Anti-tumor effects on primary tumor and metastatic lymph nodes by superselective intra-arterial concurrent chemoradiotherapy for oral cancer

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Objective: Superselective intra-arterial infusion of anti-cancer agents with concurrent delivery of external beam radiotherapy was applied to 13 previously untreated cases of oral cancer for the purpose of avoiding surgical resection of the primary tumor.

Patients and Methods: The catheter tips were placed in the tumor feeder arteries via the superficial temporal artery and/or occipital artery. The catheters were retained for 6 weeks to infuse anti-cancer agents daily with concurrent radiotherapy for 6 weeks. The total radiation dose to the primary tumor and neck were 60.0 Gy and 40.0 Gy, respectively.

Results: Complete response (CR) of the primary tumor was achieved in all 13 patients; CR of neck node metastasis was achieved in 5 out of 6 patients.

Conclusion: This strategy is quite effective for oral cancer at both the primary site and metastatic lymph nodes, and has the potential to be curative in advanced cases which are inoperable.

Resection of oral cancer, especially in advanced lesions (T3-4), causes loss of functions including speech and swallowing, and is associated with disfigurement. In order to avoid these disadvantages, an effective, non-surgical strategy for oral cancer is required. Radiotherapy and chemotherapy are non-surgical strategy. However, the results of radiotherapy alone for advanced oral cancer were poor[1, 2], and it was also nearly impossible to achieve complete response by systemic chemotherapy alone in advanced oral cancers[3, 4]. Combination of systemic chemotherapy and radiotherapy was tried for advanced oral cancer, but this strategy was mainly used as preoperative treatment and it was also hard to avoid surgery[5, 6]. Recently, superselective intra-arterial infusion and chemoradiotherapy has been introduced as new strategy for oral cancer. Robbins et al.[7, 8] inserted a catheter into the target artery by the Seldinger method via the femoral artery, and administered high-dose cisplatin (CDDP) with the result of a high percentage of local control for oral cancer. Another method of superselective intra-arterial infusion and chemoradiotherapy was introduced by Tohnai et al.[9]. In this method, a catheter was inserted into the target artery –either the lingual artery (LA), facial artery (FA), or maxillary artery (MA)– via the superficial temporal artery (STA) or occipital artery (OA). Catheterization via the STA or OA enabled the retention of the catheter for daily concurrent chemoradiotherapy, which is likely to be more effective than

sequential chemoradiotherapy [10]. Fuwa et al.[11, 12] reported excellent therapeutic results for this therapy in terms of local control of advanced oral cancer; indeed, their therapeutic results were not inferior to those of surgery. However, most advanced tumors are nourished by multiple arteries and have a high incidence of regional lymph node metastasis. Accordingly, there is room to discuss how to infuse anticancer agents to multiple arteries, and to investigate the therapeutic effects of this strategy in metastatic lymph nodes as well as the primary tumor.

In 2007, we have introduced superselective intra-arterial concurrent chemoradiotherapy (SIACC) for oral cancer patient, and we reported here 13 cases of oral cancer, including 6 cases that had metastatic regional lymph nodes, treated by SIACC using docetaxel (DOC) plus CDDP or carboplatin (CBDCA) via the STA and/or OA, and evaluated the therapeutic effects.

Materials and methods

Patients and catheterization

Twelve patients with various stages of oral squamous cell carcinoma (SCC) and one patient of mucoepidermoid carcinoma (MEC) without distant metastasis according to the TNM classification of the International Union against Cancer (UICC)[13] underwent SIACC via the STA and/or OA (table 1). All patients were primary cases and had not received any previous treatment, and surgery was contraindicative because of unresectable primary tumor and/or poor general condition and/or refusal of surgery in these cases. Patient ages ranged from 36 to 80 years (median: 60 years). For staging, a detailed physical examination and chest radiograph were performed. In addition, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonograph (US), and positron emission tomography (PET) were performed to assess the progression of lesions and exclude the possibility of distant metastasis. Six out of 13 patients had metastatic regional lymph nodes.

