ORIGINAL ARTICLE

Superselective intra-arterial chemoradiotherapy using altered blood flow compared to conventional systemic chemoradiotherapy for locally advanced oral squamous cell carcinoma: a single-center retrospective study

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Abstract

Purpose To evaluate the efficacy and safety of superselective intra-arterial (IA) chemoradiotherapy with cisplatin and transcatheter arterial embolization (TAE) on advanced oral cancer, and to compare it with that of systemic chemoradiotherapy.
Materials and methods This single-center retrospective study included 23 consecutive patients with locally advanced oral squamous cell carcinoma from November 2011 to November 2019. Of these, 15 received superselective IA cisplatin chemoradiotherapy with altered blood flow in the branches of the external carotid artery, and eight received systemic chemoradiotherapy. Medical charts were reviewed for the evaluation of patient data, drug toxicity, and antitumor efficacy.
Results Local control rate for the superselective IA infusion group, who underwent 6–7 cycles was significantly higher than that of the systemic chemotherapy group (11/13, 85% vs 3/8, 38%; $p = 0.04$). Regional control, locoregional control, disease-free survival, and overall survival rates were not significantly different between the groups ($p = 0.15$–0.907). Acute toxicity rates of grade 3 or higher were not significantly different between the IA and IV chemotherapy groups ($p = 0.221$).
Conclusion Superselective IA chemoradiotherapy with cisplatin using altered blood flow in the branches of the external carotid artery with TAE may be useful for inoperable oral cancer.

Keywords Locally advanced squamous cell carcinoma · Oral cancer · Superselective intra-arterial chemoradiotherapy

Introduction

It is difficult for locally advanced oral cancer to be controlled by radiotherapy; rather, when possible, surgery is the most effective therapy [1]. However, extensive surgery reduces quality of life and social interaction for the patient. Therefore, to improve survival rates in advanced oral cancer and to reduce post-treatment complications, chemoradiotherapy has become a viable alternative to surgery and is currently the standard of care for advanced head and neck cancer. The combination of radiotherapy and chemotherapy has been reported to have a much higher response rate than radiotherapy alone [2].

Klopp et al. [3] began the use of intra-arterial chemotherapy (iaCRT) for head and neck cancer. Subsequently, Robbins et al. [4, 5] used iaCRT with high-dose cisplatin in combination with conventional radiotherapy. This approach produced initial local control rates of approximately 90% [4].

While iaCRT is currently used to treat advanced unresectable oral cancers, standard protocols regarding how to select and deliver the drug have not yet been established. The objectives of the current study were to evaluate the efficacy and safety of superselective cisplatin iaCRT using altered blood flow in the external carotid artery branches via transcatheter arterial coil embolization in the treatment of advanced oral cancer, and to compare these results with those of systemic chemoradiotherapy (CRT).

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Materials and methods

Patient selection

We reviewed the records of 23 consecutive patients with inoperable oral squamous cell carcinoma (15 who underwent superselective IA chemoradiotherapy [iaCRT] using cisplatin and 8 who underwent systemic chemoradiotherapy [CRT]) at the Tokyo Dental College of Ichikawa General Hospital between November 2011 and November 2019. The requirement for informed patient consent was waived due to the study's retrospective design. This study was approved by the institutional review board of Tokyo Dental College of Ichikawa General Hospital (Approval No. I16-07).

Patients with T3–4 N0–3 M0–1 oral cancer judged inoperable by dentists at the oral cancer center were included in the current study. The patients' ages ranged from 51 to 91 years. Bone marrow function of the patients was maintained (leukocyte count $\geq 3000/mm^3$, platelet count $\geq 1,000,000/mm^3$). Patients had no severe dysfunction of the liver, lungs, or heart, and none had previously received radiotherapy in the head and neck region. They also had no active double cancer at the start of treatment. CRT was selected for the patients who could not stay in bed for several hours during the iaCRT (e.g., due to dementia), who hoped CRT and who had severe neck arteriosclerosis detected by computed tomography (CT). The treatment efficacy was evaluated using the RECIST v1.1 criteria.

