Efficacy of Brachytherapy Synchronized Chemotherapy with Docetaxel, Cisplatin, 5-Fluorouracil for Unresectable Head and Neck Squamous Cell Carcinoma

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Introduction

The incidence of head and neck cancer has increased and is the sixth of malignant tumors in the whole world [1,2]. HNSCC is the principal histologic subtype of this disease, accounting for >90% of all cases [3]. For patients in early stage of HNSCC, the principal treatment is surgery [4]. However, approximately two-thirds of HNSCC patients suffer loco-regionally advanced disease and untreatable by surgery. Unfortunately, the prognosis of patients with nonsurgical series is dismal [5-7]. With increasing rate of HNSCC incidence and mortality, chemoradiotherapy, seems to be one of the important treatments, and is confronted with great challenges.

Concomitant platinum-based CRT is a standard treatment for the unresectable, resectable but non-surgically treated, and postoperative high-risk patients with locally advanced head and neck squamous cell carcinoma [8]. In a randomized phase study, a sequential concurrent CRT has been shown to improve 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 the clinical settings [10].

Brachytherapy is another model that may be of relevance to 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, radioactive iodine 125 seeds implantation 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 radioactive iodine 125 seeds interstitial implantation under computed tomography (CT)/ultrasonography guidance in twenty-five patients with HNSCC was conducted in China. This radiation technique showed that the 1 year and 2 year local tumor control rates were 48.7% and 39.9%, respectively. The survival rate at 48 months was 28.3% (median: 11months). No blood vessel damage and neuropathy appeared [12].

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

Materials and Methods

Patients

From November 2009 to February 2012, twenty-three 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. 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 of 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 \(3 \times 10^9/L\), platelet count at least \(100 \times 10^9/L\), hemoglobin at least 90g/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 targeted area, number of radiation sources, and the space distribution in order to make sure that the 90% of the targeted organ receives 90% of the prescription dose.

Before the operation of the implantation, sedative drugs were administered to 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) is to gross target volume (GTV) plus 0.5 cm, appropriate position and depth, mini doses in some important tissues and organs. Finally, a second CT or MRI scan was performed 1 week after the procedure and the CT images were introduced into the TPS. The location, amount, and distribution of the seeds were performed to verify and guarantee.

Chemotherapy

TPF was started at the seventh day after operation. On the day before chemotherapy, dexamethasone (8 mg) was administered every morning for three consecutive days.

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

Evaluation of treatment

All the patients were followed from the date of iodine 125 seeds implantation. Evaluation of therapeutic efficacy was performed by CT or MRI scans at the end of the trial, as well as every 3 months after therapy was finished. The criteria for response were based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Complete response (CR) was defined as the disappearance of all target and non-target lesions and the normalization of the tumor marker levels for at least 4 weeks. A partial response (PR) was defined as at least 30% decrease in sum of the longest diameter (LD) of target lesions for at least 4 weeks. A progressive disease (PD) was defined as the sum of the longest diameter (LD) of the measurable lesions increased by \(\geq 20\%\) or appearance of new lesions. A stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Adverse reaction consisted of the events caused by brachytherapy and chemotherapy. Acute radiation-induced injuries were evaluated using the grading criteria developed by Radiation Treatment Oncology Group (RTOG) and European Organization for Research on 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).

Statistical analysis

The primary endpoint was local control, and secondary endpoints were progression-free survival (PFS), overall survival (OS), as well as short and long term toxicities. The PFS was defined as the time from the start of brachytherapy to progressive disease or death from any cause. The 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 and survival rates were estimated with 95% confidence intervals.

Results

23 patients were enrolled in this trial during November 2009 to February 2012. None of the patients dropped out of the study, and all patients achieved an objective evaluation of tumor. Table 1 shows patient’s characteristics. 15 men and 8 women were enrolled, with a median age of 59.3 years (range:
41-77 years). Of 23 patients, five patients (21.7%) had tumor stage III and eighteen (78.3%) with stage IV. The sites of tumor are shown in Table 2, consisting of tongue (42.1%), buccal mucosa (15.8%), parotid (10.5%), and floor of mouth (31.6%).