Preoperative transvenous computed tomography angiography (CTA) was performed in all cases to identify the STA, OA, and target arteries. With the patient under local anesthesia, the catheterization into the MA, FA, and/or LA was carried out via the STA and/or OA of the affected side according to Tohnai's method[9] and/or Fuwa's

method[14] (Fig. 1). Briefly, a guide-wire (GT wire, 0.016-inch in diameter, Terumo Corp., Tokyo, Japan) was inserted into the common carotid artery via the STA and/or OA. A vinyl hook-shaped catheter (NECK, 4 Fr in outer diameter, Medikit Corp., Tokyo, Japan) was inserted into the STA and/or OA along with the guide-wire, and the guide-wire was removed. Then, the catheter was drawn back under fluoroscopic guidance using contrast medium (Omnipaque® 300, Daiichi-Sankyo Corp., Japan) to insert the tip of the catheter into the target artery[9]. In cases 2 and 5, a polyurethane straight catheter (ANTHRON P-U catheter; tapering type, 5 Fr in outer diameter, Toray Medical Corp., Tokyo, Japan) was replaced with a vinyl hook-shaped catheter by the guide-wire exchange method[14] in order to place the catheter in the deep lingual artery and submental artery, respectively. Then, blue dye (Indigocarmine, Daiichi-Sankyo Corp., Japan) was injected slowly from the catheter to confirm the flow to the tumor. In cases in which the tumor was not entirely stained by blue dye infusion, an additional catheter was placed in another artery playing a role as feeder via the OA of the ipsilateral side. Finally, the catheters were fixed in the skin with sutures. When the lesion involved the contralateral side beyond the median line, another catheter was placed in the contralateral side target artery via the STA for bilateral arterial injection. After the catheterization, a CT scan was taken using a slow infusion of contrast medium

(Iopamiron 300, Schering, Japan) from each catheter in order to confirm the flow to the entire tumor.

Infusion of anticancer agents and concurrent radiotherapy

Single or double catheters were unilaterally placed via the STA and/or OA (case 2, 4, 7, 8, 9, 10, 11), and double or triple catheters were bilaterally placed via STAs and/or OAs (case 1, 3, 5, 6, 12, 13). Using a portable electrical infusion pump, 3.3 to 5 mg/m^2 of CDDP was daily infused through each catheter for one hour (total 100 to 150 mg/m^2) with adequate hydration in all cases except cases 11 and 13. In cases 11 and 13, 12 mg/m^2 of CBDCA was daily used (total 360 mg/m^2) instead of CDDP because these patients had chronic heart failure and the heart could not withstand hydration. Ten mg/m^2 of DOC was infused for one hour once a week before administration of CDDP or CBDCA in all patients (total 60 mg/m^2). For radiotherapy, external irradiation by a 6-MV x-ray was performed. The irradiation was carried out 15 minutes after initiation of arterial infusion of the first anticancer agent. The area of external irradiation included the primary lesion as well as the neck region in the cases with cervical lymph node metastasis. The patients received external irradiation at a dose of 2.0 grays (Gy) per fraction 5 times a week for 6 weeks, totaling 60.0 and 40.0 Gy in the primary lesion

and neck, respectively.

When double catheterizations were unilaterally needed but OA was not available to catheterize, the catheter via the STA was exchanged 4 weeks after initiation of treatment, and a catheter was placed in another target artery (case 5, 12, 13). Sodium thiosulfate was administered intravenously to provide effective CDDP neutralization immediately after infusion of CDDP.

Assessment and follow up after treatment

The effects of SIACC were evaluated 4 weeks after discontinuation of the treatment. Visual examination, palpation, CT scan, MRI, US, and PET were performed, and the effects were recorded according to the WHO response criteria[15]. A complete response (CR) was defined as the complete disappearance of a clinically detectable tumor for at least 4 weeks. A partial response (PR) was defined as a reduction by at least 50% of the product of the largest perpendicular dimensions of clearly measurable lesions. No change (NC) included a regression of indicator lesions insufficient to meet the criteria for response. Additionally, a biopsy of the primary lesion was carried out to assess the histological effects. The histological assessments of biopsy specimens were based on the Oboshi and Shimosato classification (grade I-IV)[16]. Grade III and IV were

assessed as a histologically complete response (CR). The follow-up term was calculated from the end of treatment.

Adverse side effects were assessed according to Standard World Health Organization (WHO) criteria[15]. The assessment items included changes in peripheral blood cell parameters, liver function, renal function, and oral mucosa, nausea, vomiting, and pain. Blood biochemical tests were conducted weekly. Peripheral blood cell count was assessed once weekly. Follow-up MRIs, ultrasonographs and chest X-rays were performed at 3 months intervals after the end of treatment.

