The ECAS system can superselectively administer anticancer drugs to numerous feeding arteries from the superficial temporal artery: A case report and literature review

KANAME SAKUMA[1], TOMOYUKI KII[1], TOKO MACHIDA[1], NOBUKAZU FUWA[2] and AKIRA TANAKA[1]

[1]Department of Oral and Maxillofacial Surgery, The Nippon Dental University School of Life Dentistry at Niigata, Niigata 951-8580; [2]Department of Radiation Oncology, Central Japan International Medical Center, Minokamo, Gifu 505-8510, Japan

Received June 25, 2023; Accepted July 31, 2023

DOI: 10.3892/mco.2023.2672

Abstract. Superselective intra-arterial chemoradiotherapy (SSIACRT) is one of the curative treatments for advanced oral cancer. SSIACRT can reportedly treat cervical lymph node metastases in the level I-IIA area by super selectively catheterizing the facial artery (FA) and infusing drugs. However, since advanced oral cancer lesions involve a number of feeding vessels, retrograde treatment requires the placement of catheters from the superficial temporal artery (STA) and occipital artery (OA). Furthermore, in the case of level IIB lymph node metastasis, the catheter must be changed because it is necessary to administer anticancer drugs to more than three routes, including the OA, when the feeding arteries of the primary tumor are combined. The external carotid artery sheath (ECAS) system used in the present study involves the insertion of a microcatheter or steering catheter from one route of the STA, allowing selection of numerous feeding vessels, including the OA. The ECAS system can facilitate the administration of chemotherapy via the STA simultaneously to the maxillary artery, lingual artery, FA and OA. The present study describes cases of maxillary gingival cancer and tongue cancer with cervical lymph node metastasis, which were treated with the ECAS system via the STA; the treatment successfully controlled both the primary tumor and cervical lymph node metastasis. In the two cases described in the present study, metastatic lymph nodes were found in the level IB and IIB region, but were successfully treated by administering cisplatin via the OA, in addition to the primary lesion. To date, to the best of our knowledge, there is no case report clearly referring to the treatment of lymph node metastasis using the ECAS system. In conclusion, SSIACRT using ECAS may be considered a useful treatment for oral cancer with cervical lymph node metastasis.

Correspondence to: Dr Kaname Sakuma, Department of Oral and Maxillofacial Surgery, The Nippon Dental University School of Life Dentistry at Niigata, 1-8 Hamaura-cho, Chuo-ku, Niigata 951-8580, Japan
E-mail: sakuma.k@ngt.ndu.ac.jp

Key words: superselective intra-arterial chemoradiotherapy, superficial temporal artery, lymph node metastasis, oral cancer, external carotid artery sheath system

Introduction

Superselective intra-arterial chemotherapy combined with radiation therapy (SSIACRT) has recently received attention for its favorable results in oral cancer (1-4). The method can be performed either by catheterization in a retrograde fashion via the superficial temporal artery (STA) and occipital artery (OA) (3) or by catheterization via the femoral artery (FA) using the Seldinger technique (4). In the latter method, inserting a catheter into multiple arteries is possible; however, since the catheter passes through the common carotid artery (CCA), catheter operation-related neurological complications can occur, which has had a 3% incidence rate (5). The former method is associated with a lower risk of cerebrovascular disease, but only one peripheral feeding artery can be selected at a time. Most advanced head and neck cancers, including oral cancers, receive blood flow and nutrition from multiple arteries, aptly called tumor-feeding arteries. Therefore, when the catheter needs to be inserted into two routes, that is, the lingual and the facial arteries, the catheter must be inserted into each of the STA and OA (3). In intra-arterial chemotherapy (IACT) via the STA, vascular selectivity is a significant factor affecting prognosis (1,2). Level II metastatic lymph nodes are often fed from sternocleidomastoid branches from OA. Which would otherwise be difficult to perform with conventional retrograde intra-arterial chemoradiotherapy without changing catheters. SSIACRT with the external carotid artery sheath (ECAS) can treat cervical lymph node metastasis at level II without changing catheters. The ECAS system was first reported in 2017 for its improvements to vascular selectivity (6). Here, we report two cases in which we were able to control a primary tumor and metastatic lymph nodes in the IIA and IIB region. We used ECAS to superselectively administer anticancer agents via three or more routes including OA for oral cancers with lymph node metastasis in the level IB to IIB regions.

