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Clinical Study

Comparative Study of Superselective Intra-Arterial Chemoradiotherapy versus Radical Surgery on Distant Metastasis for Advanced Oral Cancer

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Background. Distant metastasis is considerably more frequent in superselective intra-arterial chemoradiotherapy than other radical treatments for advanced oral cancers. However, there is no evidence supporting such claim. The purpose of this study was to report our experience in superselective intra-arterial chemoradiotherapy and conventional surgical management with particular focus on distant metastasis. *Methods*. One hundred seventy-two patients with oral squamous cell carcinoma in stages III and IV were included in this study. Retrospective analysis for DM rates and background between surgical management and superselective intra-arterial chemoradiotherapy was performed. *Results*. Distant metastasis developed clinically was detected in 24 out of 141 patients (17.0%) treated surgically and in 6 out of 31 patients (19.4%) treated with superselective intra-arterial chemoradiotherapy. There was no significant difference in the rate of distant metastasis between the 2 groups. Comparison of patients in both groups with and without distant metastasis revealed no differences in age, T classification, N classification, and treatment effect. Neck recurrence was the only significant risk factor for distant metastasis. *Conclusion*. No significant difference was found in the rate of distant metastasis between patients treated with surgical treatment and superselective intra-arterial chemoradiotherapy, and additional effort is needed to reduce the risk of distant metastasis.

1. Introduction

The introduction of superselective intra-arterial infusion of cisplatin (CDDP) with concomitant radiotherapy (RADPLAT) by Robbins et al. [1] has seen a significant increase in the treatment modal of superselective intra-arterial chemoradiotherapy (SSIACRT) for advanced head and neck cancer. However, despite the significant complete response rate, the survival rate of SSIACRT remains unsatisfactory. Two major factors leading to the poor survival rates are failures of locoregional control and distant metastasis (DM). DM is the most common mode of recurrence amongst patients with advanced head and neck cancer treated with intra-arterial cisplatin and radiotherapy (RADPLAT) [2, 3]. The incidence of DM has been reported variously with some papers describing a higher frequency in DM compared to other radical treatments. The effectiveness of the RADPLAT protocol is based on the deliveryof high dose cisplatin combined with radiation therapy to the local disease. As a result, locoregional disease control is excellent in this treatment. However, for patients with subclinical metastases or micrometastases at distant sites, DM may develop eventually as this protocol does not provide systemic treatment [4]. The eligibility criteria for RADPLAT are advanced head and neck cancer which is thought to be a high-risk group of DM. There is no evidence that occurrence of DM depends on the treatment procedure.

Table 1: Distribution by T and N classification in surgical group.

	N0	N1	N2a	N2b	N2c	Total
T2	0	15 (1)	1 (1)	21 (3)	2 (1)	39 (6)
T3	16 (2)	7 (4)		8 (3)	1	32 (9)
T4	38 (2)	10 (3)		15 (3)	7 (1)	70 (9)
Total	**54 (4)**	**32 (8)**	**1 (1)**	**44 (9)**	**10 (2)**	**141 (24)**

Number in the parenthesis means number of patients with DM.

Table 2: Distribution by T and N classification in SSIACRT group.

	N0	N1	N2a	N2b	N2c	Total
T2	0		1		2	3
T3	3 (1)	2		1	1	7 (1)
T4	4 (1)	6 (1)	1	6 (2)	4 (1)	21 (5)
Total	**7 (2)**	**8 (1)**	**2**	**7 (2)**	**7 (1)**	**31 (6)**

Number in the parenthesis means number of patients with DM.

The purpose of this study is to clarify whether DM develops more frequently in SSIACRT by means of our experience and literature review and, furthermore, to study the risk factor of DM.

