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Comparison of Radiation Therapy *vs.* Intra-Arterial Chemoradiotherapy for the Treatment of Preoperative Tongue Cancer

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Abstract

Background: We sometimes underwent intra-arterial chemoradiotherapy (IACRT) in patients with preoperative tongue cancer. Previous study could not sufficiently verify the superiority of IACRT in comparison with radiation therapy alone. To evaluate the effectiveness of IACRT for the treatment of preoperative tongue cancer, we compared the treatment results between radiation therapy alone and IACRT.

Methods and findings: A retrospective study was conducted including 10 patients with preoperative tongue cancer. Four patients underwent radiation therapy alone and 6 patients underwent IACRT.

The response rate (CR+PR) was 75% in the radiation therapy group, whereas it was 100% in the IACRT group. IACRT was more responsive than radiation therapy, however, there was no statistically significant difference between two groups (P=0.1967). The mean tumour reduction rate was 29% (SD: 7.13) in the radiation therapy group and 65% (SD: 11.08) in the IACRT group, there was a statistically significant difference between two groups (P=0.0402).

Conclusion: Compared to radiation therapy alone, IACRT resulted in higher tumour reduction rate, therefore may be a better preoperative therapy in tongue cancer

Keywords: Tongue cancer; Radiation therapy; Intra-Arterial Chemoradiotherapy (IACRT)

Introduction

Oral cavity cancer estimated to occur 1-2% in all cancer and tongue cancer was 60% of oral cavity cancer in Japan [1,2]. Surgery, radiation therapy, systemic chemotherapy, and arterial infusion chemotherapy have generally been performed as methods for treating tongue cancer. In conventional treatment approaches, local therapy for oral squamous cell carcinoma was surgery or both radiation therapy, but chemotherapy added to improve cure rates and functional outcomes [3]. Radiation therapy or chemotherapy (arterial infusion chemotherapy) has often been selected for organ preservation, because a radical resection substantially reduces the quality of life by causing dysarthria, dysphagia, masticatory disturbance, and appearance changes, etc. Furthermore, even when radical surgery cannot be performed, such as in having chronic disease cases, there is a possibility that a radical cure will be achieved with radiotherapy or chemotherapy. Minimizing the tumour volume via radiotherapy or chemotherapy enables the resection range to be minimized (organ preservation) [4].

We sometimes underwent intra-arterial chemoradiotherapy (IACRT) in patients with preoperative tongue cancer. IACRT is a therapy that arterial infusion chemotherapy and radiation therapy is done around the same time. Previous study could not sufficiently verify the superiority of IACRT in comparison with radiation therapy alone. We set a hypothesis that intra-arterial chemoradiotherapy (IACRT) is more effective than radiation therapy alone for the treatment of tongue cancer. The aim of this study is to compare the effect of IACRT with radiation therapy alone. We studied the efficacy and complications of IACRT thereof in order to apply the conclusion to the future practices.

Methods

Patients

This study is a retrospective study and approved by institutional review board and obtained the consent of the patents in Miyakonojo Medical Center. The criteria of patients defined as they had operative tongue cancer and were possible to radiotherapy. The patients comprised 10 patients with preoperative tongue cancer who had undergone radiotherapy in 4 patients and 6 patients had undergone in addition selective arterial infusion chemotherapy (IACRT) at the Departments of Radiology, from July 2014 to March 2017. These patients were referred to us for concurrent IACRT from the Departments of

Dental Oral Surgery and Otolaryngology in the Hospitals. Four patients did not undergo the arterial infusion. Three patients did not want to undergo the arterial infusion chemotherapy; one patient had the bilateral femoral arterial aneurysm. The characteristics of the 10 patients (the patients consisted of 6 males and 4 females. Their ages ranged from 53 to 83 (mean; 65) years old are summarized in **Table 1**. There were 5 T2, 4 T3, and 1 T4 cases. The nodal stages were 2 N0, 1 N1, 6 N2b, and 1 N2c. The stage was classified according to the 2010 UICC staging system. There were 1 stage II, 2 stage III, and 7 stage IV cases. All pathological diagnosis were squamous cell cancer and 4 well, 4 moderate, 2 poorly differentiated carcinomas.