Case report

Case 1. A 42-year-old female with increasing left tongue pain was referred to our institution. On initial examination, the patient had an ulcerative mass with induration at the left tongue (Fig. 1), as well as a neck mass on the left side. The tongue mass was diagnosed as a well-differentiated squamous cell carcinoma (SCC) by biopsy. Magnetic resonance imaging (MRI) showed that the tumor extended to near the center of the tongue (Fig. 2A). Contrast-enhanced computed tomography (E-CT) showed a rim-enhanced mass at level II of the left cervical area, which was located inside the sternocleidomastoid muscle (Fig. 2B). Subsequently, 18-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) demonstrated high FDG uptake at the primary tumor and cervical lymph nodes (maximum standardized uptake values=15.5 and 7.4, respectively) (Fig. 2C). Results of the distant metastasis workup was negative. Based on these findings, the diagnosis was SCC of the left tongue (T3N2bM0: Stage IVA).

The patient refused treatment by surgical resection and instead underwent retrograde intra-arterial CRT using ECAS. The ECAS (15 cm long and 5 Fr outer diameter; Toray Medical Co., Ltd., Tokyo, Japan) was made of polyurethane and surface-coated with heparin resin to prevent thrombus formation A backflow valve can be attached at its distal end (Fig. 3A), and a guidewire and microcatheter can be inserted through the valve into the ECAS (7). The ECAS was inserted in retrograde fashion through the STA, and its tip was placed between the maxillary and facial arteries. The ECAS remained indwelling during the entire 7-week course of IACT. Heparin diluted in saline was continuously pumped into the ECAS to prevent occlusion. Each weekly cycle of IACT was performed under fluoroscopic guidance. First, a contrast medium was injected through the ECAS, and a roadmap was created to identify the position of the target arteries using digital subtraction angiography (DSA). The feeding arteries of the primary tumor were the left lingual artery (lt.LA) and the left facial artery (lt.FA). The N2b (levels IB and IIA areas) metastatic lymph nodes were considered the vegetative arteries of the sternocleidomastoid branch of the left facial artery and left OA (lt.OA). Hook-type microcatheters (50 cm long and 2.3 Fr distal outer diameter; Toray Medical Co., Ltd.) were employed to select the tumor-feeding arteries (Fig. 3B). A guidewire for the microcatheter (0.016 inch in diameter, Toray Medical Co., Ltd.) was inserted into the CCA through the ECAS under fluoroscopy in a retrograde fashion. The microcatheter was then inserted along the guidewire into the CCA, and the guidewire was removed. Although not used in this case, if the external carotid artery is significantly tortuous, it may be selected with a steerable microcatheter (Merit SwiftNINJA®, Merit Medical System, Inc.) with a remotely operated flexible tip. Unlike the hook-type microcatheter, this catheter does not require a guidewire (Fig. 3C). The microcatheter was then pulled back to select the target arteries using the roadmap (Fig. 4A and B). Cisplatin was manually injected at a total dose of 50 mg/m^2 into each tumor-feeding artery at 5 ml/min once a week. IACT was performed once a week for a total of seven cycles per week. Sodium thiosulfate (STS), a cisplatin neutralizing agent, was intravenously administered at 0.4 g/mg cisplatin over 8 h

Figure 1. An ulcerative mass with a 50x42 mm induration on the left lingual margin.

