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CHEMOTHERAPY USING INTRA-ARTERIAL INFUSION FOR ORAL CANCER

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ABSTRACT

There are three historically recognized methods of intra-arterial infusion for oral cancer: Conventional intra-arterial infusion via the superficial temporal artery: Superselective intra-arterial infusion via the femoral artery (Seldinger method), New superselective intra-arterial infusion via the superficial temporal artery. Here we report a recent instance of daily concurrent chemoradiotherapy using a new superselective intra-arterial infusion. A catheter with a curved tip was inserted superselectively into the feeding artery of the tumor via the superficial temporal artery (long-term catheterization has become possible using this method). The patient with T3 tongue cancer was treated by chemoradiotherapy. Radiotherapy (total dose: 40 Gy/4weeks) and superselective intra-arterial infusion chemotherapy using docetaxel (DOC) (total dose: 60 mg/m2/4weeks, 15 mg/m2/ week) and cisplatin (CDDP) (total dose: 100 mg/m2/4weeks, 5 mg/m2/day) were concurrently performed daily, followed by surgery, after which no major complication was observed. The clinical effect was complete response (CR), and the pathological effect on the resected tumor after surgery was pathological CR. This method promises to be a new strategy of choice for the treatment of oral cancer.

Key Words: Oral cancer, Superselective intra-arterial infusion, Chemoradiotherapy

INTRODUCTION

In intra-arterial chemotherapy for oral cancer, therapeutic techniques can be roughly divided into 3 methods. The earliest method was to insert a linear catheter via the superficial temporal artery and guide the catheter to an area near a target tumor-feeding artery originating from the external carotid artery (Fig. 1-1). While this method has been frequently utilized, intratumoral concentrations of anticancer agents fluctuate. With the recent introduction of super-selective intra-arterial chemotherapy via the femoral artery using the Seldinger method (Fig. 1-2), the usefulness of concurrent therapy with radiotherapy has been documented, and this technique is also currently being employed in Japan. However, as a catheter must be inserted every time an anticancer agent is injected, severe complications such as cerebral infarction and sudden death can occur. A highly safe super-selective intra-arterial chemotherapeutic technique has therefore been developed. A catheter with a curved tip is inserted from the superficial temporal artery in retrograde fashion and placed inside a specific tumor-feeding artery for the long term (Fig. 1-3). In what follows, I discuss each of these methods and examine in greater detail the most recent use of superselective intra-arterial infusion via the superficial temporal artery.

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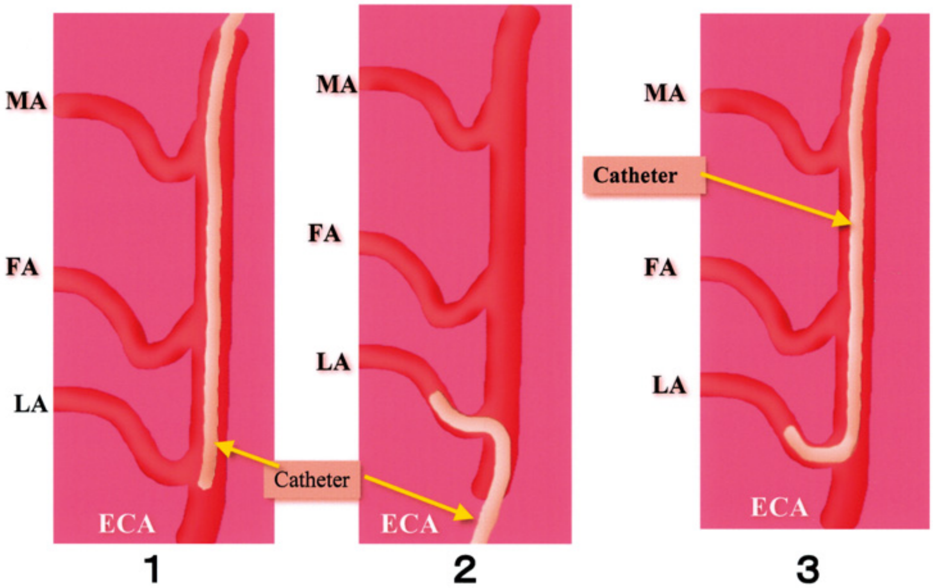

Fig. 1 1: Conventional intra-arterial infusion via superficial temporal artery.
2: Superselective intra-arterial infusion via femoral artery by Seldinger method.
3: Superselective intra-arterial infusion via superficial temporal artery.
MA: Maxillary artery; FA: Facial artery; LA: Lingual artery;
ECA: External carotid artery.

