Journal of Zhejiang University SCIENCE B
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
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Deep lingual arterial chemoembolization of tongue carcinoma with microcapsuled anticancer drug

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Received June 12, 2007; revision accepted July 13, 2007

Abstract: Objective: Microcapsule chemoembolism is a promising treatment of tumors. We describe a deep lingual arterial embolization of tongue carcinoma with microcapsuled carboplatinum. Methods: Lingual artery cast specimens from cadavers were microscopically examined, and 78 patients with tongue cancer were recruited and treated with the deep lingual arterial embolization therapy. Results: Microcapsule embolism occurred approximately at the fifth or sixth level of the deep lingual artery branches. The five-year survival rate was 88.5% (69 out of 78), and the ten-year survival rate 52.6% (41 out of 78). Conclusion: The deep lingual arterial embolization of tongue carcinoma with microcapsuled carboplatinum is an effective therapy to treat carcinoma in mid-margin or mid-body of the tongue.

Key words: Tongue carcinoma, Artery cast, Arterial chemoembolization, Deep lingual arterial embolization, Anticancer drug, Carboplatinum

doi:10.1631/jzus.2007.B0704 **Document code:** A **CLC number:** R739.8

INTRODUCTION

Microcapsule chemoembolism is a relatively new therapy to treat malignant tumors, and it was performed mainly in hepatic cancers (Esteban and Gil, 2002; Uraki *et al*., 2004; Ruben *et al*., 2005; Harris *et al*., 2001; Huang *et al*., 2006; Hayashi *et al*., 2004). During the last decade, multiple studies have reported the utilizing of selective arterial embolism with microcapsules containing anti-tumor drugs to treat malignant tumors (Diaco *et al*., 1995; Esteban and Gil, 2002; Uraki *et al*., 2004; Ruben *et al*., 2005; Munro *et al*., 2003; Harris *et al*., 2001; Hayashi *et al*., 2004). This technique can effectively interrupt the blood supply of tumor, increase concentrations of anti-tumor drugs, and prolong the drugs action time in cancerous lesions while reducing the systemic toxicity (Diaco *et al*., 1995; Huang *et al*., 2006). The incidence of the tongue cancer is the highest among oral and maxillofacial cancers. To date, however, no study has reported the utilizing of chemoembolization to treat tongue carcinoma except for cancers in some other nearby organs (Kovács and Turowski, 2002; Tsurumaru *et al*., 2007). In the present study, we treated 78 patients with lingual carcinoma by lingual artery chemoembolism with our own-produced ethyl cellulose microcapsuled carboplatinum (Gu *et al*., 2002), and obtained satisfying clinical efficacy. We investigated the correlations among lingual anatomic characteristics, the flow pathway of microcapsules, and embolism sites, as well as clinical outcomes, to develop an alternative treatment approach, other than radical surgery and radiotherapy, for certain tongue carcinomas in a wider age area (Veness, 1999).

MATERIALS AND METHODS

The investigation was approved by the Research Ethics Committee, School of Medicine, Zhejiang

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University, following the principles in the Declaration of Helsinki, and the informed consent was obtained from the study participants.

Preparation of human lingual artery cast specimens

Red and blue acetone solutions of 15% were prepared from acrylonitrile butadiene styrene (ABS) resin with moderate red and blue paints for oil paintings, respectively. Fifty-three cadavers had internal jugular veins kept opened, and after the external carotid arteries and lingual arteries were anatomically separated, stable intubations were performed in lingual arteries. Lingual arteries were infused thoroughly to fix the vascular endothelial cells successively with heparin saline and pentdialdehyde phosphorate buffer solution of 0.5%, pH 7.4, in case that the vessels shrink and dilate excessively. The prepared red and blue ABS acetone solutions were infused into the intubations in both sides until the lingual bodies stiffed, and then they were left to move into solid phase after 48 h of a warm water bath. The lingual artery cast specimens were finalized by washing with flowing water after 5~7 d of tissue removal with 36% hydrochloric acid. Then the morphology of the lingual artery cast specimens was grossly observed and viewed microscopically with the diameters and angles of the branches measured under a scanning electronic microscope (SEM) (Sun *et al*., 1997) (Fig.1).