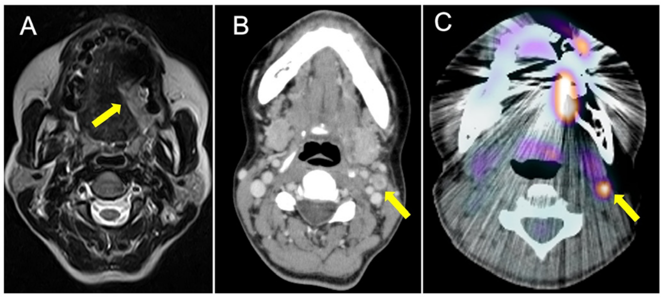

Figure 2. (A) Magnetic resonance imaging of a tumor mass spread to the left tongue near the center (arrow). (B) Enhanced computer tomography shows a ring-weighted mass 12x12 mm in size measured at level II on the left neck (arrow). (C) Imaging using 18-fluorodeoxyglucose-positron emission tomography/computed tomography revealed abnormal 18-fluorodeoxyglucose uptake (maximum standardized uptake values=14.7) of the left neck mass (arrow).

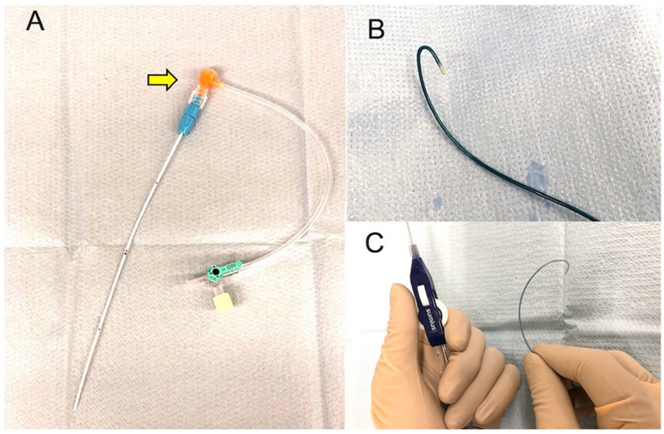

Figure 3. (A) The external carotid artery sheath system (15 cm long and 5 Fr outer diameter, Toray Medical Co., Ltd., Tokyo, Japan) made of polyurethane and surface-coated with heparin resin to prevent thrombus formation. A backflow valve can be attached at its distal end (arrow). (B) A hook-type microcatheter (50 cm long and 2.3 Fr distal outer diameter, Toray Medical Co., Ltd.). (C) A Merit SwiftNINJA® steerable microcatheter (Merit Medical System, Inc.) with a remotely operated flexible tip. The tip of the catheter can be controlled with the dial by hand.

from 1 h prior to cisplatin administration. Catheterization at the STA was performed using ECAS. A catheter was

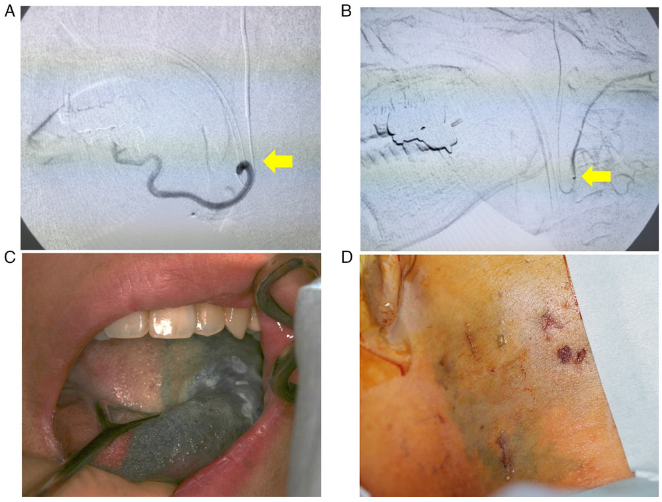

Figure 4. (A) The tip of the catheter is inserted superselectively into the left tongue artery (arrow). (B) The tip of the catheter is inserted superselectively into the left occipital artery (arrow). (C) Left tongue lesions were stained by injecting indigocarmine through the lingual artery. (D) The skin surface over the NII area was dyed by injecting a small amount of indigocarmine through the left occipital artery.