Conventional Intra-arterial Infusion via the Superficial Temporal Artery

Ever since Sullivan *et al.*[1] reported a method for inserting a linear catheter via the superficial temporal artery and placing it in an area near a target tumor-feeding artery originating from the external carotid artery, many additional studies have been reported.[2,3] As catheterization is relatively easy using this method, not only radiologists but also oral surgeons and otolaryngologists who treat head and neck cancers can readily perform this procedure. However, because the catheter is placed in the external carotid artery rather than in a tumor-feeding artery, an anticancer agent may not be reliably injected into the tumor-feeding artery, and may even pass into and through the external carotid artery. Moreover, because a linear catheter is used, its tip may easily be displaced by neck extension or flexion. To confirm whether a catheter properly placed in an external carotid artery in the vicinity of a tumor-feeding artery, a dye such as indigo carmine is generally injected. However, because the dye is injected manually, even if a catheter is displaced due to the bifurcation of the tumor-feeding artery, the high pressure created by manual injection can cause the dye to flow through the tumor-feeding artery, resulting in the false appearance of correct catheterization. Administration of an anticancer agent is not performed with a manual one-shot injection involving such high pressure. In many cases, such agents are administered in a bolus or continuous intra-arterial infusion without high pressure. Anticancer agents may thus be injected into the external carotid artery without reaching a tumor-feeding artery. For example, when inserting a catheter near the branching of the lingual artery for the treatment of tongue cancer, if the junction between the external and internal carotid arteries is low position, no problem is encountered because the internal carotid artery is physically separated from the lingual artery. However, if the junction between the external and internal carotid arteries

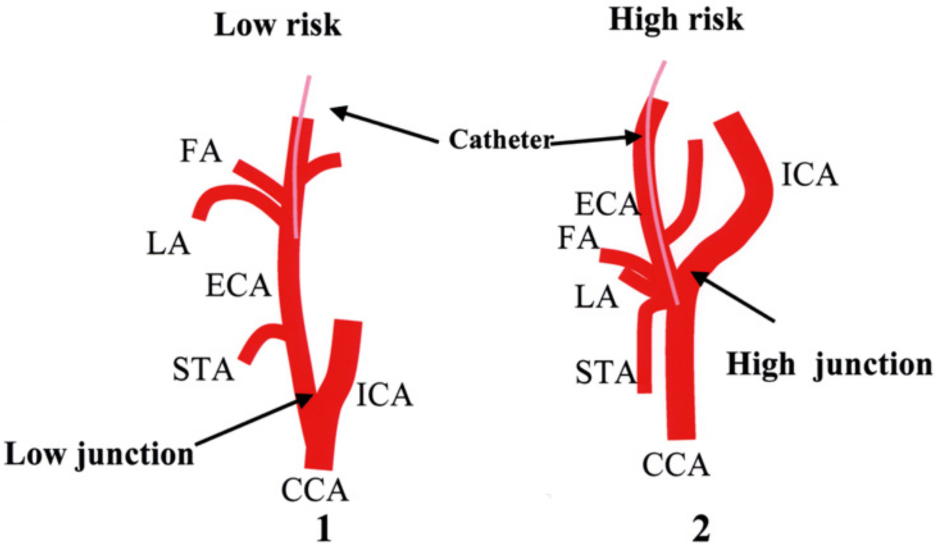

Fig. 2 Risk of cerebral infarction by conventional intra-arterial infusion
1: Low risk
2: High risk
CCA: Common carotid artery; ICA: Internal carotid artery; ECA: External carotid artery; STA: Superior thyroid artery; LA: Lingual artery; FA: Facial artery.

is high position, the lingual and the internal carotid arteries will be anatomically close. When a linear catheter is inserted, an anticancer agent may enter the internal carotid artery, and when switching drugs, clotting can increase the risk of cerebral infarction (Fig. 2). Therefore, when using this conventional method to inject an anticancer agent into a low artery such as the lingual artery, ascertaining the anatomical relationship between the external and internal carotid arteries is extremely important. This method is therefore indicated only when for some reason one can not perform super-selective intra-arterial chemotherapy via the femoral artery using the Seldinger method or super-selective intra-arterial chemotherapy via the superficial temporal artery.