Table 1 Baseline demographic details and characteristics of patients.

| Characteristics          | Number of patients (n=23) | Percentage (%) |
|--------------------------|---------------------------|----------------|
| Sex                      |                           |                |
| Male                     | 15                        | 65.2           |
| Female                   | 8                         | 34.8           |
| Age                      |                           |                |
| 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            |
| 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 (N)           |                           |                |
| N0                       | 5                         | 21.7           |
| N1                       | 3                         | 13.0           |
| N2 (a/b/c)               | 14(4/6/4)                 | 60.9(17.4/28.1/17.4) |
| N3                       | 1                         | 4.3            |
| Dosage (Gy)              |                           |                |
| Median                   | 106.7                     |                |
| Range                    | 90-120                    |                |

Response rate across primary tumor sites are shown in Table 2 and include 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%). The most frequent causes of the study were lost to follow up, voluntary withdrawal, serious adverse events and tumor recurrence. Overall, 2 patients developed new lesion with tumor progression in the first month after chemotherapy.

Table 2 Response in different sites.

| Site                  | Patient s: No. (%) | CR | PR | SD | PD | ORR (%) | DCR (%) |
|-----------------------|-------------------|----|----|----|----|---------|---------|
| 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   |

The median survival of all patients treated in our trial was 23.0 months. The OS after 1 year was 78.3% [95% confidence interval (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, 2 of cardiovascular disease. The PFS for year 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).

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.

Table 3 provides the details of toxicities in all patients. Out of 23 patients with HNSCC who accepted the treatment of brachytherapy and chemotherapy, 4 patients (17.4%) developed grade 3 and grade 4 toxicities. Although the most frequent toxicity caused by TPF was leucopenia (69.6%), but grade 4 was observed in only one patient. One of the patients showed PR and suffered from grade 3 febrile neutropenia in the third cycle of chemotherapy.

Table 3 Acute toxicity according to CTC criteria.

| Toxicity                | Grade 1-2 | Grade 3-4 |
|-------------------------|-----------|-----------|
|                         | No.   | %     | No.   | %     |
| Hematological toxicity  |        |       |       |       |
| Anemia                  | 4     | 17.4  | 0     | 0     |
| Leucopenia              | 16    | 69.6  | 2     | 8.7   |
| Thrombocytopenia        | 5     | 21.7  | 0     | 0     |
| Gastroenteric toxicity  |        |       |       |       |
| Nausea/vomiting         | 15    | 65.2  | 0     | 0     |
| Diarrhea                | 4     | 17.4  | 0     | 0     |
| Otherwise               |        |       |       |       |
| 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   |

Granulocyte-colony stimulating factor (G-CSF) was provided to the patient until white blood cells and neutrophils returned to normal levels. Unfortunately, the patient died of cardiac failure caused by chronic pulmonary heart disease at the third month after chemotherapy. Besides, gastroenteric toxicities grade 3 or higher were not seen in our study.

According to the grading criteria developed by RTOG/EORTC, 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 a dysphagia following iodine 125 seeds implantation which was improved after symptomatic treatment.

Table 4 Adverse reaction of radiation according to RTOG and EORTC criteria.

| Adverse reaction          | Grade 1-2 | Grade 3-4 |
|---------------------------|-----------|-----------|
|                           | No. | %   | No. | %   |
| 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 local advanced HNSCC, and several clinical trials have evaluated this approach for the treatment of metastatic or recurrent HNSCC setting. A phase study demonstrated the feasibility and safety of TPF followed by a simultaneous CRT in forty-nine patients with locally advanced HNSCC who had undergone neither chemotherapy nor radiation therapy. The overall responding rate was 95.4%, and the overall survival rates at 1-year and 2-year were 93.6% and 88.7%, respectively [13]. 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% [14]. Although previous research revealed a surprising antitumor activity in the patients who received concurrent CRT, there is evidence that concurrent CRT increased the incidence of adverse reactions and limited the application of the therapeutic schedule in the elderly patients [13,15]. 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 combined TPF with iodine 125 seeds implantation in advanced HNSCC patients. All unrectable patients were given a brachytherapy and not external beam radiotherapy (EBRT). Radioactive particles implantation technique is one of brachytherapeutic technologies, which has been studied in variable solid tumors including HNSCC [16-18]. Two phase II studies demonstrated the efficacy of iodine 125 seeds implantation as a surgical adjuvant to advanced recurrent head and neck cancers [19,20]. The rate of overall responding and serious complications was 89% and 5.5% respectively.
In another retrospective clinical study in very elderly patients (N=125) with tongue carcinoma, brachytherapy was associated with the control rate of the primary lesions at 86% for 5 years. The major radiation-induced injuries, including mucositis and dermatitis, were well acceptable.