Pretreatment evaluation

The primary site and cervical lymph nodes were assessed by contrast-enhanced CT and contrast-enhanced magnetic resonance imaging (MRI) prior to treatment. All patients were staged according to the 2017 UICC staging system. Four-dimensional CT angiography (4D-CTA) of the carotid artery was performed to detect the morphology and volume of the tumor, and to predict the feeding arteries before treatment. We used a CT machine Aquillion ONE (Canon Medical Systems, Otawara, Japan). Imaging was initiated 2 s after injection of contrast medium and images were taken 18 times every 2 s from 5 s later of injection. We then analyzed the vessel with SYNAPSE VINCENT (FUJIFILM, Tokyo, Japan).

Chemotherapy

Intra-arterial chemotherapy (iaCRT)

On the day before the first treatment, a peripherally inserted central catheter (PICC) was introduced through the basilic vein into the superior vena cava with US guidance.

Two radiologists with 12 and 6 years' experience in interventional radiology performed the superselective intra-arterial infusion via a catheter inserted into a branch of the external carotid artery, such as the facial artery or the maxillary artery. IA catheterizations were performed primarily through the right radial artery using a 4 Fr Simmons catheter (Gadelius Medical Co., Tokyo, Japan). If there was difficulty inserting the Simmons catheter into the cervical artery, IA catheterizations were accomplished through the femoral artery using a 4 Fr JB2 catheter (Gadelius Medical Co., Tokyo, Japan). First, cervical carotid angiography was performed to assess the vascular anatomy and any potential pathology. Then, with coaxial technique, a 2.8 Fr microcatheter (Carry HF; UTM Co., LTD, Aichi, Japan) was inserted into the external carotid artery to detect the tumor and vascular anatomy. A 1.5 Fr microcatheter (Carry Leon; UTM Co., LTD, Aichi, Japan) was then inserted into an external carotid artery branch through a 2.8 Fr microcatheter, and digital subtraction angiography (DSA) and cone beam CT during arteriography were performed to locate the feeders of the tumor. We used an AXIOM ARTIS DFA (Siemens AG, Medical Solutions, Forchheim, Germany) until June 2018 and used a Philips Azurion 7 B2015 (Philips Healthcare, Best, The Netherlands) for the remainder of the study period.

Moreover, to minimize damage to normal tissue and to enhance the effect of high-dose cisplatin infusion into the tumor feeders, blood flow in the external carotid artery branches was altered using transcatheter arterial coil embolization. When DSA of the external carotid artery branches detected the tumor feeders and the blood vessels unrelated to the tumor, we embolized the blood vessels unrelated to the tumor with coils.

Cisplatin at 100 mg/m^2 and 20 mL of 7% sodium bicarbonate were infused into each feeder at 0.1 to 0.4 mL/second, depending on the thickness of the blood vessel (infusion was faster in thicker blood vessels). The percentage of the dose of cisplatin depended on the state of the DSA and cone beam CT during arteriography. Simultaneously with the IA infusion of cisplatin, sodium thiosulfate (20 g/m^2) was administered at 90 to 360 mL/second via the PICC, depending on the cisplatin infusion speed, to neutralize the cisplatin. This protocol was performed weekly for 6 or 7 weeks.

Systemic chemotherapy (CRT)

The chemotherapy regimens for six patients were intravenous cisplatin 100 mg/m^2 given in three cycles on days 1, 22, and 43. Two patients were given 400 mg/m^2 in the first treatment and 250 mg/m^2 in remaining count of cetuximab given total eight cycles weekly for 8 weeks due to decreased renal dysfunction and old age.