Table 1: Patient characteristics.

Case	Sex	Age	T	N	Stage	Difference	Pre-therapy diameter (mm)	Post-therapy diameter (mm)	Reduction rate	Pathology effect	Arterial infusion
1	M	57	2	2b	IVA	well	22	13	40% PR	Grade II	-
2	M	74	2	0	II	well	27	16	33% PR	Grade I	-
3	F	63	3	2b	IVA	well	47	40	14% NC	Grade I	-
4	F	67	3	1	III	moderate	43	29	32 %PR	Grade I	-
5	F	55	2	2c	IVA	moderate	39	19	51%PR	Grade II	+
6	M	53	3	0	III	poor	53	31	41% PR	Grade II	+
7	F	77	2	2b	IVA	poor	23	9	60 %PR	Grade I	+
8	M	63	2	2b	IVA	moderate	27	0	100 %CR	Grade III	+
9	M	83	4	2b	IVA	moderate	51	33	42% PR	Grade II	+
10	M	59	3	2b	IVA	well	41	0	100% CR	Grade III	+

Intra-arterial chemotherapy

The arterial infusion chemotherapy was performed as one-shot infusion of anticancer drug via the femoral artery in 6 patients. Micro catheter was selectively inserted temporarily into the lingual artery which supplied the tumour through the femoral artery with Seldinger's method and the one-shot infusion of anticancer drug was performed through the catheter: The one shot infusion of anticancer drug was performed once in all patients for 20 minutes. The injected drug was cisplatin (100 mg/body/one times infusion). At the time of intra-arterial infusion of cisplatin, sodium thiosulfate (STS, 4000 mg/body) was administered through a vein. The therapy was initiated after indigocarmine (20 mg/5 ml) was diluted 2 times with physiological saline, 5 ml-10 ml was arterially injected into a micro catheter that had been inserted into the feeding vessel of a tumour and we macroscopically determined whether the tumour surface was stained. In order to reduce the tissue damage, a steroid (20 mg of prednisolone) was also arterially injected.

Radiation therapy

The radiation therapy was administered only externally. Radiation therapy was performed with 4MV linear accelerator (ONCOR Impression Plus, SIEMENS). FOV (field of view) for radiation therapy was tongue lesion and cervical lymph node area. The single doses were 2.0 Gy, 5 times per a week, with total dose of 40 Gy. All cases underwent surgery after the radiation therapy or the IACRT. Intra-arterial chemotherapy was performed during the period of radiation therapy. The start date of Intra-arterial chemotherapy was next day or several days after starting radiation therapy.

Therapeutic assessment

The clinical response was evaluated based on the tumour reduction rate on the CT, MRI and endoscopic findings by using the equation according to the RECIST guideline; tumour reduction rate (%) = (pre-therapy tumour long-side diameter – post-therapy tumour long-side diameter) x 100/pre-therapy tumour long-side diameter. Complete disappearance of the tumour was regarded as CR, a reduction by at least 30% was regarded as PR, a reduction of less than 30% was regarded as NC, and an increase was regarded as PD. We determined that CR and PR were responsive [5,6].

We assessed pathological response by evaluating the therapeutic effects on cancer cells in the excised specimens based on general rules for clinical and pathological studies on oral cancer classification as follows; grade 0 (ineffective), grade I (slightly effective, appearance of 1/3 or more of the tumour cells having proliferative ability), grade II (moderately effective, appearance of less than 1/3 of the tumour cells having proliferative ability), grade III (markedly effective, absence of tumour cells having proliferative ability). We defined grade II and III as responsive. The complications were classified according to the Common Terminology Criteria for Adverse Event V4.0 (CTCAE V4.0).

