

Clinical effectiveness of ¹²⁵I-Seed implantation in combination with nimotuzumab therapy for the advanced oral carcinoma: preliminary results

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Abstract. – **OBJECTIVE:** This study determines the short-term efficacy and toxicity of combined ¹²⁵I-seed implantation and nimotuzumab in treating the advanced oral carcinoma. ¹²⁵I-seed implantation is safe and has shown good short-term efficacy in clinical practice. Nimotuzumab is a useful biological agent for targeted therapy. Effect of ¹²⁵I-seed implantation with nimotuzumab in treating oral carcinomas remains unclear.

PATIENTS AND METHODS: From November 2011 to December 2012, 11 patients with advanced oral carcinoma (pathologic types: 7 cases of squamous cell carcinoma and 4 cases of poorly differentiated adenocarcinoma) were enrolled in our hospital. The patients did not receive surgery due to systemic disease or locally advanced cancer. All of them underwent ¹²⁵I-seed implantation with the matched peripheral doses (MPD) ranging from 90-100 Gy. The apparent activity per seed ranged from 0.6 mCi (2.22 MBq) to 0.7 mCi (2.59 MBq). Later, all patients were given nimotuzumab (200 mg, intravenous drip, weekly, for 6 weeks). The patients were then followed up and the response rate, acute/chronic radiation-induced injury, and safety of the induction treatment were analyzed.

RESULTS: Three patients achieved complete while 6 patients had partial response; yielding a response rate of 81.8%. Major adverse events included radiation-induced oral mucositis, local hemorrhage, bone marrow suppression, nausea/vomiting, and alopecia. Adverse reaction was not significantly different between the group of patients under 65 years of age and over 65 years of age ($p > 0.05$). Nimotuzumab enhanced the tumor sensitivity to brachytherapy without increasing AEs and improved the patients' life quality.

CONCLUSIONS: ¹²⁵I-seed implantation combined with nimotuzumab is effective and safe for patients with unresectable oral carcinoma.

Key Words:

Nimotuzumab, Iodine-125 seed, Oral carcinoma, Brachytherapy.

Introduction

The treatment of oral malignancies is often based on the multidisciplinary approaches using surgery and radiochemotherapy. For patients who cannot tolerate surgery due to physical status or those who refuse surgery for concerns about the damage of facial appearance, radiochemotherapy has become the main method to suppress the rapid growth of tumor cells at the advanced stage. However, both chemotherapeutic drugs and external beam radiation can cause severe damage to the normal tissues and/or their functions which limits their wide-scale application in the clinical settings. ¹²⁵I-seed implantation, as a minimally invasive brachytherapy, has shown good short-term efficacy in clinical practice and the procedure includes high safety levels and acceptable minor complications¹. Nimotuzumab is an immunobiological agent used for targeted therapy. When used in combination with radiochemotherapy, it can raise the overall response and disease control rates and prolong the progression-free survival (PFS)². However, to our knowledge, no study so far has reported therapeutic effects of ¹²⁵I-seed implantation in combination with nimotuzumab immunotherapy, targeting enhancement of the tumor sensitivity to radioactive particles. Herein, based on the clinical data obtained from 11 patients with oral malignancies that were treated at our department, we report that ¹²⁵I-seed implantation combined with nimotuzumab is a safe and effective treatment for patients with unresectable oral carcinoma.

¹²⁵I-seed implantation is a minimally invasive brachytherapy that has short-term clinical efficacy. Nimotuzumab is an immunobiological agent that has been used for targeted therapy. Clinical efficacy and safety of the combined use of ¹²⁵I-seed implantation and nimotuzumab for treating

advanced oral cancers remain unclear so far. We report the data obtained from 11 patients with unresectable oral carcinoma that were treated at our hospital center using this combination therapy.

The aim of this study was to determine the safety and clinical efficacy of ¹²⁵I-seed implantation in combination with nimotuzumab immunotherapy in patients with advanced oral carcinoma.

Patients and Methods

Patients

From November 2011 to December 2012, a total of 11 patients (5 men and 6 women; aged 42-81 years) with oral malignancies (pathologic types: 7 cases of squamous cell carcinoma and 4 cases of poorly differentiated adenocarcinoma) who were treated at our hospital center were enrolled in this study. The patients' data are listed in Table I.