Radiation therapy

External beam radiotherapy (RT) was started on Day 1. Three-dimensional conformal radiotherapy was performed with photon beam energy of 6 or 10 MV and 2 Gy/fraction/day. We defined the gross tumor volume (GTV) by CT and MRI. GTV included the volume of the primary tumor and lymph node metastases. Furthermore, the primary clinical target volume (CTV) was defined as the GTV plus a margin of 5–10 mm to cover the possible area of invasion. The nodal CTV was defined as the GTV plus a margin of 5 mm to cover the possible area of invasion. The planning target volume (PTV) for the CTV was defined as the CTV plus a margin of 5 mm to cover the possible area of set-up variations and internal organ motion. The planned total doses to the primary tumor and the metastatic lymph nodes were both 60–70 Gy/30–35 fractions. We used an ONCOR Impression PLUS (Siemens AG, Medical Solutions, Forchheim, Germany) as the RT machine and a XIO (Elekta Instruments AB, Stockholm, Sweden) as the RT planning system.

Follow-up after the treatment

All patients were evaluated by contrast-enhanced CT at 1–2-month intervals for 1 year after completion of treatment, then at 3–4-month intervals after 2 years following completion of treatment. If they were suspected to have local recurrence, they were evaluated by contrast-enhanced MRI.

Toxicity assessments

Acute adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.0 until 4 weeks after the last chemoradiotherapy or until the patient's death.

Statistical analyses

To analyze local control (LC), regional control (RC), locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) rates, survival curves were drawn using the Kaplan–Meier method. OS was calculated from the first day of chemoradiotherapy to the last follow-up or death. DFS was calculated from the first day of chemoradiotherapy until the date of local failure, metastasis to neck lymph nodes, or distant metastasis. LRC was calculated from the first day of chemoradiotherapy to the date of local failure or new- or regrowth of lymph node metastases. RC was calculated from the first day of chemoradiotherapy to the date of new- or regrowth of metastases to neck lymph nodes. LC was calculated from the first day of chemoradiotherapy to the date of local failure. The LC, RC, LRC, DFS, and OS rates were compared with the log-rank test according to the chemoradiotherapy (intra-arterial cisplatin chemoradiotherapy vs. systemic chemoradiotherapy). To evaluate differences in patient characteristics and the response to chemotherapy, Fisher's exact test was used. p values (p) < 0.05 were considered to be statistically significant. All statistical analyses were performed using EZR [6].

Table 1 There were no statistically significant differences between the two groups in terms of sex, age, tumor lesion, or tumor staging

	IA infusion (N = 15)	Systemic chemotherapy (N = 8)	p values
Gender			p = 0.66
Male	11 (73%)	5 (63%)	
Female	4 (27%)	3 (37%)	
Age			
Median	74	71.5	
Range	51–88	54–84	
Lesion			p = 0.735
Tongue	4 (27%)	3 (38%)	
Upper gingiva	4 (27%)	2 (25%)	
Lower gingiva	6 (40%)	2 (25%)	
Oral floor	1 (6%)	10	
Buccal mucosa	0	1 (12%)	
Staging (T)			p = 0.578
T3	1 (6%)	1 (12%)	
T4a	11 (74%)	7 (88%)	
T4b	3 (20%)	0	
Staging(N)			p = 0.0891
N0	8 (53%)	2 (25%)	
N1	0	3 (38%)	
N2a	0	0	
N2b	4 (27%)	2 (25%)	
N2c	3 (20%)	1 (12%)	
N3	0	0	
Staging(M)			p = 0.348
M0	15 (100%)	7 (88%)	
M1	0	1 (12%)	

Results

Patient characteristics

Patient characteristics are shown in Table 1. There were no statistically significant differences between the two groups in terms of sex, age, tumor lesion, or tumor staging.

Intra-arterial chemotherapy

Six to seven cycles of IA infusions were delivered in 87% of the patients (13/15). One patient underwent four cycles and one underwent only one cycle of chemotherapy. One patient was unable to undergo 6–7 cycles of chemotherapy because of toxicity in the form of acute heart failure. For another patient, the reason was personal circumstances. Thus, we excluded these two cases from *Response to therapy and survival.*

Systemic chemotherapy

The chemotherapy regimen for six patients was intravenous cisplatin at a dose of 100 mg/m^2. Three patients underwent three cycles and two patients underwent two cycles of chemotherapy. One patient completed only one cycle due to toxicity. The chemotherapy regimen for two patients was an intravenous cetuximab protocol. One patient completed eight cycles, and one patient underwent only six cycles of chemotherapy due to liver damage.