inserted superselectively into the left OA via the STA. The anticancer drug was administered through the OA at a total of 105 mg/body targeting the lymph node metastasis in the IIA to IIB cervical region. The tongue lesions were treated with cisplatin at 235 mg/body from LA and 190 mg/body from FA to the oral floor and tongue base. After catheterization, flow check DSA was performed to ensure appropriate catheter placement. Indigotindisulfonate sodium (indigocarmine) was used to dye the tongue and skin surface of the level IIA to IIB cervical lymph nodes as confirmation of the treatment (Fig. 4C and D). External irradiation was planned after appropriate immobilization using a thermoplastic mask and three-dimensional CT-based techniques. We performed irradiation on the primary lesion and both sides of the neck. The total dose delivered to the primary tumor and the metastatic cervical lymph node sites was 68 Gy/34 fractions. Treatment proceeded as indicated.

The acute adverse events (classified according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events v. 4.0) observed within 1 month after treatment included grade 3 oral mucositis and dermatitis, grade 2 neutropenia, and grade 1 paronychia. No major complications such as cerebral infarctions or other neurological complications were observed. During the follow-up period, E-CT, FDG-PET/CT, and MRI of the primary lesion were performed to evaluate the treatment outcomes. E-CT and MRI showed indistinctive masses of the primary lesion and nodal metastases. FDG-PET/CT showed a lack of FDG uptake in both the primary tumor and cervical lymph nodes (Fig. 5A and B). Overall, the imaging findings indicate that the primary lesion and cervical lymph nodes were effectively controlled with the treatment. The patient has shown no evidence of disease progression, both in the primary lesion and the cervical lymph node area, or distant metastasis 5 years after the treatment.

Case 2. A 76-year-old female with an enlarging right upper gingival ulcer was referred to our institution. On initial

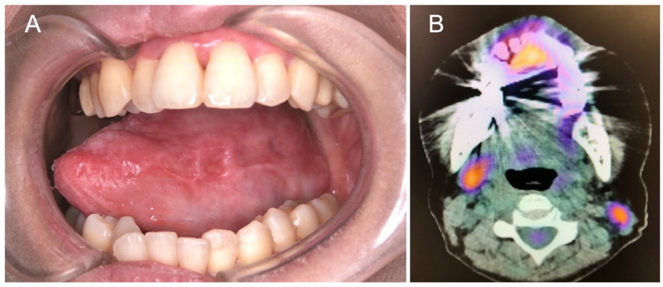

Figure 5. (A) The ulcer on the left tongue disappeared and the induration improved. (B) The 18-fluorodeoxyglucose-positron emission tomography/computed tomography findings revealed that the 18-fluorodeoxyglucose accumulations of the primary lesion and cervical lymph node had disappeared. Remaining accumulation is diagnostic only for inflammation in the sternocleidomastoid muscle.

Figure 6. Perforated ulcerative mass with induration of the upper right gingiva.

examination, the patient had an ulcerative mass with induration at the right upper gingiva (Fig. 6), as well as a neck mass on the right side. The gingival ulcer was diagnosed as a well-differentiated SCC by biopsy. MRI showed that the tumor extended to the right lateral pterygoid (Fig. 7A). E-CT showed a rim-enhanced mass at levelIIB of the right cervical area, which was located inside the sternocleidomastoid muscle (Fig. 7B). FDG-PET/CT demonstrated high FDG uptake at the primary tumor and cervical lymph nodes (Fig. 7C and D). Results of the distant metastasis workup was negative. The diagnosis was SCC of the right upper gingiva (T4aN2bM0: Stage IVA). The patient underwent retrograde intra-arterial CRT using ECAS as in Case 1. Since the external carotid artery was significantly tortuous, the FA and OA were selected using a Merit SwiftNINJA® steerable microcatheter (Merit Medical system, Inc.) with a remote-controlled flexible tip in this case with reference to the report by Nomura *et al* (7) (Fig. 8A). Cisplatin at 50 mg/m^2 was manually infused into each tumor-feeding artery selected once per week in the operating room at a rate of 5 ml/min. SSIACRT was performed once a week for a total of seven cycles per week. After the catheter was inserted into the feeding vessel, flow check was performed by DSA and contrast-enhanced CT to ensure proper catheter placement (Fig. 8A-D). Indigocarmine was used to confirm staining of