Results

Catheterization

In case 1, catheters were placed in the left facial artery, left lingual artery and right lingual artery via the left STA, left OA and right STA, respectively. In case 5, catheters were placed in the bilateral LA via each STA; then the right catheter was exchanged for a catheter in the FA at 4 weeks, and additional SIACC was followed for 2 weeks. In case 9 and 10, a catheter was placed in the maxillary artery via the STA, and another catheter was placed in the facial artery via the ipsilateral OA. In case 12, catheters were placed in the right LA and left FA via each STA, and SIACC was performed for 4

weeks. Catheters were exchanged for catheters in the right FA and left LA via each STA, and followed by additional SIACC for 2 weeks.

CT scans taken after catheterization with slow infusion of contrast medium (Iopamiron 300, Schering, Japan) from the catheter(s) showed the flow of the contrast medium to the artery-fed regions (Fig. 2).

Treatment results and complications

At the primary sites, SIACC achieved clinical and pathological CR in all patients. Four or 6 weeks after, neck dissection was performed in three cases (case 5, 6 and 9), and histological CRs of lymph nodes were confirmed in two cases (case 6 and 9). In the 3 cases (case 1, 10, and 11) that had metastatic lymph nodes, CR of metastatic lymph nodes was confirmed in assessments by CT, MRI, echo and PET examinations 4 to 6 weeks after SIACC (Fig. 3a, 3b), although recurrence of metastatic lymph nodes was observed at 6 months after the SIACC and neck dissection was performed in case 10. Recurrence of the primary tumor was observed in case 5 and 8 at 7 and 4 months after the SIACC, respectively, and salvage operations were performed. In two cases, distant metastases were detected 6 months after the SIACC (case 9, 11).

In one case (case 11), sepsis occurred because of the catheter infection. In

two cases (case 1, and 3), the tips of the catheters were dislocated from the target artery during the treatment, and replacement of catheters was required. Grade 3 or greater toxic changes included leukopenia in one case (case 5), and stomatitis in all cases. All patients had dry mouth and sticky saliva during and after treatment. Nausea due to infusion chemotherapy was mild and tolerable (Grade 1). No patients showed creatinine or serum transaminase level elevation. There were no transient or persistent central nervous complications. Furthermore, no treatment-related death was observed. Most of the patients have required nutritional support through a nasogastric tube because of severe stomatitis. However, after such treatment, all patients were capable of oral ingestion. After SIACC, the tumor tissue was replaced by scar tissue. Although the scar tissues were harder than normal tissues, there were no dysarthria and dyspnea in all cases.

Discussion

Catheterization

Recently, significant anticancer effects have been reported for SIACC [17-19]. However, the choice of target artery is quite important for this therapy, since most advanced tumors have multiple arteries as feeders. Fuwa et al.[17] chose to place the catheter in the external carotid artery when several arteries were feeding the tumor. However, the concentration of anticancer agent infused in the tumor tissue from catheters superselectively placed in target arteries was more than twice higher than that from a catheter placed in the external carotid artery[9]. Accordingly, it makes sense to superselectively catheterize into the multiple arteries that feed the tumor in advanced cases. Catheterization into the LA, FA, and MA from the STA is quite available because the STA is technically easy to expose[9, 11, 14]. Furthermore, the OA is an also a useful artery for achieving catheter placement in the FA or LA, though it is relatively difficult to expose because it exists deep from the skin surface[20]. Accordingly, two routes of approach from the STA and OA for catheterizations among LA, FA, and MA is a promising strategy for applying SIACC to advanced cases (case 1, 7, 9 and 10). However, catheterization via OA might be contraindicative when metastatic lymph nodes exist in the region close to the OA. Additionally, when the OA was below the

target arteries (case 5, 12, and 13), it could not be used for catheterization to the target artery. Replacement of the catheter into a different target artery during the course of treatment via the STA is another option in advanced cases (case 5, 12, and 13).

Reaction of primary tumor and metastatic lymph node

Four to 6 weeks after the treatment, a biopsy of the primary site was carried out, and clinical as well as pathological assessment revealed CR in all cases. Although it was formerly believed that CDDP enhanced tumor responses to radiation[21, 22], Tanaka et al.[23] have experimentally shown that CDDP did not affect cellular radiosensitivity, but that irradiation significantly enhanced CDDP-sensitivity. Therefore, they concluded that an effective protocol would involve the concurrent administration of CDDP with radiotherapy and further administration following completion of radiotherapy in order to achieve higher CDDP sensitivities. Enhancement of susceptibility to CDDP in tumor cells subjected to radiotherapy was likely the cause of CR of the primary sites of all cases.