Radiotherapy

In the IA infusion group with six or seven cycles, the mean radiation dose was 67.2 Gy (range 48–78 Gy). In the systemic chemotherapy group, the mean radiation dose was 71.0 Gy (range 60–82 Gy).

Response to therapy and survival

The response rates and disease control rate were 100% in both the IA infusion group and systemic chemotherapy group. In the iaCRT group with 6 or 7 cycles, all patients showed a complete response of the primary tumor and nodal metastases (Figs. 1, 2). The median period of LC was 430 days (range 35–843 days) and the median period of RC was 420 days (range 46–759 days). The median period of LRC was 235 days (range 35–759 days). The median period of DFS was 163 days (range 35–759 days). The median period of OS was 459 days (range 47–843 days). Relapse was detected in seven patients: only primary site, two patients; only cervical lymph node, four patients; and only lung metastasis, one patient. Cervical lymph node dissection was performed in all four patients with cervical lymph node relapse.

In the CRT group, five patients (63%) achieved a complete response of the tumor and nodal metastases. Three patients (38%) achieved a partial response of the tumor and nodal metastases. The median period of LC was 200 days (range 93–2382 days), the median period of RC was 187 days (range 77–1072 days), and the median period of LRC and DFS was 142 days (range 77–490 days). The median period of OS was 767 days (range 166–2472 days). A relapse was detected in seven patients: only primary site, two patients; only cervical lymph node, three patients;
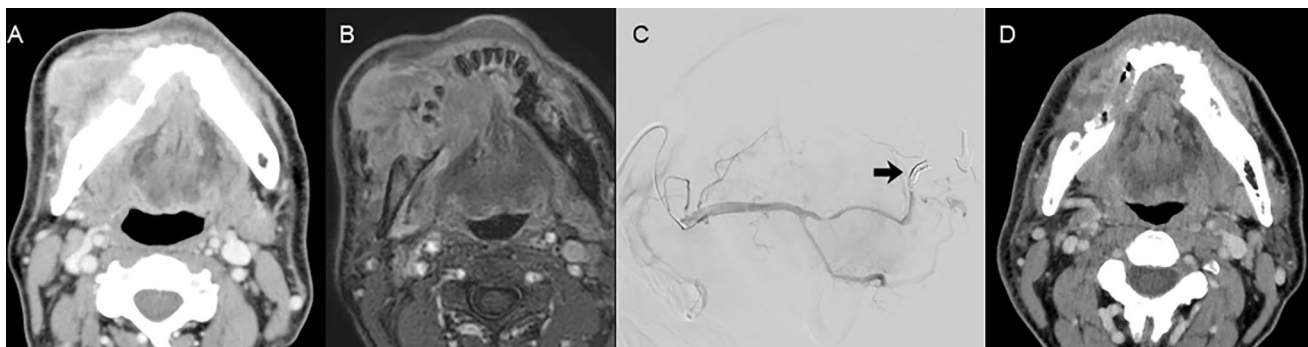