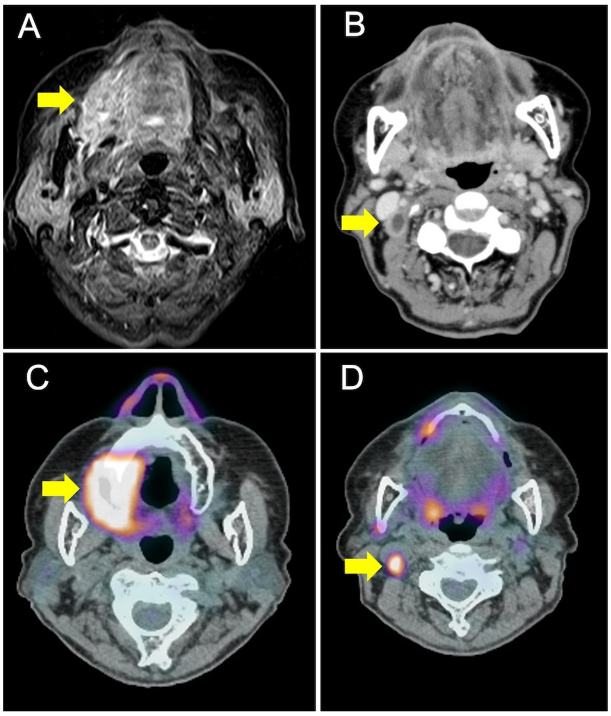

Figure 7. (A) Magnetic resonance imaging shows a carcinogenic mass extending from the right maxilla to the pterygoid muscle (arrow). (B) Enhanced computer tomography shows a ring enhanced mass 10x12 mm in size measured at level II B on the right side of the neck (arrow). 18-Fluorodeoxyglucose-positron emission tomography/computed tomography imaging reveals abnormal 18-fluorodeoxyglucose uptake (maximum standardized uptake values=15.5) of the (C) right maxillary and (D) right side of the neck (arrows).

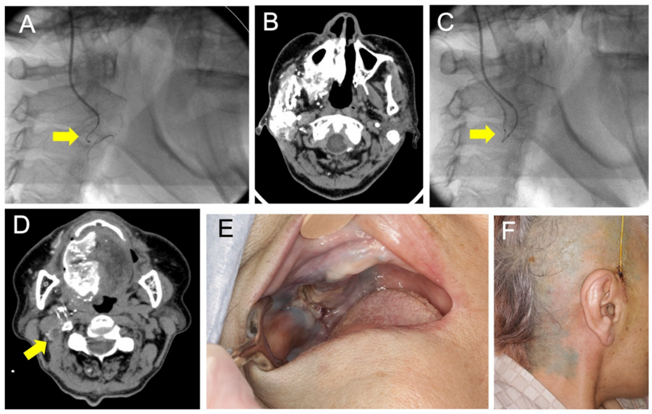

Figure 8. (A) The tip of the catheter is inserted superselectively into the right facial artery (arrow). (B) The maxillary artery was administered retrogradely directly from the external carotid artery sheath, and the administration area was confirmed with a contrast medium from the maxilla to the pterygoid muscle. (C) The tip of the catheter is inserted superselectively into the right occipital artery (arrow). (D) The occipital artery was superselected with a microcatheter, and a contrast medium confirmed the metastatic lymph nodes in the IIb area (arrow). (E) Right gingival lesions were stained by injecting indigocarmine through the right maxillary artery. (F) The skin surface over the NIIb area disease was dyed by injecting of a small amount of indigocarmine through the right occipital artery.