Inclusion Criteria

The inclusion criteria were as follows: (1) Patients with unresectable lesions, or those who were receiving radiotherapy (with locally advanced tumors or poor general condition), or those who voluntarily asked for ¹²⁵I-seed implan-

tation and nimotuzumab treatment; (2) those who were at clinical stage III or IV (based on the TNM staging criteria established by the International Union against Cancer); (3) those with a performance status (PS) score of ≤3; (4) those with an expected survival of >6 months; (5) those with a Karnofsky score of ≥80; and (6) those with normal routine blood test results as well as normal heart, liver and kidney functions. All patients signed the informed consent forms and the study was approved by the Institutional Ethics Committee.

¹²⁵I- seed Implantation

Planning

¹²⁵I radioactive seeds (kindly provided by Beijing Astro Technology Ltd. Co) had an apparent activity per seed of 0.6 mCi (2.22 MBq) to 0.7 mCi (2.59 MBq), a half-life of 59.6 days and a matched peripheral dose (MPD) of 90-120 Gy. Spiral CT scan was performed before the implantation. After the axial images were reconstructed, CT images were introduced into a computer-based treatment plan system (TPS) to fit the 3-dimensional (3D) profiles of the tumor and its surrounding major organs/tissues. Using the TPS, we calculated the required radiation dosage in

Table I. Patients' data.

Case#	Gender	Age (yrs)	Stage	Location	Pathology	Tumor size (cm ²) before treatment
1	Male	59	T3N2M0, stage IV	Tongue root	Well-differentiated squamous cell carcinoma	5 × 5
2	Male	81	T4N2M0, stage IV	Right parotid gland	Mucoepidermoid carcinoma	4 × 3
3	Female	44	T3N0M0, stage III	Left side of tongue	Well-differentiated squamous cell carcinoma	3 × 2
4	Female	81	T4N1M0, stage IV	Right upper jaw	Well- and moderately-differentiated squamous cell carcinoma	3 × 3
5	Female	42	T2N1M2, stage III	Left parotid gland	Myoepithelial carcinoma	2 × 2
6	Male	71	T4N2M1, stage IV	Floor of mouth	Well-differentiated squamous cell carcinoma	2 × 4
7	Female	62	T1N2M0, stage IV	Palate	Mucoepidermoid carcinoma	4 × 4
8	Male	77	T2N2M0, stage IV	Right side of tongue	Well-differentiated squamous cell carcinoma	5 × 4
9	Male	66	T2N2M0, stage IV	Palate	Mucoepidermoid carcinoma	3 × 3
10	Female	75	T3N1M0, stage IV	Left lower jaw	Moderately and well-differentiated squamous cell carcinoma	4 × 3
11	Female	55	T3N0M0, stage III	Left upper jaw	Moderately differentiated squamous cell carcinoma	2 × 4

targeted area, numbers of radiation sources, and 3D arrangement in order to make 90% of the targeted organ receive 90% of the prescription dose and the average radiation dose of the organ at risk being less than 30 Gy.

Seed Implantation

The patients were fasted for food and water 4h before surgery. Sedative drugs were administered 0.5 h before surgery. The seeds were implanted under local or general anesthesia. Body surface was positioned in accordance with the treatment plan before the seeds were implanted, with a space between the needle tract and the seeds ranging 1.0-1.5 cm.

Verification After the Procedure

A second spiral CT scan was performed 1-2 days after the procedure and the CT images were introduced into the TPS. A supplementary implantation was performed when “cold spots” were found in the targeted area. The actual matched peripheral dose (MPD) was calculated and the locations, amount, and distribution of the seeds were verified.

Nimotuzumab Immune Therapy

Nimotuzumab treatment (200 mg, weekly, for 6 consecutive weeks) was given before and after the seed implantation. Oral dexamethasone (8 mg, before breakfast in the morning, for 3 consecutive days) was initiated one day before the treatment. Routine blood test was performed every three days during the treatment. At the end of each cycle, the liver function, kidney function, and blood sugar levels were measured and the routine urine and stool tests were performed. For the patients with decreased white blood cells and neutrophils, granulocyte colony-stimulating factor support was provided until these cells returned to normal levels.