Statistics

The chi-square test for independence or the Fisher exact test was used for comparison of the two groups (radiation therapy group *vs.* IACRT group). We also examined the complications associated with these procedures. Survival time was calculated from the initial date of treatment to the first occurrence of the relevant events. Overall survival was defined as the time between the initial date of treatment and death. A statistical examination was conducted by using the Log-Rank test. We regarded P<0.05 as a significant difference. All statistical analyses were performed using software Stat view (SAS, USA, Cary).

Results

There was no statistically significant differences by T factor, N factor, stage factor, and the degree of tissue differentiation of squamous cell cancer (well, moderately, and poor) between two groups **(Table 2)**.

Table 2: Patient characteristics of the analysed cohort and comparisons between radiation therapy group and intra-arterial chemoradiation therapy group [**Note:** NS - Not significant.]

Variables	Total	Radiation therapy group	Intra-arterial chemo-radiationtherapy group	P value
Patients (n)	10	440	660	
Age (mean y SD)	65.1 (10.02)	65.2 (7.13)	65.0 (12.26)	0.9718 NS
Sex (n. %)				
Male	6 (60%)	2 (50%)	4 (66%)	
Female	4 (40%)	2 (50%)	2 (33%)	0.598 NS
T stage (n, %)				
T2	5 (50%)	2 (50%)	3 (50%)	
T3	4 (40%)	2 (50%)	2 (33%)	
T4	1 (10%)	0 (0%)	1 (16%)	0.833NS
N stage (n, %)				
N0	2 (20%)	1(25%)	1(16%)	
N1	1 (10%)	1(25%)	0 (0%)	
N2b	6 (60%)	2(50%)	4 (66%)	
N2c	1 (10%)	0(0%)	1(16%)	0.5009NS
Stage (n, %)				
II	1(10%)	1(25%)	0 (0%)	
III	2(20%)	1(25%)	1 (16%)	
IVA	7(70%)	2(50%)	5 (83%)	0.3745NS
Differentiation (n, %)				
Well	4 (40%)	3 (75%)	1 (16%)	
Moderate	4(40%)]	1(25%)	3(50%)	
Poor	2(20%)	0(0%)	2(33%)	0.1534 NS
Clinical response (n, %)				
CR	2 (20%)	0 (0%)	2 (33%)	
PR	770	375	466	
NC	110	125	00	0.2397 NS
Clinical effective response (n, %)				
CR+RR	9 (90%)	3 (75%)	6 (100%)	

NC	1 (10%)	1 (25%)	0 (0%)	0.197 NS
Tumor reduction rate (mean, % SD)	51% (28.35)	29% (11.08)	65% (27.47)	0.0402
Pathological response (n, %)				
Grade I	4 (40%)	3 (75%)	1 (16%)	
Grade II	4 (40%)	1 (25%)	3 (50%)	
Grade III	2 (20%)	0 (0%)	2 (33%)	0.1534 NS
Pathological effective response (n, %)				
Grade II+III	6 (60%)	1 (25%)	5 (84%)	
Grade I	4 ((40%)	3 (75%)	1 (16%)	0.0651 NS
Mucositis (n, %)				
Grade II	8 (80%)	3 (75%)	5 (83%)	
Grade III	2 (20%)	1 (25%)	1 (16%)	0.7469 NS

The clinical response rate was classified into CR in 2 cases, PR in 7 cases, NC in 1 case. In radiation group, 3 cases were PR and 1 case was NC. In IACRT group, 2 cases were CR and 4 cases were PR. The response rate (CR+PR) was 90% in all patients. 75% in radiation group, and 100% in IACRT group **(Table 1)**.

IACRT was more responsive than radiation therapy, however, there was no statistically significant difference between two groups (P=0.1967). The mean of tumour reduction rate was 51% in all patients. 29% in radiation group and 65% in IACRT group. There was statistically significant difference between two groups (P=0.0402).