Superselective Intra-arterial Infusion via the Femoral Artery by Seldinger Method

Lee *et al.*[4,5] first reported super-selective intra-arterial chemotherapy via the femoral artery using the Seldinger method, and Robbins *et al.*[6,7] reported the usefulness of concurrent therapy with radiotherapy. At present, this method is mostly selected for the administration of super-selective intra-arterial chemotherapy for head and neck cancer. In recent years, high-dose cisplatin (CDDP) and sodium thiosulfate (STS), a neutralizer, have been administered to the subclavian vein to prevent complications. Using this method, an anticancer agent can be injected into a tumor-feeding artery in a narrow area, greatly contributing to the treatment of head-and-neck cancer. In addition, this method allows anticancer agents to be injected into a feeding artery other than the external carotid artery, e.g., injecting anticancer agents into the thyrocervical trunk, a branch of the subclavian artery, has been found highly useful in the treatment of large cervical lymph node metastasis.[8] However, severe complications such as cerebral infarction and sudden death have been reported; Lee *et al.*[5] warned of these complications from the beginning and in Japan, Shiga *et al.*[9] have reported both cerebral infarction and death, thus calling into question the safety of this method which requires that a catheter must be inserted through the common carotid artery every time an anticancer agent is injected. As a result, clots can travel through the internal carotid artery to cause adverse reactions. Kumar *et al.*[10] conducted a collaborative study in the U. S. to compare institutions that frequently performed radiochemotherapy using the Seldinger method with those that did not. They reported that therapeutic outcomes were more favorable for institutions that did not do so, the frequently performed radiochemotherapy using the Seldinger method, and that for those frequencies of severe complications such as cerebral infarction and death were higher. Since, in most institutions, catheterization is performed by radiologists rather than by otolaryngologists, head-and-neck surgeons or oral surgeons who initially see patients with head-and-neck cancer, collaboration with radiologists plays an important role. As a catheter can not be placed for a long period of time, daily concurrent radiochemotherapy is not possible. When combining chemotherapy and radiotherapy, several studies have shown that better therapeutic results can be obtained using concurrent therapy,[11,12] the superiority of which is now a proven fact. The Seldinger method, however, is incompatible with daily concurrent intra-arterial chemotherapy and radiotherapy.

Superselective Intra-arterial Infusion via the Superficial Temporal Artery

This method was developed to overcome the disadvantages associated with those mentioned above. A curved catheter is inserted from the superficial temporal artery in retrograde fashion into a specific tumor-feeding artery,[13-16] and the usefulness of this method in combination with radiotherapy has been reported.[17-19]

Methods of catheterization and chemoradiotherapy

Before catheterization, angiography of the maxillofacial region was necessary to identify the main tumor-feeding arteries and to ascertain the morphology of the tumor-feeding artery originating from the external carotid artery. In super-selective intra-arterial chemotherapy via the superficial temporal artery, the catheters used are modified 4F angiography catheters with a curved tip, of which there are 5 different kinds. Angiography is performed to ascertain the morphology of the target tumor-feeding artery so that a suitable catheter may be selected. A guidewire is inserted into the external carotid artery via the superficial temporal artery (Fig. 3-1), after which a catheter is introduced along the guide wire (Fig. 3-2). After the guide wire is removed from the external carotid artery (Fig. 3-3), the catheter is then advanced toward the tumor-feeding artery (Fig. 3-4).[13-16] Once the catheter is in place, angiography is performed to check the flow (Fig. 4-1). The catheter is sutured at several places around the auricle and remains fixed for 1–2 months (Fig. 4-2).