Evaluation of Therapeutic Efficacy

The evaluation of therapeutic efficacy was mainly based on the Response Evaluation Criteria in Solid Tumors (RECIST): a complete response (CR) was defined as the disappearance of all target and non-target lesions and 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; and a stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The following two formulas were used:

- Response rate (RR) = (CR+PR)/number of all cases
- Disease control rate (DCR) = (CR+PR+SD)/number of all cases

Adverse Reactions

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)³.

Statistical Analysis

To evaluate safety according to age, we compared the adverse reaction between the group of patients under 65 years and the group of patients over 65 years. Toxicity and Radiation-induced injuries for patients under 65 years and over 65 years were using the χ^2 test for categorical variables. Measurement data were analyzed by the statistical software SPSS 13.0 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered to be statistical difference.

Results

Post-¹²⁵I-seed Implantation Observations

¹²⁵I-seed implantation was successfully performed in all the patients. The implanted seeds were 17-93 in number (mean: 46). After the procedure, the TPS dose verification showed that the mean MPD was 98 Gy. Two patients experienced slight PD after the surgery for whom a supplementary implantation was performed at the second post-operative month. All patients completed the 6-week nimotuzumab immunotherapy.

Short-Term Clinical Efficacy

According to the half-life of ¹²⁵I-seeds, the prescription dose could be reached 59.6 days after the seed implantation. Therefore, a second CT scan for evaluating the tumors was arranged two months after the surgery. Of the 11 patients, 3 achieved CR (one such case is shown in Figure 1), 6 PR, and 1 SD, yielding a RR of 81.8%. The local DCR was 90.9%. One patient with squamous cell carcinoma of the tongue was found unresponsive to the ¹²⁵I-seed implantation and showed local recurrence; therefore, a second implantation was performed.

Toxicities and Adverse Events

The acute radiation-induced injuries were mainly presented as radiation-induced mucositis and radiation-induced dermatitis. The radiation-induced mucositis was mainly limited to grade 2 (5 cases of grade 1 and 3 cases of grade 2), while the radiation-induced dermatitis was mainly grade 1 (2 cases of grade 1 and 2 cases of grade 2). No grade 3 or higher toxicities (i.e. acute or late radiation injuries that affect the quality of life) were found during this study. One patient with squamous cell carcinoma of the tongue root suffered

from a sore and swollen throat following the ¹²⁵I-seed implantation which was improved after symptomatic treatment. The main adverse reactions of nimotuzumab (listed in Table II) included neutropenia, fatigue, nausea and mild liver damage, which were alleviated after symptomatic treatment (e.g. pain-relieving, anti-inflammatory, or anti-emetic medications) and nutritional support. Grade 1/2 (but without 3/4) leukopenia was observed. However, there was not a significant difference between the group of patients under age 65 years and over 65 years of age for toxicities and adverse events ($p > 0.05$) (Table II). No skin rash or allergic reaction was noted.

Discussion

Surgery is a common treatment for oral malignancies. However, chemotherapy and radiotherapy may become the first choice for patients who are diagnosed with III-b or V stage tumors or the patients who refuse surgery due to their poor general health status or concerns about post-surgical facial effects. Regarding such patients, although either chemotherapy or radiotherapy can somehow control the growth and metastasis of advanced cancer, the efficacies of these treatments remain suboptimal⁴. In addition, the harm-