The pathological therapeutic effects of the lesions that were extracted during surgery was classified into grade I in 4 cases (40%), grade II in 4 cases (40%), and grade III in 2 cases (20%). In radiation group, 3 cases were grade I and 1 case was grade II. In IACRT group, 1 case was grade I, 3 cases were grade II, and 2 cases were grade III. The response rate (grade II and III) was 60% for all cases, 25% for the radiation group, and 83% for IACRT group. IACRT was more responsive than radiation therapy, however, there was no statistically significant difference between two groups (P=0.0651).

Mean follow up period was 26 months (range, 3.3 - 45.9 months). The overall 1 and 3-year survival rates were 100% and 90%, respectively **(Figure 1)**.

One patient of IACRT group died for recurrence after 17.5 month. Because nobody died in patient of radiation therapy group, comparison of survival rate by IACRT group *vs*. radiation therapy group could not be calculated.

The complications were classified by CTCAE V4.0 into all cases of oral mucositis and 8 cases of Gr II, 2 cases of Gr III, as complications at the acute stage.

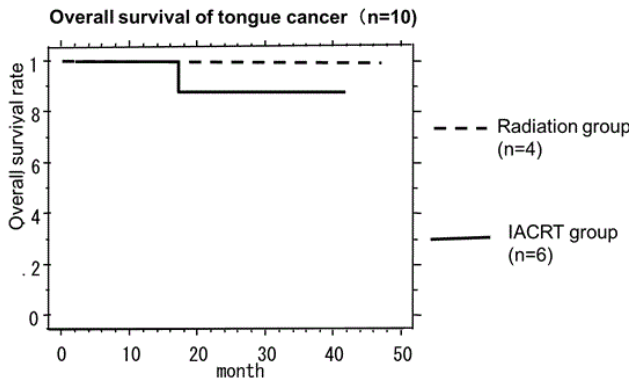

Figure 1: A Kaplan-Meier plot showing over overall survival of all tongue cancer patients (n=10).

There was no statistically significant difference between radiation therapy group and IACRT group in the complication grade of mucositis (P=0.0651). There was 1 case of Gr II platelet count decrease in radiation therapy group. There was no nervous system disorder like the brain infarction.

Case

Patient was 59-year-old man with tongue cancer (T3, N2b, M0, stage IVA). Tumour was located in left side edge of tongue, that diameter was 41 mm at pre-therapy, that was diagnosed well differentiated squamous cell carcinoma by tissue biopsy **(Figure 2a)**.

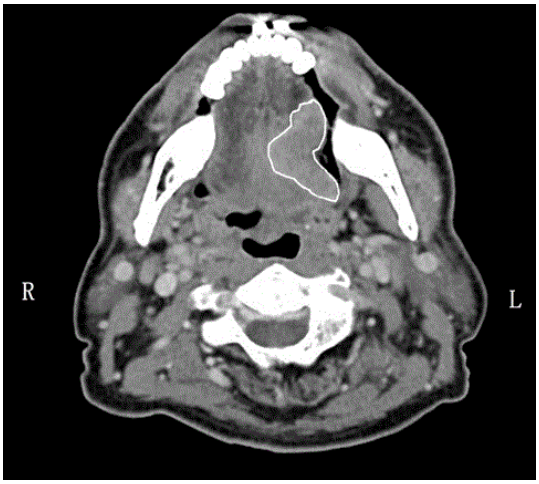

Figure 2a: CT imaging of pre-therapy. Tumour was located in left side edge of tongue, that diameter was 41 mm.

Radiation therapy was done total 40 Gy/20 fraction and intra-arterial chemotherapy was done the following day of radiation therapy start. Cisplatin (100 mg) was infused from lt. tongue artery in 20 minutes **(Figure 2b)**.