2. Patients and Methods

Inclusion criteria were as follows: oral squamous cell carcinoma (OSCC), Union for International Cancer Control (UICC) TNM classification stage III to IV, World Health Organization (WHO) performance status (PS) 0-1. Distant metastasis at first medical consultation and prior history of other head and neck malignancy were excluded. Medical records of a consecutive series of patients suffering from Stage III and IV oral cancer at the Department of Oral and Maxillofacial Surgery, Hirosaki University Hospital, between 1991 and 2011 were reviewed retrospectively. Until 2003, surgical treatments were performed for all oral cancers which were thought to be operable, and since 2003 SSIACRT was introduced as radical treatment for advanced oral cancer instead of surgical treatment. The indication of SSIACRT was cases in which any surgical procedure might result in severe functional loss regardless of how ideally reconstruction was performed and/or inoperable cases. In contrast, indication of surgical treatment was resectable OSCC in which excellent functional and cosmetic results could be obtained after contemporary reconstruction.

The study group was comprised of 172 patients with OSCC in stages III and IV with 115 males and 57 females. One hundred forty-one oral cancer patients received surgical therapy and 115 out of 141 patients received postoperative radiation. Thirty-one patients received SSIACRT. The distribution of patients by T and N classification of surgical and SSIACRT groups is shown in Tables 1 and 2. Both groups were suitable for comparison in the rate of DM because there was no statistically significant difference at the point of age, sex, T and N classification, and primary sites (Table 3). Primary tumor and metastatic cervical lymph nodes were assessed by physical examination, computed tomography (CT), and magnetic resonance imaging (MRI). CT was used for examination of distant metastasis in lung and abdomen as well. Since 2005, positron emission tomography CT (PET-CT) has been introduced for whole body examination.

2.1. Surgical Management. Operable patients underwent resection of the primary tumor with/without simultaneous neck dissection and were reconstructed by various free flaps. Postoperative radiotherapy was employed when pathological staging revealed multiple positive cervical lymph nodes or extracapsular (extranodal) spread (ECS). Primary tumor and all nodal areas were irradiated to 50–66 Gy.

2.2. Procedure of SSIACRT. Treatment procedure of SSIACRT was as follows. Primary tumor and all nodal areas were irradiated to 50 Gy in 25 fractions, 5 fractions a week, over a period of 5 weeks, immediately followed by a boost of 16 Gy in 8 fractions to all involved areas, including the primary tumor (total dose 66 Gy). All patients received 2 or 3 times concurrent intra-arterial DOC (40 mg/mm^2) and CDGP (80 mg/mm^2) infusion every 4 weeks as was previously reported by Kobayashi et al. [5].

Anticancer drugs were partially delivered to the regional neck area in patients with bulky nodal diseases confirmed to have multiple feeding arteries. The dose of drug for each feeder of bulky nodal diseases was determined by CT angiography (CTA). When the number of feeding arteries was more than 4 or the feeding artery was not identified by microcatheter, an arterial redistribution technique was used. Unnecessary branches of the ECA were embolized with microcoils (Trufil Pushable coil, Codman, Raynham, MA, USA, and Tornade Embolization Microcoil, Cook, Bloomington, IN, USA) via microcatheter. The procedure was performed within the extent of the ECA. Drug infusion, procedure was performed in the radiology suite by interventional radiologists. This treatment has been approved by the appropriate ethical committees of Hirosaki University Hospital, Hirosaki, Japan.

2.3. Follow-Up after Treatment. Routine follow-up included monthly clinical examination in the first year and bimonthly examination up to 3 years. Clinical examination was continued every 3 or 4 months up to 5 years. Routine CT including oral, cervical, and lung was performed once every 6 months during the first 3 years after treatment and subsequently once a year or when clinically indicated.

2.4. Statistical Methods. Difference in categorical variables was analyzed by chi-square test, or if cell counts were less than 5, the Fisher exact test was used. Continuous variables were compared using Student's t-test. The Kaplan-Meier method was used to estimate the overall survival rate and the log-rank test was used to compare the overall survival between the 2 groups. The analyses were performed using the SPSS. Statistical significance is claimed for two-sided P value of less than 0.05.

Table 3: Comparison of surgery and SSIACRT group.