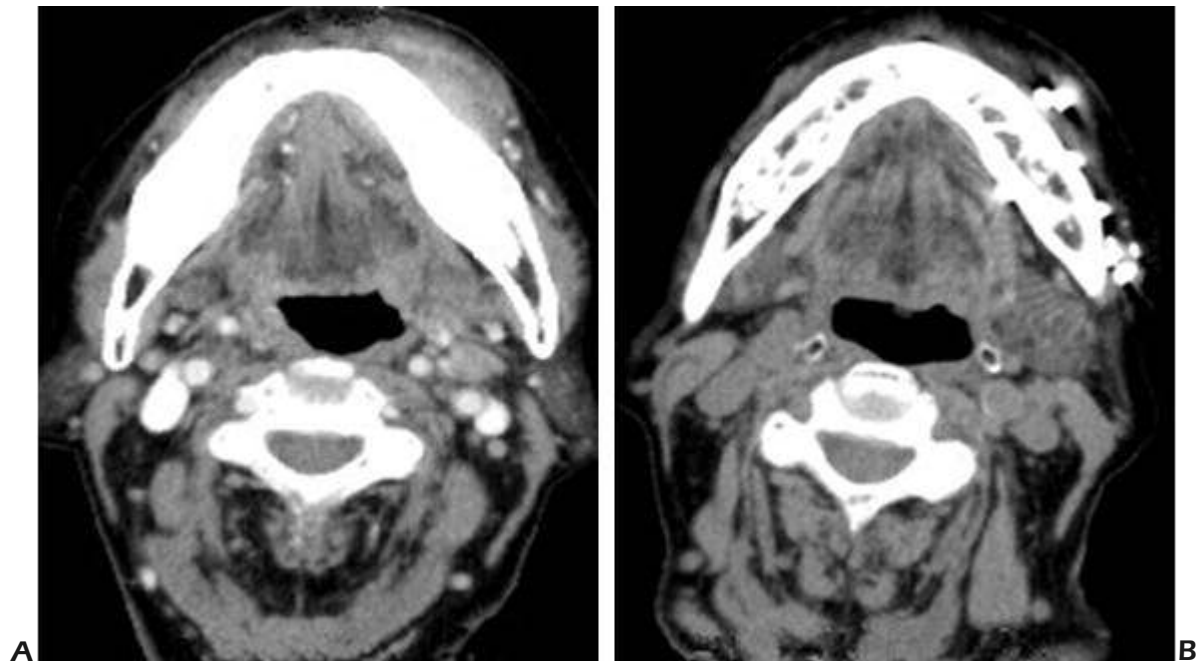


Figure 1. Axial CT images of squamous cell carcinoma of the left gingiva in one patient are shown: (A) before treatment; (B) two months after treatment.

Table II. Adversereaction of combined ¹²⁵I-seed implantation and nimotuzumab between the group of patients under age 65 years and over 65 years of age.

Adverse reaction	Age <65 (n=5)		Age >65 (n=6)		p value
	Grade 1	Grade 2	Grade 1	Grade 2	
	n %	n %	n %	n %	
Radiation-induced mucositis	2 40	1 20	3 50	2 33.3	0.054
Radiation-induced dermatitis	1 20	1 20	1 16.7	1 16.7	0.485
Neutropenia	1 20	2 40	2 33.3	2 33.3	0.593
Fatigue	3 60	1 20	1 16.7	4 66.7	0.755
Nausea	1 20	1 20	2 33.3	1 16.7	0.292
Mild liver damage	2 40	1 20	1 16.7	3 50	0.535

ful effects of chemotherapy and radiotherapy on normal tissues and their function can lead to the intolerance of these therapies in patients with advanced tumors who are already in poor general condition; restraining the treatment doses to avoid intolerance also lowers the effectiveness of the therapy. Therefore, it is highly desirable to develop a more effective and less harmful therapy in clinical practice.

Epidermal growth factor receptor (EGFR) is an extracellular receptor widely expressed in the epithelial tissue. Over-expression of the EGFR is associated with tumor cell proliferation, angiogenesis, resistance to apoptosis, and sensitivity to chemotherapy and radiotherapy. Since EGFR is defined as a potent target for cancer therapy, targeted molecular therapy has become a promising approach to enhance the efficacy of cancer therapy. Specific inhibition of various key targets that are involved in carcinogenesis has been proven to inhibit tumor cell growth, invasion, and metastasis. Moreover, overexpression of EGFR was found in more than 90% of head and neck cancers. Grandis et al⁵ reported that EGFR expression in tumor tissue of oral and head and neck squamous cell carcinoma (HNSCC) was significantly higher than that of adjacent normal tissue. Also, the expression levels of EGFR and its ligands were found to correlate negatively with the disease-free survival. Thus, EGFR was reported as a potent target for the treatment of oral malignancies.

Nimotuzumab is the first humanized therapeutic monoclonal antibody against EGFR. Nimotuzumab has been approved for the treatment of squamous cell carcinoma of head and neck in countries including China, Cuba, India, Argentina, and Columbia. Nimotuzumab binds to the extracellular domain of EGFR, competing with the ligands of EGFR, thereby inhibiting EGF binding and blocking its signal transduction. The