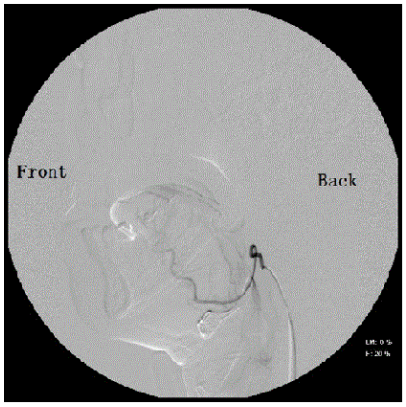

Figure 2b: Digital subtraction angiography of left lingual artery by sagittal plane view. We infused indigo carmine from this point and determined macroscopically the stain of tongue tumour surface and infused steroid (20 mg of prednisolone) and cisplatin (100 mg).

Two week after therapy, tumour diameter was vanished by MRI imaging **(Figure 2c)**.

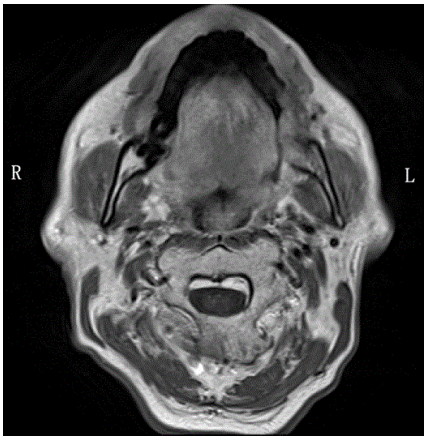

Figure 2c: MRI enhanced T1 weighted imaging of post intra-arterial chemoradiotherapy. Tumour was not appeared.

A month after therapy, subtotal resection and lymphadenectomy was done. Pathologically, there were no viable cancer cells, chemoradiation effect was grade 3 **(Figure 2d)**.

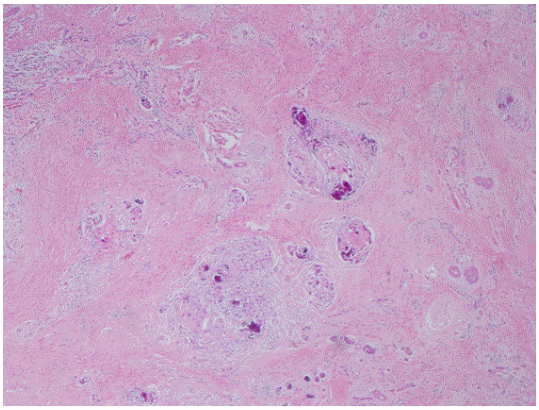

Figure 2d: Microscope imaging (x40) of resected lesion tissue after intra-arterial chemoradiotherapy. There were lamina propria and muscle tissue and foreign body reaction for keratinization or calcification. Viable cancer cells were not appeared.

Discussion

Surgery or radiation therapy has mainly been performed as a treatment option for head and neck cancer. As to chemotherapy, therapy has been performed with a variety of protocols, wherein selective arterial infusion chemotherapy or alternatively a combination of selective arterial infusion chemotherapy and radiotherapy has been performed with the aim of preserving functionality via reductive surgery [4].

The intra-arterial infusion chemotherapy is advantageous over the intravenous injection since it allows a higher concentration of anticancer agent to flow selectively into the tumour, thereby killing more tumour cells with lower toxicity. Furthermore, it is

believed that recent improvements in fluoroscopes now provide a safer selective arterial infusion and enhance the adaptation of this therapy.

Recently, arterial infusion chemotherapy has been reviewed due to a report by Robbins [7] of good achievements for head and neck cancer. There are several reports regarding IACRT for tongue cancer, Kano [8] reported that the 5 y survival rate was 90% and the 5 y local control rate was 92% in 13 cases which did four cycle of cisplatin infusion (100-120 mg/mm^2) from superficial temporal artery approach concurrently with radiation therapy with a total dose of 66-70 Gy. They reported all patients achieved a CR in the primary site. Tomidokoro [9] reported the 3 y local control rate to be 82% and the 3 y survival rate to be 100% in 11 cases with tongue cancer at stage III-IV, wherein involved in IACRT with cisplatin (100 mg/body) and docetaxel (40 mg/body) by 2-4 times a radiation period via femoral artery approach and a total radiation dose of 60 Gy. They reported 10 cases (91%) achieved CR and 1 case (9%) achieved PR [9].