	Surgery group (%) (n = 141)	SSIACRT (%) (n = 31)	Chi-square test
Age			
Mean ± SD	64.7 ± 12.3	62.1 ± 11.9	N.S. (P = 0.13)
Sex			
Male	92 (65.2)	23 (74.2)	N.S. (P = 0.31)
Female	49 (34.8)	8 (25.8)	
T			
T2	39 (27.7)	3 (9.7)	N.S. (P = 0.09)
T3	32 (22.7)	7 (22.6)	
T4	70 (49.6)	21 (67.7)	
N			
0	54 (38.3)	7 (22.5)	N.S. (P = 0.06)
1	32 (22.7)	8 (25.8)	
2a	1 (0.7)	2 (6.5)	
2b	44 (31.2)	7 (22.6)	
2c	10 (7.1)	7 (22.6)	
Site			
Tongue	41 (29.1)	11 (35.5)	N.S. (P = 0.24)
Floor of mouth	23 (16.3)	5 (16.1)	
Upper gum	18 (12.8)	8 (25.8)	
Lower gum	45 (31.9)	5 (16.1)	
Buccal mucosa	14 (9.9)	2 (6.5)	

SSIACRT: superselective intra-arterial chemoradiotherapy.
Number in the parenthesis means percentages.

Table 4: Comparison of DM rate.

	Surgery	SSIACRT	Statistics
DM (−)	117 (83.0)	25 (80.6)	N.S.
DM (+)	24 (17.0)	6 (19.4)	

Number in the parenthesis means percentages.

3. Results

3.1. Rate of DM. DM was detected clinically in 24 out of 141 patients (17.0%) treated surgically and in 6 out of 31 patients (19.4%) treated with SSIACRT. All DM were revealed by follow-up CT. There was no significant difference in the rate of DM between surgical and SSIACRT groups (Table 4). The age at diagnosis of the primary tumor ranged from 40 to 80 years (median 63.3 years) in surgical group and from 44 to 79 years (median 63.6 years) in SSIACRT group. The average months from initial diagnosis to DM was 11.7 (1 to 35 months) in surgical group and 10.2 (1 to 28 months) in SSIACRT group. Eighty-three percent of the patients treated with SSIACRT and 92% treated surgically developed DM within 24 months.

3.2. Primary Site and DM. In surgical group, the sites of primary tumor were tongue in 11 patients, floor of the mouth in 2 patients, lower gum in 9 patients, upper gum and buccal mucosa in 1 patient, respectively. However, in SSIACRT group, the sites were tongue in 3 patients and floor of the mouth, upper gum, and lower gum in 1 patient, respectively. The DM rates of each primary site in surgical and SSIACRT group are 26.8 and 27.2% in tongue, 8.7 and 20% in floor of the mouth, 5.6 and 12.5% in upper gum, 20% for both groups in lower gum, and 7.1 and 0% in buccal mucosa, respectively (Table 5).

3.3. The Organ of DM. The organs of DM in surgical group were lung in 17 patients, bone in 3 patients, lung and bone in 2 patients, lung and liver in 1 patient, and skin in 1 patient. The organs of DM in SSIACRT group were lung in 4 patients, lung and liver in 1 patient, and cavernous sinus in 1 patient (Table 6).

3.4. Relationship between Variables and DM. Correlation between clinical characteristics and DM is shown in Table 7 in each group. Comparison of each patient with DM and without DM revealed no differences in age, T classification, N classification, and treatment effect. Patients with neck recurrence developed DM significantly in both groups (Table 7).

3.5. Comparison of Survival Rate with and without DM. According to Kaplan-Meier method, the 5-year overall survival rate for patients in surgical group with and without DM were 0% and 66.1%, respectively, with a significant difference

Table 5: Primary site and DM.

Site	Surgery		SSIACRT	
	Number	Number of DM (%)	Number	Number of DM (%)
Tongue	41	11 (26.8)	11	3 (27.2)
Floor of the mouth	23	2 (8.7)	5	1 (20)
Upper gum	18	1 (5.6)	8	1 (12.5)
Lower gum	45	9 (20.0)	5	1 (20)
Buccal mucosa	14	1 (7.1)	2	0
Total	**141**	**24 (17.0)**	**31**	**6 (19.4)**

Number in the parenthesis means percentages.