Having used this method to treat stage III or IV oral cancer, we here present the results of the most effective daily concurrent therapy, comprising radiotherapy combined with intra-arterial chemotherapy using docetaxel (DOC) and CDDP. Figure 5 shows the treatment schedule. The total dose of irradiation was 40 Gy (2 Gy/day, 10 Gy/week), and that of DOC was 60 mg/m^2 (15 mg/administration/week, recommended dose (RD), while the total dose of CDDP was 100 mg/m^2 (5 mg/day). Surgery was performed 4 weeks later, and the histopathological effects of concurrent radiochemotherapy were ascertained from resected tumors. When combining radiotherapy and chemotherapy, the timing of anticancer agent administration plays an important role, and the antitumor effects of such agents are greater in concurrent therapy. The anticancer agent was thus injected in a bolus through the intra-arterial catheter whenever radiotherapy was performed.

Case presentation

The case of a typical patient is presented below:

A 58-year-old man presented with tongue cancer (T3N1M0) (Fig. 6-1). Under local anesthesia, a catheter was inserted into the lingual artery using this method, with postoperative flow imag-

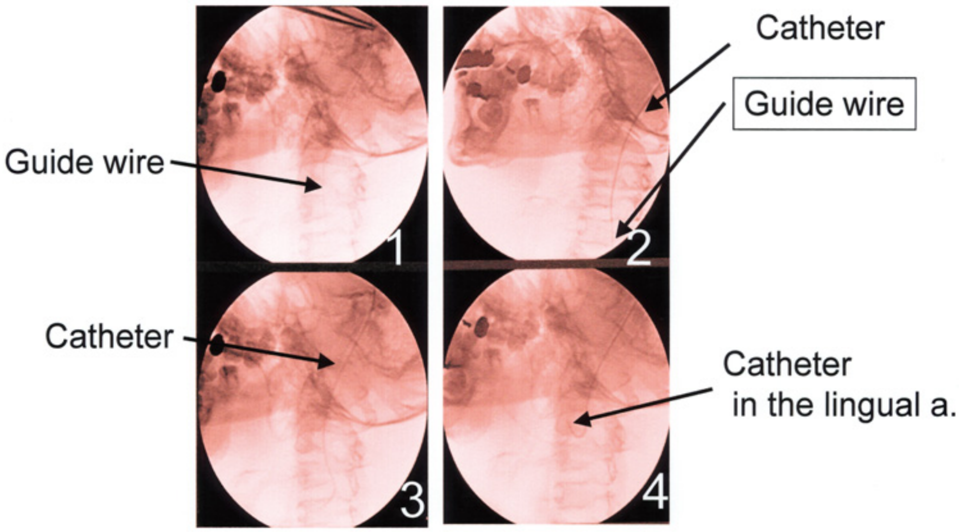

Fig. 3 1: Guide wire inserted into superficial temporal artery.
2: Catheter introduced along guide wire.
3: Guide wire removed from external carotid artery.
4: Catheter moved up toward lingual artery.