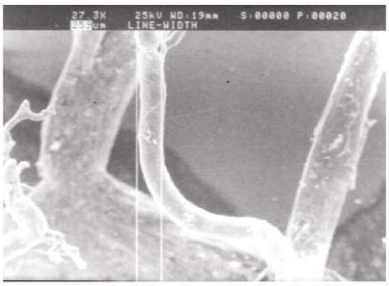

Fig.1 The morphology of lingual artery branches under a scanning electronic microscope (SEM)

Patients

Seventy-eight patients with tongue cancer, 43 males and 35 females, aged from 27 to 65 years old, treated at the Second Affiliated Hospital, School of Medicine, Zhejiang University, since 1993, were enrolled in the study. The original sizes of carcinomas were from 1 to 6 cm in diameter. Nine cases had lingual carcinoma originating from preexisting leukplakia, while others were all de novo squamous cell carcinomas. The majority of these carcinomas were located at the mid-margin or mid-body of the tongue, with 2 cases near the base and 3 cases at the ventral tongue near the floor of the mouth.

Surgical procedures

External carotid and lingual arteries were anatomically identified after neck skin incisions, and then stable intubations (Fig.2) in the lingual artery were performed, into which our own-produced carboplatinum microcapsules were infused. Twenty-one cases were embolized directly with catheterization alone, while the remaining 57 were catheterized and embolized during radical neck lymph nodes dissection. All the mandibles of the 78 patients were kept intact without resection.

Fig.2 Instrument for chemoembolization intubation: microinfusion pump

RESULTS

Lingual artery cast specimens

We observed that the shapes of the lingual artery cast specimens were similar to the appearance of the tongue (Fig.3), and the blood vessels in each side of the tongue were separated by the fibro diaphragm at the axis of the tongue, while connected with each other by the capillary net at the tip of the tongue. The deep lingual artery ran ahead along the boundary of medial and median one-third of the half tongue lineally, and then went in a waveringly pattern to the tip of the tongue, keeping close to the mucous membrane of the dorsal tongue, when observed laterally. Vessel branches were distributed into every region of the tongue body, with most branches running vertically to

the dorsal tongue; branches to the lateral and medial came next in sequence, and branches to the ventral tongue arose as the last. The branches differed in length. The longer ones arrived at the submucous membrane after 7 or 8 levels of branching, and a few lower and thinner branches, together with the shorter ones, constituted the lingual muscle-vessel nets. They, mostly, also ran up to the submucous membrane of the dorsal tongue, forming the submucous membrane capillary nets, while connecting widely with the submucous membrane-vessel nets of the other side of and the base of the tongue. Such anatomic properties revealed the shape of the lingual arterial cast as a sheet of fine lace in morphology. The mean diameters of vessels at the fifth and sixth levels were measured to be (252.2±99.4) μm and (162.1±76.0) μm, respectively, under the SEM.

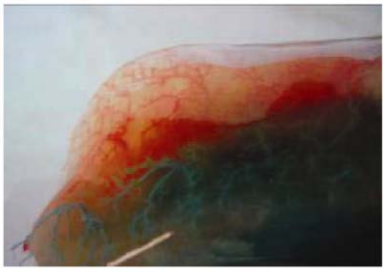

Fig.3 Presentation of tongue vasculature

Clinical outcomes

There was neither complication found after infusion or embolization, nor the treatment-related or immediate post treatment death in the study. On the first day after embolization, congestion and swelling occurred in the embolized site, but not the tip and base of the tongue. After about 3 d of the procedure, the area farther from the tumor site was observed to gradually become necrotic, with the surface turning grey-yellowish. Patients who suffered a pain in the area were treated. The diameter of the necrotic area was smaller than that of the congestion reaction area. It was probably due to the proliferating vasculature around the tumor (Shang *et al*., 2006; Uehara *et al*., 2004), which benefited the microsphere or microcapsule embolization. The necrotic area was resected two weeks after the operation, and four samples of the lingual tissue of 1 mm in diameter were taken from different sites around the resected margin in every patient, and prepared for histopathologic evaluation. An expanded resection was performed when one or more of the four sites were found positive for carcinoma cells. Fifty-nine cases were given an additional resection of the lingual body tissue along the necrotic separation margin to secure no recurrence.

The results of the sites, changes of the lingual carcinoma size, and embolism are listed in Table 1. We defined the complete elimination (CE) of tumor as histopathologically negative for all five sites, and the partial elimination (PE) as any one of the five sites was histopathologically positive. Consequently, five PE patients were later proved to be positive with carcinoma cell at the dissected margin histopathologically after an additional expanded resection three weeks after embolism, and the other 73 cases were negative clinically and histologically (Fig.4 and Fig.5).