potent ability of nimotuzumab in inducing apoptosis of tumor cells, inhibiting tumor cell proliferation, and preventing tumor-related angiogenesis has been proven by *in vitro* and *in vivo* studies⁶. Furthermore, the anti-tumor effects of nimotuzumab have also been confirmed by several clinical trials. In this regard, Crombet et al⁷ performed a study of nimotuzumab combined with radiation therapy in patients with advanced head and neck cancer. In this study, the 3-year overall survival rates were reported to be 66.7% in the group receiving the optimal dose of 200 mg nimotuzumab for treatment of oral cancer and HNSCC in patients who had no indication for surgery. Moreover, a randomized controlled study² of 106 advanced cancer patients without indications for surgery reported that the complete regression rate in the group with nimotuzumab plus radiotherapy was 59.5% vs. 34.2% in the group with placebo plus radiotherapy; median survival was 22.7 and 12.5 months, respectively. Those data show that nimotuzumab with radiotherapy has better CR and survival rates in patients with oral cancer. These studies have also revealed a strong synergistic effect of the combined treatment of nimotuzumab and radiotherapy which increases the sensitivity of oral cancer cells to radiotherapy.

In general, higher radiation doses are required for better therapeutic efficacy but higher radiation doses often cause damage to the normal tissue. Brachytherapy, also called internal radiation (e.g. ¹²⁵I-radioactive seed implantation therapy), allows for delivering higher radiation doses more specifically to the target area(s) of the body as opposed to the conventional radiation therapy (external beam radiation). Currently, brachytherapy technique is being used, as adjuvant therapy after surgical resection or alone, to treat the advanced oral malignancies worldwide^{8,9}.

Regarding the 11 patients herein treated for advanced oral malignancies, the age varied from 42-81 years and the tumors were located at different sites, such as tongue, palate, parotid gland, jaw, and gums. These tumors were of different histological types, such as squamous cell carcinoma and adenocarcinoma. The post-operative evaluation by CT scan showed that the local disease control rate (DCR) reached 90.9% at 2nd month after surgery. In this study, the 3 cases with complete remission were of poorly differentiated adenocarcinoma and 1 case with partial remission was of mucoepidermoid carcinoma of the palate, suggesting that the adenocarcinoma might be relatively more sensitive to ¹²⁵I brachytherapy. These findings are consistent with those reported by a previous study¹⁰. These data support that the adenocarcinoma located in the oral, head and neck regions could be effectively treated by brachytherapy. Besides, in our study, one female patient was diagnosed with myoepithelial carcinoma of the left parotid gland. One year after brachytherapy, a small mass (1×1 cm²) appeared in the left parotid gland and a connective tissue-wrapped ¹²⁵I implant was found during biopsy. Post-operative pathology showed fibrous tissue-like change, implicating the brachytherapy-induced tumor degeneration.

The common adverse events (AEs) associated with nimotuzumab immune therapy include chills, fever, asthenia, rash, hypotension/fluctuating blood pressure, headache, dizziness, drowsiness, nausea/vomiting, anorexia, diarrhea, elevated transglutaminase/alkaline phosphatase, mucositis, and microscopic hematuria. Most of these adverse reactions were found in our patients during nimotuzumab therapy; however, the toxicities were only of grade 1 or 2 and were alleviated by supportive symptomatic treatment, causing no effect on the course of treatment. Of note, these AEs did not add to the side effect of ¹²⁵I-brachytherapy and the radiation-induced mucositis was mainly limited to grade 2 (4 cases of grade 1 and 7 cases of grade 2), while the radiation-induced dermatitis was mainly of grade 1 (9 cases of grade 1 and 2 cases of grade 2). No grade 3 or higher toxicities i.e. acute or late radiation injury that affects quality of life was observed during our study. The plausible reasons for fewer side effects seen during the combination therapy of nimotuzumab and ¹²⁵I-brachytherapy include: (1) nimotuzumab binds with high affinity to tumor cells that overexpress the EGFR while it bind with low affinity to normal cells

that poorly express the cognate receptor; (2) nimotuzumab, being a fully humanized monoclonal antibody, is better than cetuximab in terms of skin rash¹¹; and (3) the exposure dose and area for ¹²⁵I-brachytherapy are carefully determined by an excellent design through a high-precision TPS system which enables exposing 90% area of targeted tumor to 90% of irradiation dose whereas the average exposure dose of organs at risk remains small. Furthermore, brachytherapy itself is a minimally invasive surgery that can be carried out under local anesthesia, avoiding occurrence of serious complications.