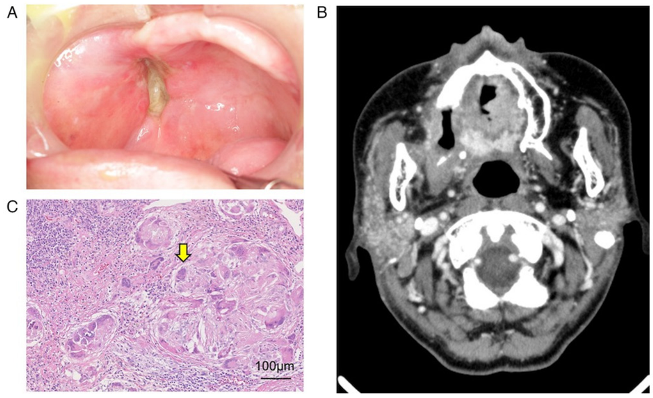

Figure 9. (A) The ulcer on the right upper gingival disappeared and the induration improved. (B) No recurrence was found on contrast-enhanced computed tomography of the maxillary gingival lesion. (C) Metastatic lymph nodes dissected from the neck show tumor coagulative necrosis and foreign body giant cells (arrow).

the skin surface of the maxillary gingival tumors and level IIb cervical lymph nodes (Fig. 8E and F). We administered cisplatin at 280 mg/body through the MA and 120 mg/body through the FA to the primary tumor. For the metastatic lymph nodes in the IIb region, cisplatin was administered through the OA at 60 mg/body. External irradiation was planned after appropriate immobilization using a thermoplastic mask and three-dimensional CT-based techniques. The primary lesion was irradiated with 60 Gy/30 times and the right neck was irradiated with 40 Gy/20 times. The acute adverse events observed in Case 2 within 1 month after treatment included grade 3 oral mucositis and dermatitis and grade 2 neutropenia. No major complications were observed. During the follow-up period, e-CT, MRI, and tissue biopsy of the primary lesion were performed to evaluate treatment outcomes. The maxillary gingival tumor showed no viable tumor cells on biopsy, and e-CT showed no tumor recurrence (Fig. 9A and B). The overall follow-up evaluation indicates that the primary lesion and cervical lymph nodes were effectively controlled with the treatment. Right side modified radical neck dissection was performed after intra-arterial catheter treatment. The histopathological findings of the dissected specimen showed that the lymph nodes were grade III (Fig. 9C).

Discussion

Oral cancer with cervical lymph node metastasis is generally treated by surgery, however dysfunction due to surgical resection is unavoidable. Our case report involved a patient who refused surgical resection (Case 1) and another patient whose case was considered difficult to operate. Good treatment results were achieved in both cases by selecting multiple branches of the external carotid artery from the STA on the same day and flushing out the chemotherapeutic agent from the body. Treatment of the include cervical lymph nodes using three routes simultaneously from the STA without replacing the catheter has not been previously reported. Given its potential efficacy, the technique should be considered in future treatment strategies.

SSIACRT can be performed using the Seldinger method (4,5) performed from the femoral artery or the HFT method of placing the catheter retrogradely from the STA (1,2,8). The advantage of the HFT method is that it allows long-term catheter placement without the intervention of a radiologist, and it can be used concurrently radiation, so that a high antitumor effect can be expected (1-3). Mitsudo *et al* (9) reported that the 3-year OS and locoregional control rates were 81.5% (Stage III, 94.7%; Stage IV, 64.9%) and 80.3% (Stage III, 89.7%; Stage IV, 72.1%), respectively, for tongue cancer of 95 patients who underwent daily retrograde IACRT with the two-channel method combined with RT. Meanwhile, Takayama *et al* (10) reported that the 3-year OS, PFS, and LC rates were 87.0, 74.1, and 86.6%, respectively, for tongue cancer 33 patients who underwent weekly conventional retrograde IACRT combined with proton beam therapy and systemic chemotherapy. Another advantage is the very low intracerebral complication rates due to thrombus because the catheter is not manipulated in the common carotid artery. However, multiple feeding arteries necessitate catheter replacement and complicates management (3,11).