We confirmed that metastatic lymph nodes had completely disappeared in 5 cases out of 6 (83.3 %) in the present cases. On the other hand, Hitchcock et al.[24] reported that approximately 53.7 % patients had residual lymph nodes after receiving

definitive radiotherapy or radiotherapy with general chemotherapy for SCC at the base of tongue. Glicksman et al.[25] reported that 54.0 % patients had residual lymph nodes after receiving concurrent platinum-based general chemotherapy and hyperfractionated radiotherapy for head and neck cancer. The reasons for the better result in our cases may be the higher concentration of anticancer agents in the metastatic lymph nodes. Because the submental artery, which is one of the branches of the facial artery, plays a main role in blood supply to the submandibular region[26], it could be assumed that submandibular lymph nodes are fed from the submental artery and other branches of the facial artery. Accordingly, the cancer cells in the submandibular lymph nodes might be susceptible to the current treatment when anticancer agents were superselectively infused from the facial artery. Indeed, metastatic lymph nodes in the submandibular region completely disappeared in the cases in which facial arteries were catheterized (case 1, 6, 9, 10, and 11) (Fig. 2). Additionally, metastatic lymph nodes at level I of the contralateral side (case 1 and 10), and at levels II, III and IV of the ipsilateral side (case 10) also disappeared after treatment (Fig. 3a, 3b). Although further investigation is required to clarify the precise mechanisms, lymphatic flow from the primary lesion might play an important role in the concentration of anticancer agents into the metastatic lymph nodes.

In conclusion, SIACC has the potential to be an important treatment strategy for oral cancer, and could achieve complete remission of locally advanced lesions as well as metastatic lymph nodes.