Table 6: The organs of DM.

The organ	Surgery group	SSIACRT
Lung	17 (70.8)	4 (66.6)
Bone	3 (12.5)	0
Lung + bone	2 (8.3)	0
Lung + liver	1 (4.2)	1 (16.7)
Skin	1 (4.2)	0
cavernous sinus	0	1 (16.7)
Total	**24**	**6**

Number in the parenthesis means percentages.

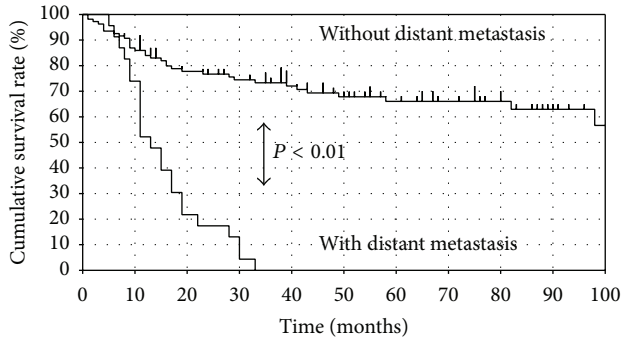

Figure 1: Overall survival rates of surgery group. 5-year overall survival rate of patients with and without DM were 0% and 66.1%, respectively. There is a significant difference between the 2 groups (log-rank test).

(Figure 1). On the other hand, the 5-year overall survival rate in SSIACRT group with and without DM were 0% and 100%, respectively, with a significant difference (Figure 2).

3.6. Comparison of Survival Rate between Surgical and SSIACRT Groups. Five-year overall survival rates of surgery and SSIACRT group were 57.6% and 76.9%, with a median follow-up duration of 31 months and 39 months, respectively. There is a significant difference between the 2 groups (log-rank test) (Figure 3).

4. Discussion

Surgical treatment and chemoradiotherapy are the 2 major treatments for advanced oral cancer. NCCN guidelines in 2011

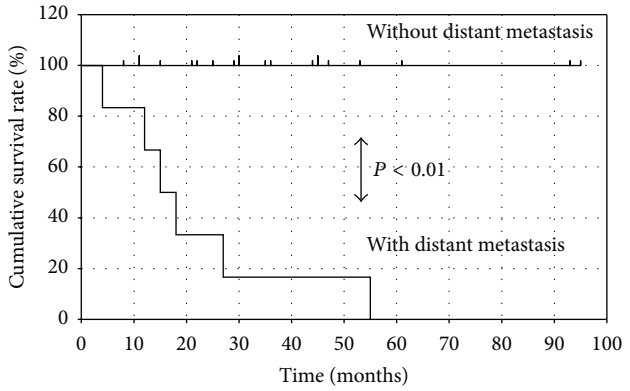

Figure 2: Overall survival rates of SSIACRT group. 5-year overall survival rate of patients with and without DM were 0% and 100%, respectively. There is a significant difference between the 2 groups (log-rank test).

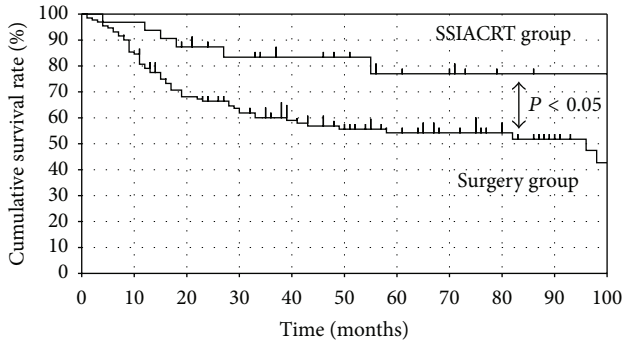

Figure 3: Comparison of 5-year overall survival rate between surgery and SSIACRT group. 5-year overall survival rates of surgery and SSIACRT group were 57.6% and 76.9% with a significant difference between the 2 groups (log-rank test).

recommended surgical treatment for all stages of oral cancer except T4b. Surgical treatment for oral cancer using various reconstructive techniques were thought to be functionally established to avoid the risk of severe xerostomia, taste disorder, and osteoradionecrosis that might develop after chemoradiation therapy [6]. However, wide surgical resections were required to secure a clear surgical margin during the primary operation, which often resulted in postoperative

Table 7: Relationship between variables and DM.