In arterial infusion chemotherapy for oral cancer, vascular selectivity has been reported to influence prognosis (1). Mitsudo *et al* (3) performed SSIACRT from two routes, STA and OA, and obtained a high therapeutic effect against T3 and T4 oral cancers. However, in cervical lymph node metastasis, the therapeutic effect varies with the metastatic level. Furthermore, when a catheter is placed in the FA, flow is observed in cervical I and IIa regions of the ipsilateral neck. In many cases, an effect of Grade III or higher on the Ooboshi-Shimosato classification was obtained. On the contrary, the therapeutic effect is poor at levels IIb, III, and below where no flow is observed. Furthermore, SSIACRT is ineffective in cervical lymph node metastasis in areas IIb, III, and above (3). The reason for this is the difficulty in selecting the feeding artery with a catheter. In our previous report, blood flow in the level II region was dominated by the OA, which makes conventional SSIACRT effective. However, during treatment via OA and LA, administration of therapy to FA becomes impossible (11). The ECAS system we performed used a 5 Fr P-U catheter in the ECA between the STA and FA or MA, and through a valve attached to its distal end, a hook-type or steerable microcatheter can be inserted into ECAS. Therefore, we could administer treatment via the STA to LA, FA, MA, and OA on the same day, without needing to replace the catheter. In the two cases treated in the present study, CDDP could be dispensed to the sternocleidomastoid muscle branch of the OA, so that the IIb region could be treated. In our previous report, we described a case in which N3 lymph node metastasis was drained to the OA and cured, but in reality, several catheter replacements were necessary, which was a rather complicated procedure (11). Compared with that case, using the ECAS system facilitated the chemotherapeutic agent to the arteries via three routes without changing the catheter. This method could be introduced in hospitals where facilities and manpower are insufficient. Furthermore, as mentioned above, the two types of catheters can be used according to the degree of meandering of the ECA (6,7,12). A steerable microcatheter that can control the tip of the catheter 180 degrees at hand has been effective for blood vessels with a meandering ECA that cannot be selected with a hook-type catheter (7,13). In Case 1 of the present report, the external carotid artery only meandered slightly, thus, the hook-type microcatheter was used in the treatment. However, in Case 2, the meandering of the ECA was extensive, thus requiring the use of a steerable microcatheter to facilitate artery selection.

Nomura *et al* (7) reported that blood vessel selectivity was 88% for hook-type microcatheters and 94% for steerable microcatheters. However, the steerable microcatheter is relatively more expensive. The issue of cost should be addressed in the future. In conclusion, SSIACT via the ECAS system effectively treated oral cancer with cervical lymph node metastasis. Since a steerable microcatheter or a hook-type microcatheter was used, LA, FA, OA, and MA were selected from STA, avoiding catheter replacement, which is necessary in conventional retrograde arterial. It was thought that oral cancer with cervical lymph node metastasis can be sufficiently treated by using the ECAS system only with the approach from the superficial temporal artery.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KS, TK, TM, NF and AT made substantial contributions to the conception and design, acquisition of data, and analysis and interpretation of data. KS and TK confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patients provided written informed consent for the publication of data and images.

Competing interests

The authors declare that they have no competing interests.