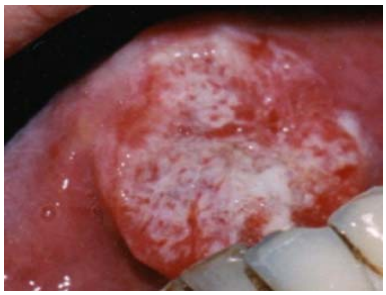

Fig.4 A tongue carcinoma before lingual arterial chemoembolization

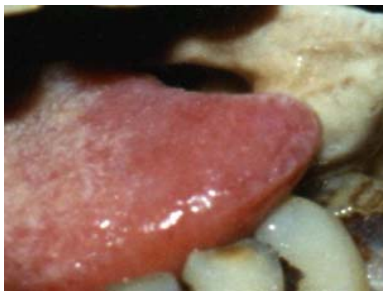

Fig.5 Carcinoma tissue could be separated after two weeks post-chemoembolization

Among the 78 patients, 69 (88.5%) were found to be cancer-free after 5 years post the procedure and 41 patients (52.6%) after 10 years. Tumor recurred to a total of 17 patients (21.8%) from 2 to 10 years after the treatment. The recurrence-free survival rate at 5 years is higher than 81%, and the recurrence proportion is lower than 32.4% in the published data (Veness *et al*., 2003).

Table 1 Sites of lingual carcinoma and embolism results

Cases	Carcinoma sites	Carcinoma size (cm)	Embolism results	Effect
34	Mid-margin of left or right side	3.0×3.0~5.5×6.0	Necrosis and separation along the carcinoma margin	CE
29	Mid-margin of left or right side	1.0×1.5~3.0×2.5	Necrosis and separation about half of the tongue	CE
10	Mid-ventral tongue	1.0×1.5~2.0×2.0	Necrosis and separation along the carcinoma margin	CE
2	Margin near the base	About 2.0×2.5	Tumor shrank, with partial necrosis and separation	PE
3	Ventral tongue near the floor of mouth	4.0×4.0~5.5×6.0	Tumor shrank, with partial necrosis and separation	PE

CE: Complete elimination; PE: Partial elimination

DISCUSSION

Due to the anatomic properties of lingual arterial branches and the hyperplasic blood flow and vessels around the tumor (Kimura *et al*., 2001), the microcapsules are easily able to flow to the tumor region which is the first site after being infused into the lingual artery, and then onto the margin and the dorsum of the tongue. The base and tip of the tongue are difficult for blood flow containing microcapsules to produce embolism because of the additional resistance of blood flow from the connecting capillary net. This was confirmed by the dyed sequence of time for different sites of the tongue using medical blue in the cadavers cast investigation of the current study. The first site was the tumor and its surrounding region; the next one was the margin, back and abdomen of the tongue; and the last one was the base and tip of the tongue. The quantity of medical blue dyed in each level of the tongue also came out in the same sequence. After embolism infusion, the tumor vessels will be embolized, and the tumor will develop a compromised blood supply, necrosis, and separation from the designed site (Jang *et al*., 2004).

The blood supply in the tongue is one of the richest in the oral-maxillo-facial region (Dockery and Fraher, 2007), whereas the extent of necrosis and separation are related to the infusion pressure and the quantity of microcapsules infused in a unit time, as well as the dosage of the embolism, in addition to the site and size of the cancer. The excessively low infusion pressure or excessively fast infusion velocity, therefore, will lead to positioning the microcapsules embolism in the main stem or large branches instead of arriving at the fifth or sixth branch level, resulting in improper necrosis. In the present study, we suspended 200~300 mg of car boplatinum in 30~40 ml of meglumine iothalamate, and followed a stable infusion procedure by using the microinfusion pump (Fig.2), allowing the microcapsules to arrive at a proper vessel level.

Our carboplatinum microcapsules average (214.0±48.0) μm in diameter (Gu *et al*., 2002), while microcapsules used in the embolisation are usually between 40 and 300 μm (Sun *et al*., 1997; Ross and Chang, 2002; Kato *et al*., 1981). Drug particles can be seen scattering among the reticular ethyl cellulose braces under the SEM, with many holes on the surface. The content of carboplatinum in the microcapsule was 51.4% (v/v) and the release rate was 62.4% per day tested in vitro (Gu *et al*., 2002). Since the fifth and sixth levels of vessel branches are (252.2±99.4) μm and (162.1±76.0) μm in diameter, respectively, our microcapsules can be positioned right between these two levels of the vessel branches, resulting in no substantial necrosis of the tongue.

CONCLUSION

The lingual artery chemoembolization with proper microcapsules possesses promising therapeutic effects in treating patients with carcinomas in the mid-margin or mid-body of the tongue. Chemoembolization appears to be effective in eliminating lingual tumors in these areas without any other painful or deforming extensive procedures, and improving the quality of life for patients (Iguchi *et al*., 2006).

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