Although the evidence that local tumor control has been improved by brachytherapy, treatment failure or even death caused by postoperative recidivation and metastasis has been reported from time to time [21,22]. We hypothesized that combining targeted radiation and concomitant chemotherapy might improve therapeutic effect, reduce adverse reaction and metastasis. Our data present that these cases achieved an overall responding rate of 78.3%. In the reference trial by Ahn et al. this rate was 95.4%. However, the occurrence rate of grade 3 and grade 4 adverse reactions were apparently higher than that in our study [13]. 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 and based upon tumor location. In general the responding rate across parotid was higher than that of other primary tumor sites. Although these findings are based on a very small sample size, but are consistent with the previous findings of Zheng et al. and warrant further research [23]. Iodine 125 particles has a half-life of 59.6 days and slowly emits gamma rays to gross tumor volume after being implanted. All patients were admitted for three cycles of TPF regimen in a week after brachytherapy. The results did not illustrate that the chemotherapy enhanced risk of treatment related radiation damage. As reported by several studies, the damage grades of acute radiation-induced injuries did not show any change after TPF and no case of grade 3 and grade 4 late complications were recorded [16,24]. This finding suggests that the brachytherapy synchronized with chemotherapy can be used as a safe combination therapy for advanced OSCC. An additional cellular-level study is presently ongoing to investigate the synergy and cytotoxicity of iodine 125 seed combined with chemotherapy drugs on the tongue squamous carcinoma cell line.

Patients in our study showed a survival advantage to this therapeutic scheme. An overall survival of 60.9% and progression-free survival of 52.2% was achieved at 2 years, respectively. Out of twenty-three patients, four patients 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 by Jiang et al. was designed for CT or ultrasound-guided iodine 125 seeds implantation, and showed that the 2 years overall and progression-free survival rate was 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 [25,26]. Therefore, we believe that the brachytherapy in association with systematic administration of chemotherapy drugs can inhibit the rapid growth of head and neck squamous carcinoma cells [27-29].

Conclusion

The present study shows a promising efficacy and safety of the combined treatment of iodine 125 seeds implantation based brachytherapy along with TPF for unresectable head and neck squamous cell carcinoma. Randomized controlled studies with larger sample size and extended follow-up data are required to further verify the clinical significance of this method.

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References

1. Dwivedi RC, Kazi RA, Agrawal N, Nutting CM, Clarke PM, et al. (2009) Evaluation of speech outcomes following treatment of oral and oropharyngeal cancers. Cancer Treat Rev 35: 417-24.
2. Warnakula Suriya S (2009) Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 45: 309-316.
3. Al-Swiab JN, Chen CH, Chuang HC, Fang FM, Tasi HT, et al. (2010) Clinical, pathological and molecular determinants in squamous cell carcinoma of the oral cavity. Future Oncol 6: 837-850.
4. Chinn SB, Spector ME, Bellile EL, Rozek LS, Lin T, et al. (2014) Efficacy of induction selection chemotherapy vs. primary surgery for patients with advanced oral cavity carcinoma. JAMA Otolaryngol Head Neck Surg 140: 134-142.
5. Agarwal JP, Nemade B, Murthy V, Ghosh-Laskar S, Bodruckkar A, et al. (2008) Hypofractionated, palliative radiotherapy for advanced head and neck cancer. Radiother Oncol 89: 51-56.
6. Das S, Thomas S, Pal SK, Isiah R, John S (2013) Hypofractionated palliative radiotherapy in locally advanced inoperable head and neck cancer: CMC Vellore experience. Indian J Palliat Care 19: 93-98.
7. Mohanti BK, Umapathy H, Bahadur S, Thakar A, Pathy S (2004) Short course palliative radiotherapy of 20 Gy in 5 fractions for advanced and incurable head and neck cancer: AllMS study. Radiother Oncol 71: 275-280.
8. NWizu T, Ghi MG, Cohen EE, Paccagnella A (2012) The role of chemotherapy in locally advanced head and neck squamous cell carcinoma. Semin Radiat Oncol 22: 198-206.
9. Budach W, Hehr T, Budach V, Belka C, Dietz K (2006) A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 6: 28.
10. May JT, Rao N, Sabater RD, Boudri H, Caudell JJ, et al. (2013) Intensity-modulated radiation therapy as primary treatment for oropharyngeal squamous cell carcinoma. Head Neck 35: 1796-1800.
11. Meng J, Meng QF, Gu QP, Si YM, Zheng H, et al. (2013) Radioactive seed implantation combined with prosthesis denture in treatment of oral and maxillofacial malignancy. Cell Biochem Biophys 67: 1529-1532.
12. Jiang YL, Meng N, Wang JJ, Ran WQ, Yuan HS, et al. (2010) Percutaneous computed tomography/ultrasonography-guided permanent iodine-125 implantation as salvage therapy for recurrent squamous cell cancers of head and neck. Cancer Biol Ther 9: 959-966.