References

1. Fuwa N, Kodaira T, Furutani K, Tachibana H, Nakamura T, Nakahara R, Tomoda T, Inokuchi H and Daimon T: Intra-arterial chemoradiotherapy for locally advanced oral cavity cancer: Analysis of therapeutic results in134 cases. Br J Cancer 98: 1039-1045, 2008.
2. Fuwa N, Kodaira T, Furutani K, Tachibana H, Nakamura T, Nakahara R, Tomoda T, Inokuti H and Daimon T: Arterial chemoradiotherapy for locally advanced tongue cancer: Analysis of retrospective study of therapeutic results in 88 patients. Int J Radiat Oncol Biol Phys 72: 1090-1100, 2008.

3. Mitsudo K, Koizumi T, Iida M, Iwai T, Nakashima H, Oguri S, Kioi M, Hirota M, Koike I, Hata M and Tohnai I: Retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy for stage III and IV oral cancer: Analysis of therapeutic results in 112 cases. Radiother Oncol 111: 306-310, 2014.
4. Robbins KT, Storniolo AM, Kerber C, Seagren S, Berson A and Howell SB: Rapid superselective high-dose cisplatin infusion for advanced head and neck malignancies. Head Neck 14: 364-371, 1992.
5. Robbins KT, Kumar P, Wong FS, Hartsell WF, Flick P, Palmer R, Weir AB III, Neill HB, Murry T, Ferguson R, *et al*: Targeted chemoradiation for advanced head and neck cancer: Analysis of 213 patients. Head Neck 22: 687-693, 2000.
6. Ii N, Fuwa N, Toyomasu Y, Takada A, Nomura M, Kawamura T, Sakuma H and Nomoto Y: A novel external carotid arterial sheath system for intra-arterial infusion chemotherapy of head and neck cancer. Cardiovasc Intervent Radiol 40: 1099-1104, 2017.
7. Nomura M, Fuwa N, Toyomasu Y, Takada A, Ii N, Nomura J and Yamada H: A comparison of two types of microcatheters used for a novel external carotid arterial sheath system for intra-arterial chemotherapy of head and neck cancer. Jpn J Radiol 36: 622-628, 2018.
8. Tohnai I, Fuwa N, Hayashi Y, Kaneko R, Tomaru Y, Hibino Y and Ueda M: New superselective intra-arterial infusion via superficial temporal artery for cancer of the tongue and tumour tissue platinum concentration after carboplatin (CBDCA) infusion. Oral Oncol 34: 387-390, 1998.
9. Mitsudo K, Hayashi Y, Minamiyama S, Ohashi N, Iida M, Iwai T, Oguri S, Koizumi T, Kioi M, Hirota M, *et al*: Chemoradiotherapy using retrograde superselective intra-arterial infusion for tongue cancer: Analysis of therapeutic results in 118 cases. Oral Oncol 79: 71-77, 2018.
10. Takayama K, Nakamura T, Takada A, Makita C, Suzuki M, Azami Y, Kato T, Hayashi Y, Ono T, Toyomasu Y, *et al*: Treatment results of alternating chemoradiotherapy followed by proton beam therapy boost combined with intra-arterial infusion chemotherapy for stage III-IVB tongue cancer. J Cancer Res Clin Oncol 142: 659-667, 2016.
11. Sakuma K, Koizumi T, Mitsudo K, Ueda J, Hayashi Y, Iwai T, Hirota M, Kioi M, Yoshii H, Kaizu H, *et al*: Retrograde superselective intra-arterial chemoradiotherapy combined with hyperthermia and cetuximab for carcinoma of the buccal mucosa with N3 lymph node metastasis: A case report. Oral Radiol 2: 1-7, 2018.
12. Inaba Y, Arai Y, Sone M, Aramaki T, Osuga K, Tanaka H and Kanemasa K: Experiments for the development of a steerable microcatheter. Cardiovasc Intervent Radiol 40: 1921-1926, 2017.
13. Soyama T, Yoshida D, Sakuhara Y, Morita R, Abo D and Kudo K: The steerable microcatheter: A new device for selective catheterisation. Cardiovasc Intervent Radiol 40: 947-952, 2017.