Fig. 1 A 53-year-old man with lower gingival cancer (T4a N0 M0) without primary illness. **a**, **b** Lower gingival cancer was detected based on preoperative contrast-enhanced 4D-CT and contrast-enhanced MRI results. **c** The right lingual artery, facial artery, and inferior alveolar artery were detected as the feeders of the lesion based on the contrast-enhanced 4D-CT and angiogram results. As the microcatheter was inserted into the facial artery and DSA detected that the right superior labial artery did not supply the tumor, we embolized the right superior labial artery using coils (arrow). Superselective IA infusion was performed via a catheter inserted into the right lingual artery, facial artery, and inferior alveolar artery. **d** Contrast-enhanced CT 5 months after IA infusion showed complete response of the lesion
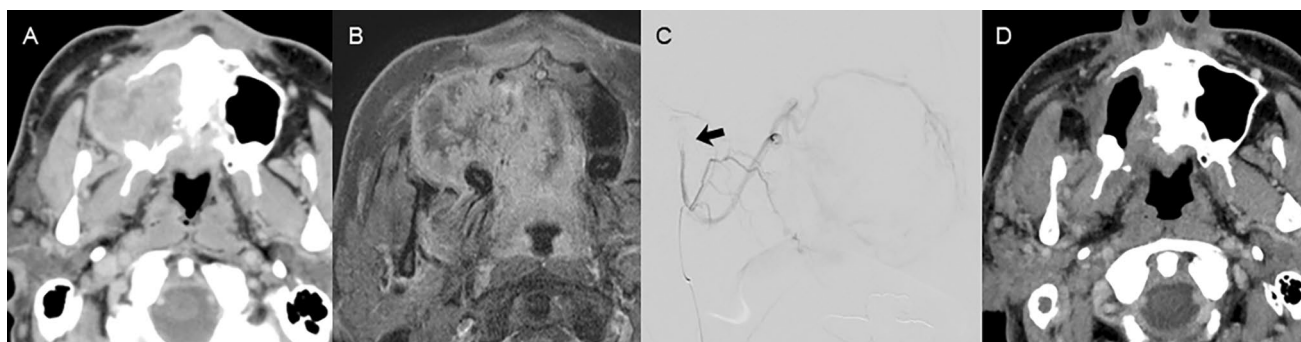
Fig. 2 A 51-year-old man with upper gingival cancer (T4a N2b M0) with hypertension and type 2 diabetes. **a**, **b** Upper gingival cancer was detected based on the preoperative contrast-enhanced 4D-CT and contrast-enhanced MRI results. **c** The right maxillary artery was detected as the feeder of the lesion based on the contrast-enhanced 4D-CT and angiogram results. Based on the DSA results, the right middle meningeal artery was proven not to supply the tumor; therefore, we embolized the artery using coils (arrow). Superselective IA infusion was performed via a catheter inserted into the right maxillary artery. **d** Contrast-enhanced CT 4 months after IA infusion showed complete response of the right upper gingival cancer
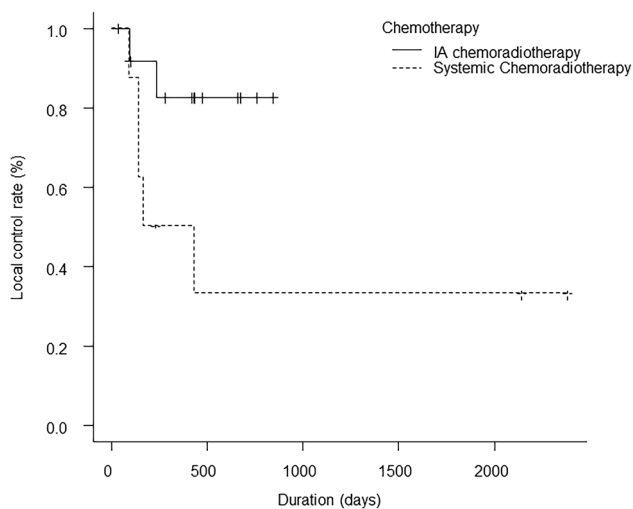

Fig. 3 Kaplan–Meier curves for LC rate of patients treated with IA infusion and systemic chemotherapy. The black continuous line represents the IA infusion group; the black dotted line, the systemic chemotherapy group. The median LC was 430 days in the IA infusion group and 200 days in the systemic chemotherapy group. LC rate of the IA infusion group was significantly higher than that of the systemic chemotherapy group (11/13, 85% vs 3/8, 38%; $p = 0.0437$). There was a statistically significant between-group difference in the LC rates

Toxicity

A summary of the acute toxicities in the iaCRT and CRT groups is shown in Table 2. Acute toxicity rates of grade 3 or higher showed no significant difference between the IA infusion and systemic chemotherapy groups ($p = 0.221$; Table 3).