Variables		SSIACRT			Surgery		
		DM (−)	DM (+)	Statistics	DM (−)	DM (+)	Statistics
Age		61.8	63.3	N.S.	65.5	63.6	N.S.
T classification	1, 2	3	0	N.S.	33	6	N.S.
	3, 4	22	6		84	18	
N classification	0	5	2	N.S.	50	4	N.S.
	1	7	1		24	8	
	2	13	3		43	12	
Occurrence of primary recurrence*	(+)	2	1	N.S.	24	9	N.S.
	(−)	23	5		93	15	
Occurrence of neck recurrence*	(+)	2	4	$P < 0.01$	8	7	$P < 0.01$
	(−)	23	2		131	14	
Treatment effect	PR	3	1	N.S.			
	CR	22	5				

*Persistent tumor was considered to be a recurrence.
Difference in Age category was analyzed by Student's t-test and others difference in the categorical. Othere datas were analyzed by chi-square test.

loss of organ function especially for advanced oral cancer. Robbins reported that superselective intra-arterial infusion of cisplatin with concomitant radiotherapy (RADPLAT) had a high complete response rate (90.5%) at the primary site, while for the regional region it was 70.7%. However, the 5-year disease-free and overall survival rates for patients suffering from the disease were 53.6% and 38.8%, respectively [2]. These poor outcomes are considered to be unacceptable regardless of the good response at the primary site. Although local and regional control of head and neck cancer has improved, DM has become an increasingly common cause of death [7]. DM was the most common mode of recurrence among patients with advanced head and neck carcinoma treated with RADPLAT [3]. DM after superselective intra-arterial chemoradiotherapy (SSIACRT) is considered to be more frequent in head and neck cancer; however, it remains unclear whether the rate of DM after SSIACRT is higher than that of other radical managements.

The rates of DM after intra-arterial chemoradiotherapy were reported to be around 6~26.6% [3, 4, 8–10]. On the other hand, the rates after intravenous chemoradiotherapy were around 16~26.6% [10–12]. Recently, Rasch et al. reported a multicenter randomized phase 3 trial of 239 patients with advanced head and neck cancer in The Netherlands where they concluded that treatment effect of intra-arterial chemoradiotherapy was not superior to intravenous chemoradiotherapy and the rates of DM in both treatments were the same, which was 26.6% [10]. Since the rate of DM after surgical management was reported to be around 17~36.7%, the rate of DM seemed to be the same between SSIACRT and other radical treatments [7, 13–17].

One of the reasons the rate of DM was considered to be higher in SSIACRT was because most of the cases enrolled in this treatment were in advanced stages. Advanced oral cancer has a higher tendency for DM no matter what the treatment methods were. Therefore, a higher rate of DM is not only restricted to SSIACRT. In this study the rate of DM was 19.4% in SSIACRT group, which was similar to the reports above. The rate of DM in surgical group was 17%; therefore, there is no statistical difference between them.