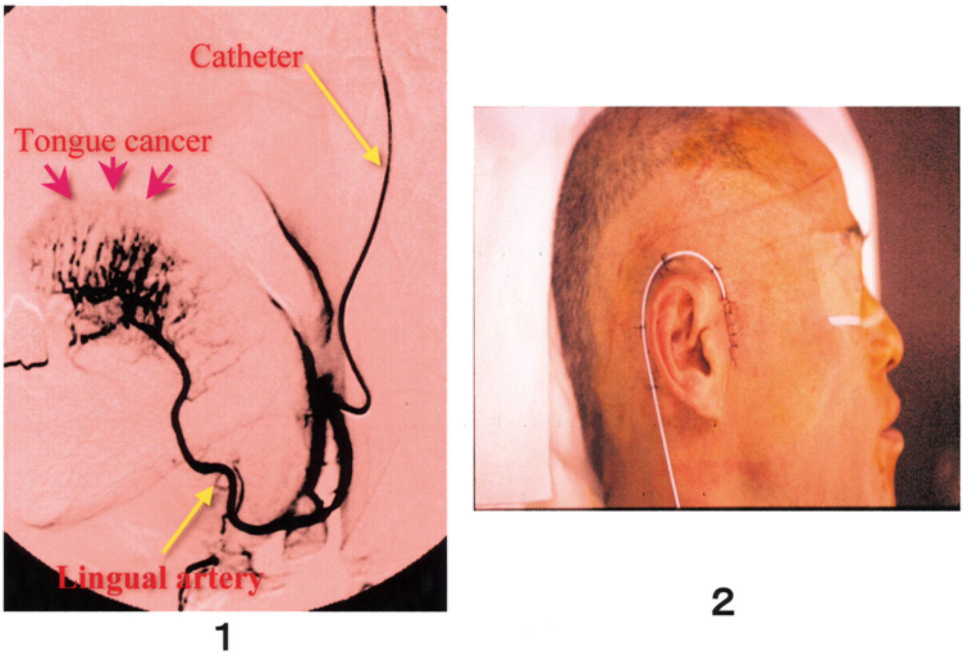

Fig. 4 1: Angiography for flow check after catheterization.
2: Fixation of catheter.

ing confirming that the catheter was correctly inserted (Fig. 6-2). Daily concurrent combination therapy (radiotherapy 40 Gy, chemotherapy DOC 60 mg/m^2, and CDDP 100 mg/m^2) was performed for 4 weeks, and CR was achieved 4 weeks after the end of preoperative therapy (Fig. 6-3). Tumor resection, radical neck dissection and reconstruction of the tongue were promptly performed. Histopathological analysis of the resected tongue showed no tumor cells on cross-sections (Fig. 6-4) (Grade IV

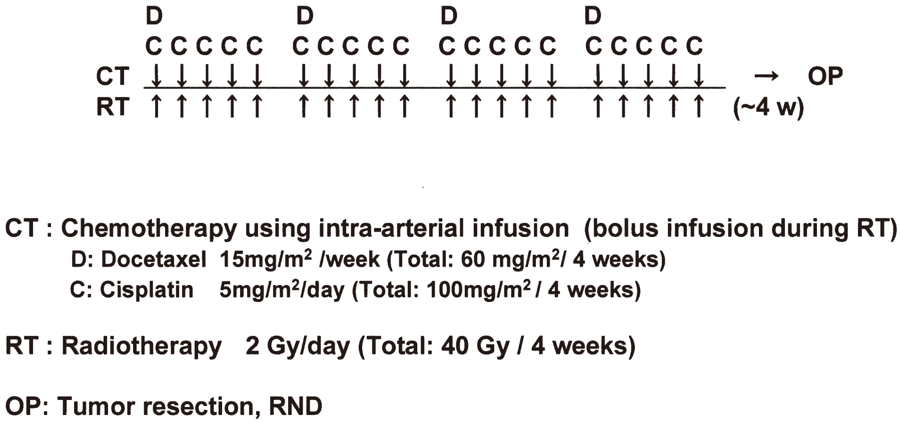

Fig. 5 Treatment schedule of chemoradiotherapy using intra-arterial infusion.