Discussion

The prognosis with a single modality such as radiotherapy alone for locally advanced oral cancer is poor [1]. Therefore, chemoradiotherapy has become the standard-of-care treatment. However, the relatively high systemic toxicity of cisplatin is a dose-limiting factor [7, 8]. Concurrent iaCRT with cisplatin and neutralization by sodium thiosulfate aims to deliver a higher dose of cisplatin to the tumor with minimal systemic toxicity [9]. Notably, Robbins et al. [4, 5] reported initial local regional response rates higher than 90%.

There are two major methods for iaCRT, classified as selective arterial infusion through the femoral artery and retrograde selective infusion via the superficial temporal artery and/or the occipital artery [9–11]. In the latter, two catheters can be inserted into tumor-feeding arteries and daily concurrent chemoradiotherapy can be added. The duration of administration is longer, and the dose of cisplatin is lower, than in the once-weekly rapid intra-arterial superdose cisplatin with concurrent radiotherapy (RADPLAT) method by Robbins [10, 11]. However, for this procedure, the anterior ear is incised to expose the superficial temporal artery or occipital artery. Moreover, in cases of locally advanced cancer, physicians cannot insert catheters into several tumor-feeding arteries simultaneously. Robbins et al. [12] reported good results of RADPLAT for T4 head and neck cancer. With the method described here, we can divide cisplatin

both primary and cervical lymph node, two patients. Cervical lymph node dissection was performed in patients who had cervical lymph node relapse, except for one patient who had primary and cervical lymph node relapse.

LC rate of iaCRT group was significantly higher than that of the CRT group (Fig. 3, 11/13, 85% vs 3/8, 38%; $p = 0.0437$). The RC, LRC, DFS, and OS rates showed no significant difference between the iaCRT and CRT groups ($p = 0.15, 0.238, 0.257$, and 0.907, respectively).

Table 2 A summary of the acute toxicities in the iaCRT and CRT groups

	IA infusion (N=15)						Systemic chemotherapy (N=8)					
	Gr0-2	Gr3	Gr4	Gr5	Gr3≦	ALL	Gr0-2	Gr3	Gr4	Gr5	Gr3≦	ALL
Hemo												
WBC	7	1	0	0	1 (7%)	8 (53%)	4	2	0	0	2 (25%)	6 (75%)
Neutro	8	0	0	0	0	8 (53%)	5	1	0	0	1 (13%)	6 (75%)
Hb	7	1	1	0	2 (13%)	9 (60%)	1	1	0	0	1 (13%)	2 (25%)
Plat	2	1	0	0	1(7%)	3(20%)	1	0	0	0	0	1(13%)
Non-hemo												
Fever	3	0	0	0	0	3 (20)	1	0	0	0	0	1 (13)%
Erythema	1	0	0	0	0	1 (7%)	0	0	0	0	0	0
Diarrhea	1	0	0	0	0	1 (7%)	1	0	0	0	0	1 (13%)
Nausea	1	0	0	0	0	1 (7%)	1	0	0	0	0	1 (13%)
Acute renal failure	2	0	0	0	0	2 (13%)	0	0	0	0	0	0
Cerebral infarction	1	0	0	0	0	1 (7%)	0	0	0	0	0	0
Dermatitis	1	0	0	0	0	1 (7%)	4	0	0	0	0	4 (50%)
Pyelonephritis	0	0	0	1	1 (7%)	1 (7%)	0	0	0	0	0	0
Mucositis	10	3	0	0	3 (20%)	13 (87%)	5	3	0	0	3 (38%)	8 (100%)
Cholecystitis	1	0	0	0	0	1 (7)%	0	0	0	0	0	0
Acute heart failure	1	0	0	0	0	1 (7)%	0	0	0	0	0	0
Hiccups	0	0	0	0	0	0	2	0	0	0	0	2 (25%)
Pneumonia	0	1	0	0	1 (7)%	1 (7)%	1	0	0	0	0	1 (13%)
Hyperkalemia	0	0	0	0	0	0	1	1	0	0	1 (13%)	2 (25%)
Hypokalemia	1	0	0	0	0	1 (7%)	0	0	0	0	0	0
Hyponatremia	0	0	0	0	0	0	0	2	0	0	2 (25%)	2 (25%)
Liver dysfunction	0	0	0	0	0	0	1	0	0	0	0	1 (13%)