Historically, there have been three different kinds of IACRT methods. The conventional method employed catheterization into external carotid artery via a superficial temporal artery or a superior thyroid artery. Recently, super selective intra-arterial chemotherapy with catheterization into the lingual artery has become popular. Two types of super selective methods have been used, the first one utilizes the transfemoral Seldinger's approach and temporary infusion, the second one is the method of Hattori, Fuwa and Tohnai (HFT) in which a retrograde approach via the superficial temporal or the occipital artery and continuous infusion are used [10]. Previously, we used to use the HFT method for head and neck cancer therapy, but continuous catheterization often occurred obstruction of catheter or artery. Serious complications (infection of catheter inserting portion, aneurysmal hematoma or meningitis) were induced. Now we are using the Seldinger's method.

I thought tongue ca. is especially better adaptation disease for IACRT than other neck and head cancer. Lingual artery is mainly branching from extra carotid artery and feeding vessel of tongue ca. [11,12]. A procedure of catheterization in lingual artery is more easily than inferior alveolar artery for gum cancer or facial artery for buccal mucosa cancer.

In our study, the reduction rate by the degree of histopathological differentiation in squamous cell cancer (mean reduction rate was 46% in 4 case of well differentiated, 56% in 4 case of moderate differentiated, 50% in 2 case of poor differentiated) not show a significant difference. One patient died from local recurrence. She had poorly differentiated squamous cell cancer and her histological therapeutic effect was grade I. Konstantin et al. reported that the 5-year survival rate by degree of histopathological differentiation in oral cancer was 42% in well, 36% in moderate, and 0% in poor [13]. As to IACRT, it is believed that the degree of histological differentiation or clinical therapeutic effects have little effect on the survival rate.

In our study, the response rate (grade II and III) was 83% for IACRT group by the pathological therapeutic effects. According to a report by Ikushima [14], the response rate (grade II – IV in Oboshi's classification) was 98% for IACRT in preoperative oral cavity cancer, comparing the histological therapeutic effects of the poor response group having grade 0 – I with the good response group having grade II – IV, the survival rate of the good response group was significantly better.

We compared the effect of the radiation therapy alone with the IACRT for the treatment of preoperative tongue cancer. In previous study, Kawasaki [15] compared the effect of the radiation therapy alone (10 cases) with the IACRT (14 cases) for the treatment of preoperative head and neck cancer, that the histological response rate (more than Grade IIA in Oboshi's classification) was 30% in radiation group and 79% in IACRT group, they concluded that the therapeutic effect of IACRT was significantly greater than that of radiation therapy alone. Their study was different from our study in some point that their half cases of patients (12 of 24) was gum cancer and tongue cancer was 3 cases, mean total dose of radiation was 27.3 Gy with 60Co-radiotherapy (40 Gy with linear accelerator in our study), their intra-arterial chemotherapy method was HFT method (trans femoral Seldinger's approach in our study).

In previous studies, bone marrow suppression, vomiting, diarrhoea, hair loss, stomatitis, mucosal damage, localized pain, edema, and cerebrovascular disorder were reported as complications related to arterial infusion therapy [16,17]. Balm et al. encountered 3.8% cases of death at grade V [16]. In our cases, at the acute stage, all patients suffered from mucositis where its severity was grade II in 80% and grade III in 20%. Serious complication with grade IV or V was not observed.

Limitation

There was a possibility of selection bias because this study was retrospective study. Moreover, only 10 patients were included in this study. Future studies with a larger number of patients are needed to establish the efficacy of IACRT for tongue cancer.

In conclusion, compared to radiation therapy alone, IACRT resulted in higher reduction rate. IACRT may be a better preoperative treatment for tongue cancer.

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