	
	N	*%*	*N*	*%*
Hematological toxicity				
Anemia	4	17.4	0	0
Leucopenia	16	69.6	2	8.7
Thrombocytopenia	5	21.7	0	0
Gastrointestinal toxicity				
Nausea/vomiting	15	65.2	0	0
Diarrhea	4	17.4	0	0
Others				
Local hemorrhage	9	39.1	0	0
Alopecia	6	26.1	0	0
Febrile neutropenia	0	0	1	4.3
Dysphagia	3	13.0	2	8.7

Table 4. Adverse reactions to radiation according to RTOG and EORTC criteria

Adverse reactions	*Grade 1-2*		*Grade 3-4*	
	N	*%*	*N*	*%*
Skin	5	21.7	0	0
Mucosa	13	56.5	0	0
Jaw	2	8.7	0	0
Salivary glands	5	21.7	0	0
Temporomandibular joint	0	0	0	0

Discussion

Concurrent CRT is currently one of the most powerful modalities for the treatment of locally advanced HNSCC, and several clinical trials have evaluated this approach for the treatment of metastatic or recurrent HNSCC. A phase II study demonstrated the feasibility and safety of TPF followed by a simultaneous CRT in 49 patients with locally advanced HNSCC who had undergone neither chemotherapy nor radiation therapy. The ORR was 95.4%, and the OS rates at 1 and 2 years were 93.6% and 88.7%, respectively [15]. In another trial, patients with functionally inoperable carcinomas of the pharynx and larynx treated with concurrent CRT showed a local control rate of 86.1% [16]. Although previous research revealed a surprising antitumor activity in patients who received concurrent CRT, the results showed that concurrent CRT increased the incidence of adverse reactions and limited the application of the therapeutic schedule in the elderly patients [15,17]. Therefore, the focus of head and neck cancer therapy has currently shifted to minimally

invasive targeted treatments, particularly the targeted radiation.

In this study, we tested a novel anticancer strategy of TPF combined with iodine 125 seeds implantation in advanced HNSCC patients. All unresctable patients were given brachytherapy, and not external beam radiotherapy (EBRT). The radioactive particles implantation technique is one of brachytherapeutic technologies, which has been studied in different solid tumors including HNSCC [17-19]. Two phase II studies demonstrated the efficacy of iodine 125 seeds implantation as a surgical adjuvant to advanced recurrent head and neck cancers [20,21]. The rates of overall response and serious complications were 89% and 5.5% respectively.

In another retrospective clinical study in very elderly patients (N=125) with tongue carcinoma, brachytherapy was associated with 86% DCR of the primary lesions at 5 years. The major radiation-induced side effects, including mucositis and dermatitis, were well tolerated.

Although the evidence that local tumor control has been improved by brachytherapy, treatment failure or even death caused by postoperative recurrence and metastasis has been reported from time to time [22,23]. We hypothesized that combining targeted radiation and concomitant chemotherapy might improve the therapeutic effect and reduce adverse reactions and metastasis. Our data show that patients achieved an overall response rate of 78.3% in the present trial. In 2007, in the study by Ahn et al. this rate was 95.4%. However, grade 3 and 4 adverse reactions were apparently higher compared with our study [15]. Our preliminary experiments also showed that iodine 125 seeds implantation does not add to the toxicities in patients with oral and maxillofacial malignancy [11]. On the other hand, the most unexpected but not surprising result was that the therapeutic effect was different in different tumor locations. In general the response rate in parotid was higher than that of other primary tumor sites. Even though these findings are based on a very small sample size, they are consistent with the previous findings of Zheng et al. (2012) and warrant further research [24].

Iodine 125 particles have a half-life of 59.6 days and slowly emit gamma rays to gross tumor volume after being implanted. All patients were admitted for 3 cycles of TPF chemotherapy, a week after brachytherapy. The results did not show that chemotherapy enhanced the risk of radiation-related damage. Several authors have reported that the grades of acute radiation-induced injuries did not show any change after TPF and no case of grade 3 and 4 late complications was recorded [17,25]. This finding suggests that brachytherapy plus concomitant chemotherapy can be used as a safe combination therapy for advanced oral squamous cell carcinoma. An additional cellular-level study is presently ongoing to investigate the synergy and cytotoxicity of iodine 125 seed combined with chemotherapeutic drugs on a tongue squamous carcinoma cell line by our team.

Patients in our study attained a survival advantage with this therapeutic scheme. An OS of 60.9% and PFS of 52.2% were achieved at 2 years. Out of 23 patients, 4 died of cardiovascular disease and local recurrence. Unfortunately, several clinical trials have not worked well in treating HNSCC with iodine 125 seeds implantation alone. The study conducted in 2010 by Jiang et al. was designed for CT or ultrasound-guided iodine 125 seeds implantation, and showed that the 2-year OS and PFS rates were only 28.3 and 39.9%, respectively [12]. Iodine 125 seeds implantation was deemed suitable for the treatment of slowly proliferating tumors in the head and neck region, such as malignant salivary gland tumors [26,27]. Therefore, we believe that brachytherapy in association with systemic administration of chemotherapeutic drugs can inhibit the rapid growth of HNSCC cells [28].

In conclusion, the present study showed a promising efficacy and safety profile of the iodine 125 seeds implantation brachytherapy along with concomitant TPF for unresectable HNSCC. Randomized controlled studies with larger sample size and prolonged follow-up data are required to further verify the clinical significance of this method.

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Conflict of interests

The authors declare no confict of interests.

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