Table 3 Fisher's exact test showed that there were no statistically significant differences between the two groups in terms of acute toxicity Grade 3 or higher

Acute toxicity of grade 3 or higher	IA infusion	Systemic	$p=0.221$
Presence	5	5	
Absence	10	3	

into several tumor-feeding arteries, including opposite-side arteries. Antegrade selective infusion needs careful interventional radiology technique and may cause severe toxicities such as cerebrovascular accidents [12]. In this report, one patient had cerebral infarction. However, it was unknown whether this was related to the procedure, because she had the stroke on the day before the 7th cycle of IA infusion.

To limit damage to normal tissue and to enhance the effect of chemotherapy, we altered the blood flow of the external carotid artery branches with transcatheter arterial coil embolization to prevent drug from flowing into normal tissue and to infuse higher doses of cisplatin to the tumor. In general, cisplatin has been a key drug for oral cancer patients. A benefit of cisplatin is its first pass effect through the tumor bed, and IA infusion is preferable as it injects a high concentration of cisplatin before the drug enters the venous circulation [13]. Cisplatin is excreted and detoxified by the kidney and liver before the next circulation. For that reason, the concentration of cisplatin during the next circulation is at the same level as with IV infusion. Furthermore, altering the blood flow in the branches of the carotid artery by embolizing the arteries unrelated to the tumor enables higher concentrations of the drug to be injected. To increase the therapeutic advantage of cisplatin, we should decrease tumor plasma flow [14]. This can be achieved by IA infusion into as small an artery as possible through the microcatheter.

Moreover, the plasma clearance of cisplatin should be increased for better response. This can be achieved using the neutralizing agent thiosulfate. Thiosulfate bonds covalently with cisplatin, forming a complex that is devoid of toxicity and antitumor activity [15]. Plasma clearance of cisplatin can be increased when neutralization occurs in the plasma.

Although Robbins et al. [9, 16] reported that cisplatin at a dosage of 150 mg/m^2 was administered once a week for only four cycles, it is known that repeating cisplatin infusion is more effective, as it increases the radiosensitization efficacy of the cisplatin. For this reason, in this study we used a cisplatin dosage of 100 mg/m^2 and repeated seven cycles with reference of JCOG1212, RADPLAT–MSC [17].

However, some studies indicate that IA chemoradiation is not superior to intravenous chemoradiation for advanced head and neck cancer [18, 19]. In our study approach, the LC rate of IA infusion with 6–7 cycles was superior to that of intravenous systemic chemotherapy. Moreover, the RC rate showed no significant difference between the IA infusion and systemic chemotherapy groups. In future cases of inoperable oral cancer with lymph node metastasis, IA infusion combined with cervical lymph node dissection can be a treatment option. There are some limitations to this study including its retrospective design and execution in only a single institution. Moreover, the number of patients was small, especially in the systemic chemotherapy group among whom there was variability in chemotherapy dose.

Conclusion

Superselective IA chemoradiotherapy with cisplatin using altered blood flow in the external carotid artery branches may be useful for inoperable oral cancer. Nevertheless, as only a small sample size was available for assessing this method, further studies are needed to determine the best chemoradiotherapy protocol for improving the outcomes of patients with advanced oral cancer.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest associated with this manuscript.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.'

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