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Legends to figures

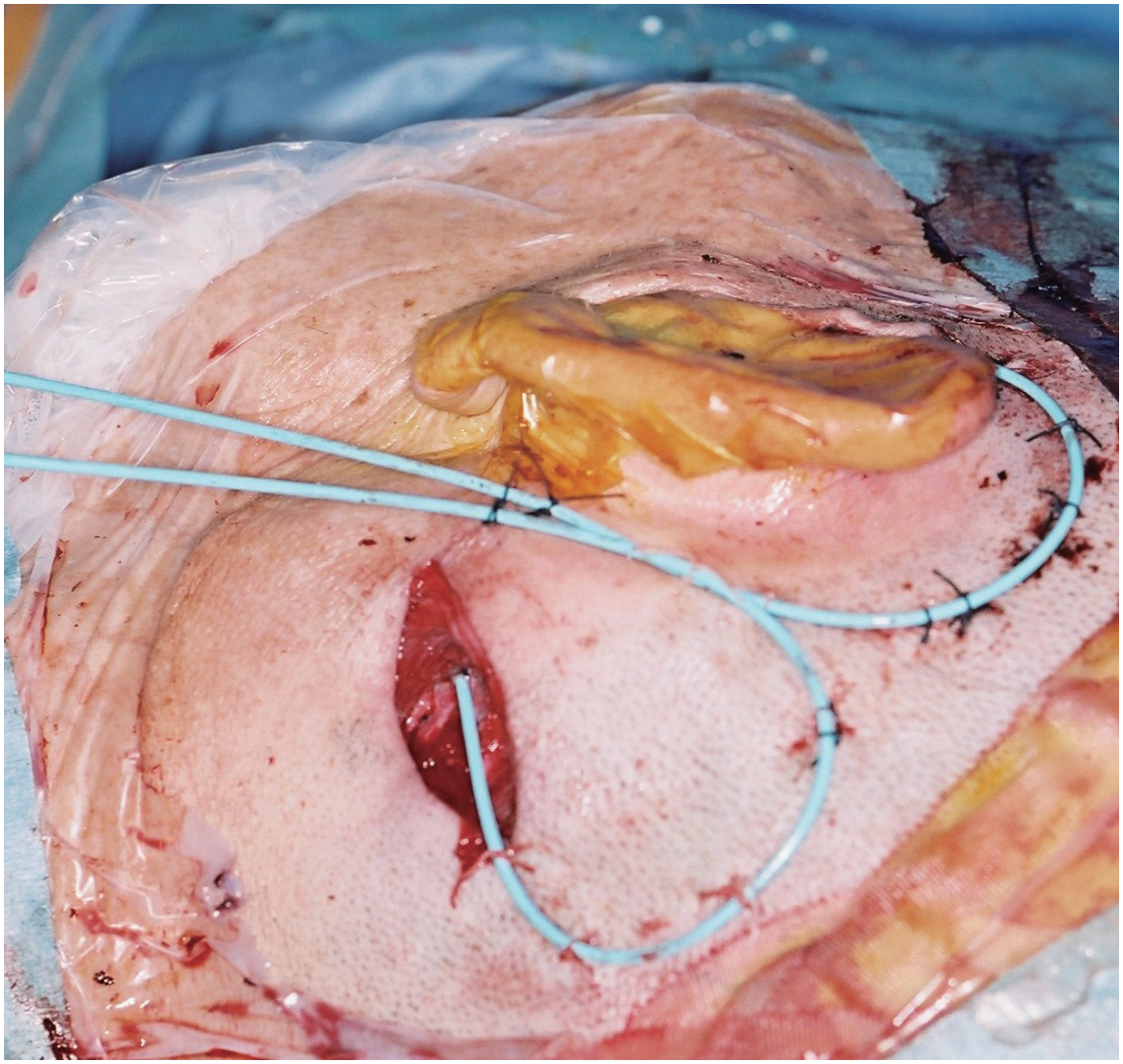

Fig. 1: Catheter placement in the left facial artery and left lingual artery via superficial temporal artery (STA) and occipital artery (OA), respectively (case 1).

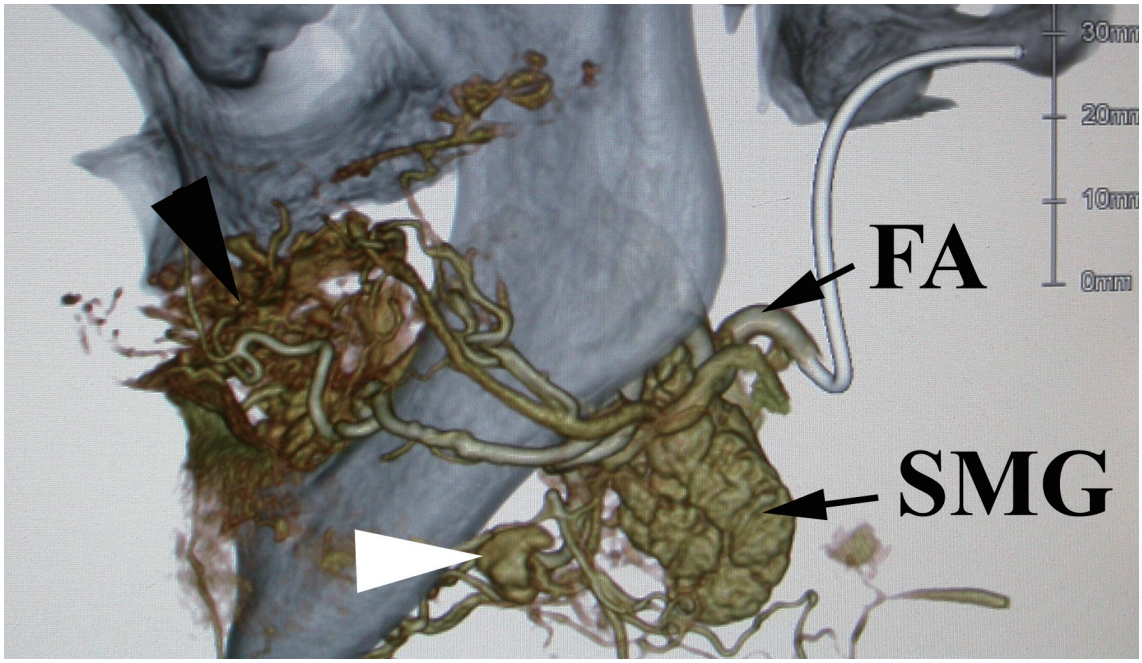

Fig. 2: CT scan with slow infusion of contrast medium from catheter in case 10. The catheter was placed in the facial artery (FA) via the occipital artery (OA). Flow of contrast medium to primary tumor (black arrow) as well as the metastatic lymph node (white arrow) is shown. (FA, facial artery; SMG, submandibular gland)