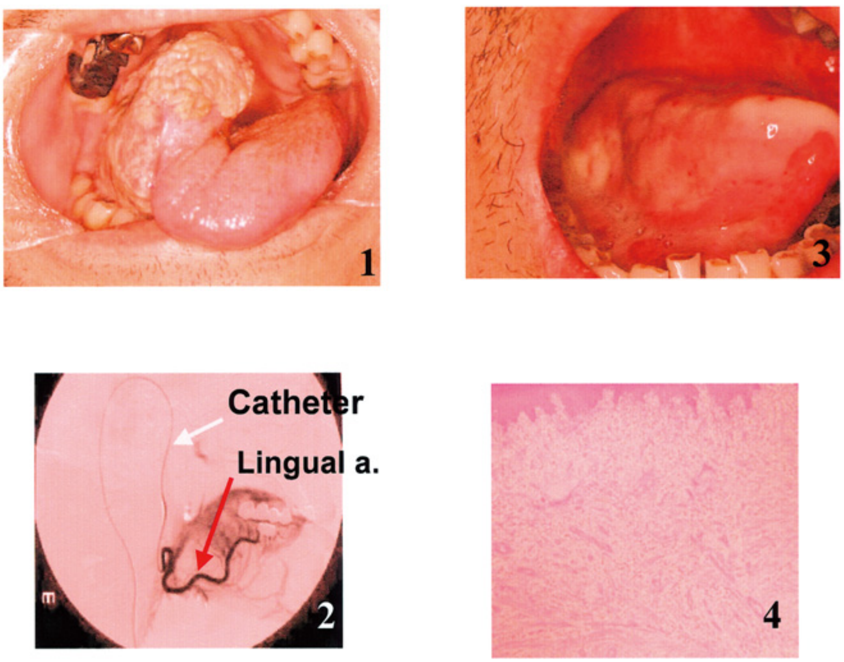

Fig. 6 1: Tongue cancer (before treatment).
2: Angiography for flow check after catheterization to lingual artery.
3: After chemoradiotherapy.
4: Histopathological effect (Grade III by Ohboshi-Shimosato Classification: No viable tumor cells).

according to the classification by Ohboshi and Shimosato).

DISCUSSION

To ascertain intratumoral concentrations of anticancer agents in patients with tongue cancer, platinum concentrations of carboplatin (CBDCA) were measured.[15,16] The intratumoral concentrations were significantly higher for the new method than for conventional methods via the superficial temporal artery. Using such conventional methods, no platinum concentration was found in some cases (Fig. 7). This suggests that the tip of a linear catheter can easily be dislodged peripherally from the branch to a tumor-feeding artery in the external carotid artery. Furthermore, with the new method, a catheter can be left in place for a long period of time, allowing for concurrent intra-arterial chemotherapy and radiotherapy. As with the present study, extremely favorable therapeutic effects can be obtained by administering anticancer agents intra-arterially at the same time as radiotherapy. Furthermore, catheter manipulation in the new method is kept inside the external carotid artery, resulting in reducing risk of the adverse reactions associated with the Seldinger method. However, the rate of insertion of catheter is not 100% in the new method, and countermeasures need to be established for cases where catheterization is unduly difficult.[19] This method is indicated for oral cancer with feeding arteries originating from branches of the external carotid artery, such as the lingual, facial or maxillary artery, while super-selective intra-arterial chemotherapy using the Seldinger method is indicated for the other arteries. In each patient, angiography needs to be performed to analyze tumor-feeding vessels before deciding which method is more appropriate.

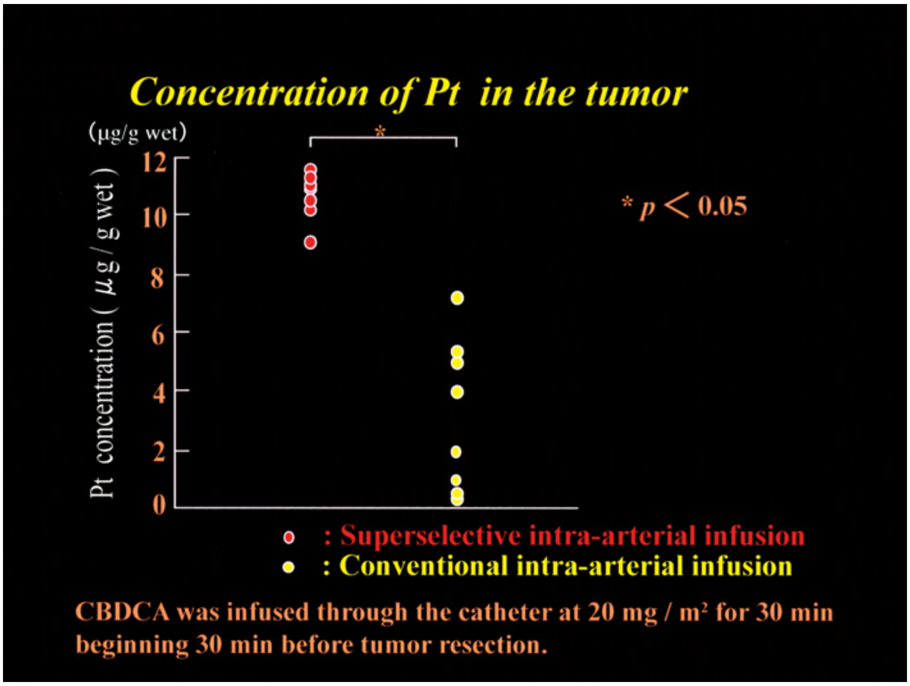

Fig. 7 Platinum concentration in tumor.

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