13. Ahn JS, Cho SH, Kim OK, Lee JK, Yang DH, et al. (2007) The efficacy of an induction chemotherapy combination with docetaxel, cisplatin, and 5-FU followed by concurrent chemoradiotherapy in advanced head and neck cancer. Cancer Res Treat 39: 93-98.

14. Semrau S, Schmidt D, Lell M, Waldfahrer F, Lettmaier S, et al. (2013) Results of chemoselection with short induction chemotherapy followed by chemoradiationon surgery in the treatment of functionally inoperable carcinomas of the pharynx and larynx. Oral Oncol 49: 454-460.

15. Lyman GH, Dale DC, Crawford J (2003) Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol 21: 4524-4531.

16. Jiang YL, Meng N, Wang JJ, Ran WQ, Yuan HS, et al. (2010) Percutaneous computed tomography/ultrasonography-guided permanent iodine-125 implantation as salvage therapy for recurrent squamous cell cancers of head and neck. Cancer Biol Ther 9: 959-966.

17. Ruge MI, Simon T, Suchorska B, Lehrke R, Hamisch C, et al. (2011) Stereotactic brachytherapy with iodine-125 seeds for the treatment of inoperable low-grade gliomas in children: long-term outcome. J Clin Oncol 29: 4151-4159.

18. Ruge MI, Kickingereder P, Grau S, Dorn F, Galdiks N, et al. (2013) Stereotactic iodine-125 brachytherapy for the treatment of WHO grades II and III gliomas located in the central sulcus region. Neuro Oncol 15: 1721-1731.

19. Vikram B, Hilaris BS, Anderson L, Strong EW (1983) Permanent iodine-125 implants in head and neck cancer. Cancer 51: 1310-1314.

20. Khalilur R, Hayashi K, Shibuya H (2011) Brachytherapy for tongue cancer in the very elderly is an alternative to external beam radiation. Br J Radiol 84: 747-749.

21. Zhang L, Chen LH, Wang J, Mu W, Zhou DQ, et al. (2014) CT-guided radioactive (125) I seed implantation treatment of multiple pulmonary metastases of hepatocellular carcinoma. Clin Radial 69: 624-629.

22. Jiang YL, Meng N, Wang JJ, Jiang P, Yuan HS, et al. (2010) CT-guided iodine-125 seed permanent implantation for recurrent head and neck cancers. Radiat Oncol 5: 68.

23. Zheng L, Zhang J, Zhang J, Song T, Huang M, et al. (2012) Preliminary results of (125)I interstitial brachytherapy for locally recurrent parotid gland cancer in previously irradiated patients. Head Neck 34: 1445-1449.

24. Jiang P, Jiang Y, Wang JJ, Meng N, Ran W, et al. (2011) Percutaneous ultrasonography-guided permanent iodine-125 implantation as salvage therapy for recurrent head and neck carcinomas. Cancer Biother Radiopharm 26: 753-757.

25. Glaser MG, Leslie MD, Coles I, Cheesman AD (1995) Iodine seeds in the treatment of slowly proliferating tumours in the head and neck region. Clin Oncol (R Coll Radiol) 7: 106-109.

26. Zhang J, Zheng L, Huang MW, Liu SM, Jia LF, et al. (2011) Radioactivity seeds interstitial brachytherapy treating malignant salivary gland tumors. Beijing Da Xue Xue Bao 43:272-275.

27. Fronie A, Bunget A, Afrem E, Preoţescu LL, Corlan Puşcu D, et al. (2013) Squamous cell carcinoma of the oral cavity: clinical and pathological aspects. Rom J Morphol Embryol 54: 343-348.

28. Gomez-Roca C, Koscielny S, Ribrag V, Dromain C, Marzouk I, et al. (2011) Tumour growth rates and RECIST criteria in early drug development. Eur J Cancer 47: 2512-2516.

29. Denis F, Garaud P, Bardet E, Alfiomani M, Sire C, et al. (2003) Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. Int J Radiat Oncol Biol Phys 55: 93-98.