Conclusions

The present study shows a promising short-term effectiveness of the combined treatment of ¹²⁵I-radioactive seed implantation based brachytherapy along with nimotuzumab immunotherapy for advanced oral malignancies. Nimotuzumab markedly enhanced the tumors' sensitivity to the brachytherapy without increasing AEs and improved the patients' quality of life. Given that the adenocarcinoma was found to be more sensitive to the combined treatment, other novel therapeutic approaches can also be tested for efficacy in different histological types of oral malignancies. Randomized controlled studies with larger sample sizes and extended follow-up data will be further required to verify the clinical significance of combined brachytherapy-immunotherapy approach for the treatment of advanced oral malignancies.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) JIANG YL, MENG N, WANG JJ, RAN WQ, YUAN HS, QU A, YANG RJ. Percutaneous computed tomography/ultrasonography-guided permanent iodine-

- 123 implantation as salvage therapy for recurrent squamous cell cancers of head and neck. *Cancer Biol Ther* 2010; 9: 959-966.
- 2) RODRÍGUEZ MO, RIVERO TC, DEL CASTILLO BAHÍ R, MUCHOLI CR, BILBAO MA, VINAGERAS EN, ALERT J, GALAINENA JJ, RODRÍGUEZ E, GRACIAS E, MULÉN B, WILKINSON B, DE ARMAS EL, PÉREZ K, PINEDA I, FRÓMETA M, LEONARD I, MULLENS V, VIADA C, LUACES P, TORRES O, IZNAGA N, CROMBET T. Nimotuzumab plus radiotherapy for unresectable squamous-cell carcinoma of the head and neck. *Cancer Biol Ther* 2010; 9: 343-349.
 - 3) DCTD, NCI, NIH, DHHS. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0. <http://ctep.cancer.gov>, Publish Date: August 9, 2006, Online Date: March 31, 2003.
 - 4) KURTIN SE. Systemic therapies for squamous cell carcinoma of the head and neck. *Semin Oncol Nurs* 2009; 25: 183-192.
 - 5) GRANDIS JR, MELHEM MF, BARNES EL, TWEARDY DJ. Quantitative immunohistochemical analysis of transforming growth factor- and epidermal growth factor receptor in patients with squamous cell carcinoma of the head and neck. *Cancer* 1996; 78: 1284-1292.
 - 6) DIAZ MIQUELI A, ROLFF J, LEMM M, FICHTNER I, PEREZ R, MONTERO E. Radiosensitisation of U87 MG brain tumors by anti-epidermal growth factor receptor monoclonal antibodies. *Br J Cancer* 2009; 100: 950-958.
 - 7) CROMBET T, OSORIO M, CRUZ T, ROCA C, DEL CASTILLO R, MON R, IZNAGA-ESCOBAR N, FIGUEREDO R, KOROPATNICK J, RENGINFO E, FERNÁNDEZ E, ALVÁREZ D, TORRES O, RAMOS M, LEONARD I, PÉREZ R, LAGE A. Use of the humanized anti-epidermal growth factor receptor monoclonal antibody h-R3 in combination with radiotherapy in the treatment of locally advanced head and neck cancer patients. *J Clin Oncol* 2004; 22: 1646-1654.
 - 8) CANO ER, LAI SY, CAYLAKLI F, JOHNSON JT, FERRIS RL, CARRAU RL, SNYDERMAN CH, GOODING WE, SIMENTHAL AA JR, MYERS EN. Management of squamous cell carcinoma of the base of tongue with chemoradiation and brachytherapy. *Head Neck* 2009; 31: 1431-1438.
 - 9) SHAN XF, CAI ZG, ZHANG JG, ZHANG J, GAO Y, YU GY. Management of sialoblastoma with surgery and brachytherapy. *Pediatr Blood Cancer* 2010; 55: 1427-1430.
 - 10) ZHANG J, ZHENG L, HUANG MW, LIU SM, JIA LF, SHI Y, YU GY, ZHANG JG. Radioactivity seeds interstitial brachytherapy treating malignant salivary gland tumors. *J Peking Univ Health Sci* 2011; 43: 272-275. [Article in Chinese]
 - 11) RAMAKRISHNAN MS, ESWARAIAH A, CROMBET T, PIEDRA P, SAUREZ G, IYER H, ARVIND AS. Nimotuzumab, a promising therapeutic monoclonal for treatment of tumors of epithelial origin. *MAbs* 2009; 1: 41-48.