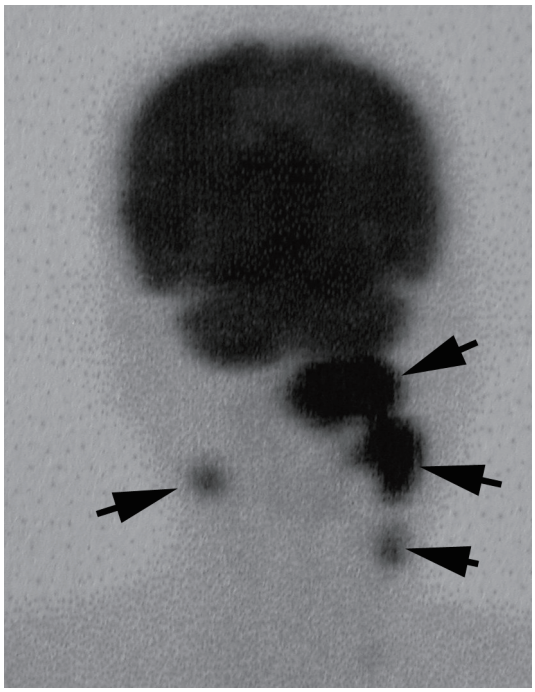

Fig. 3a: Positron emission tomography (PET) before treatment in case 10. Primary tumor and metastatic lymph nodes were observed in both sides of the neck.

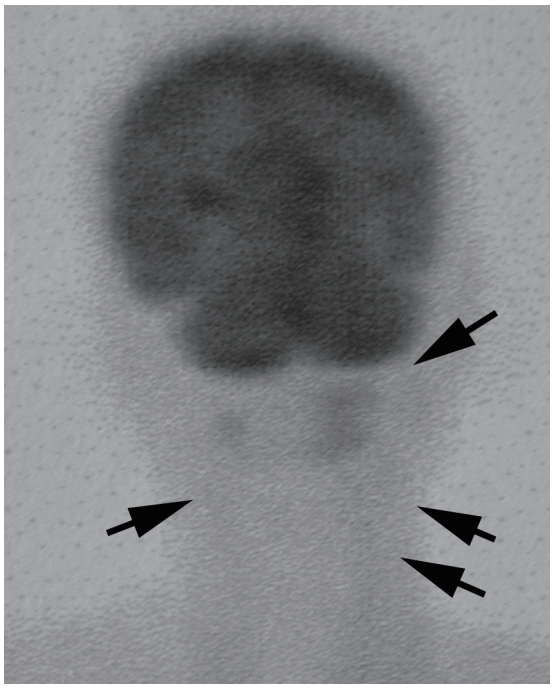

Fig. 3b: Positron emission tomography (PET) 6 weeks after the treatment in case 10. The findings of the PET revealed the complete response of the primary tumor and metastatic lymph nodes.

Case	age	gender	histological diagnosis	primary tumor site	TNM classification	pathological response of primary tumor	response of metastatic lymph nodes	target artery	follow up term (M)	recurrence
1	57	M	SCC	tongue	T4N2cM0	CR	CR	lt LA via the OA lt FA via the STA rt LA via the STA	26	-
2	42	M	SCC	tongue	T3N0M0	CR	----	lt LA via the STA	16	-
3	51	M	SCC	tongue	T3N0M0	CR	----	rt trunk of LA and FA via the STA lt LA via the STA	25	-
4	69	M	SCC	tongue	T3N0M0	CR	----	lt LA via the STA	13	-
5	36	F	SCC	tongue	T4N2bM0	CR	PR	bilateral LA via the STA rt FA via the SAT	7	+
6	60	F	SCC	tongue	T2N2cM0	CR	CR	lt trunk of LA and FA via STA rt LA via the STA	9	-
7	61	F	SCC	tongue	T3N0M0	CR	---	lt LA via the OA lt FA via the STA	6	-
8	62	M	SCC	maxillary sinus	T4N0M0	CR	----	lt MA via the STA	4	+
9	58	M	SCC	hard palate	T2N1M0	CR	CR	lt MA via the STA lt FA via the OA	9	-
10	74	M	SCC	upper alveolus	T4N2cM0	CR	CR	lt MA via the STA lt FA via the OA	9	+
11	58	M	MEC	lower alveolus	T4N3M0	CR	CR	rt FA via the STA	8	-
12	76	M	SCC	lower alveolus	T2N0M0	CR	----	bilateral FA via the STA bilateral LA via the STA	17	-
13	80	M	SCC	oral floor	T2N0M0	CR	----	lt FA via the STA lt LA via the STA rt FA via the OA	2	-

SCC: squamous cell carcinoma, MEC: mucoepidermoid carcinoma, MA: maxillary artery, FA: facial artery, LA: lingual artery, STA: superficial temporal artery, OA: occipital artery