Patients who were treated by SSIACRT developed DM during treatment period in lung and cavernous sinus, respectively. In general, anticancer drugs would flow systemically when infused intra-arterially, but the rate of DM has not improved. The severe hematologic toxicity which we previously reported revealed that there was systemic drug distribution in SSIACRT [5]. The high DM rate might be due to the concentration of anticancer drug circulated systemically, which due to dilution is insufficient to control the growth of cancer cells in the site of DM. This suggests that intravenous and intra-arterial infusion of anticancer drug with radiation may not be effective for the prevention of DM. As for RADPLAT, systemic distribution of CDDP has been neutralized by sodium thiosulfate during the cisplatin infusion. An intergroup phase 3 comparison of standard radiation therapy and concurrent intravenous chemoradiotherapy (CRT) for advanced head and neck cancer revealed that concurrent CRT was more effective than radiation for survival rate, but there was no significant difference in the percentage of DM [11]. Furthermore postoperative chemoradiotherapy improved progression-free survival rate, overall survival rate, and local and regional control more than radiation alone, but there was no significant difference in the percentage of DM as well [16, 17].

In the meantime, docetaxel (DOC), cisplatin (CDDP), and 5-fluorouracil (TPF)-based induction chemotherapy followed by hyperfractionated radiotherapy reduced the incidence of DM (10%) but increased the local-regional failures (30%) which continued to be the major impediment to cure in this regimen [18]. If induction chemotherapy reduces the rate of DM significantly, chemotherapy prior to SSIACRT will be effective to prevent DM. However the selection of anticancer analogues would be difficult because although TPF is a promising regimen for induction chemotherapy, TPF resembles the anticancer drugs we use in our protocol (P = CDGP, T = DOC). It remains a question mark whether the

same good results could be obtained in SSIACRT after TPF induction chemotherapy. There has been no solution found and therefore further research is needed.

DM occurred in not only intra-arterial chemotherapy but also CRT and surgical management. Therefore, the control of DM is important to improve the outcomes of patients with advanced oral cancer. Survival in advanced oral cancer depends on the control of DM from the fact that all patients with DM died eventually and patients without DM survived in each group of this study. Five year overall survival rate of patients without DM treated with SSIACRT is 100%. It is important to identify the risk factors of DM and effort should be done for prevention of DM.

Histological criteria such as extracapsular spread (ECS) and multiple positive nodes were found to be related to the increment of the incidence of DM [7, 19]. In this study, ECS was unknown in positive nodes because pathological examination was not performed. The location of the primary tumor, T stage, N stage, primary recurrence, and treatment results have not resulted in the development of DM.

There was no significant difference between the 2 groups where P value was 0.06 for N-stage, the most important risk factor for poor prognosis. The rate of DM was the same; nevertheless, more cases of N2c in SSIACRT group indicated that SSIACRT is not inferior to surgical treatment.

Due to limited cases, the rate of DM in the floor of mouth and the maxilla was higher than those of surgical group. There was only 1 singular case for floor of mouth and maxilla, respectively. In particular, the patient with oral floor carcinoma was in advanced stage which was diagnosed as T4bN2cM0. In general, treatment results of oral floor cases were acceptable and similar to the other site which was showed in previous report [5]. Locoregional disease control seems to be related to DM; however, other than neck recurrence there is no significant difference in between in this study. Nevertheless, the increment of successful locoregional control rate, overall survival rate decreases due to the development of DM. Locoregional control in SSIACRT is acceptable; therefore, prevention of DM is more crucial [5]. Only neck recurrence affected the development of DM significantly in both radical treatments. The rate of neck recurrence in SSIACRT group seemed to be more often than surgical group. However, there was no significant difference between the 2 groups. Patients with neck recurrence will be treated by neck dissection because neck dissection was not performed as initial treatment in SSIACRT group. From this study, effort to reduce neck recurrence is important for the prevention of DM but at present it is difficult to overcome these problems.

Lung is the organ with the most frequent DM rates after radical treatment for advanced oral cancer. Metastatic lung cancer could be treated radically by radiotherapy. Stereotactic body radiation therapy (SBRT) offers a high local control rate with minimal toxicities in early-stage non-small-cell lung cancer (NSCLC). A local control rate of Stage 1 NSCLC after SBRT is approximately 90% [20, 21]. Patient with oligometastases, a small number of metastatic lesions limited to an organ, has been considered a candidate for curative treatment recently because long term survival can be expected. Since the effectiveness of SBRT for primary lung cancer was reported [22], awareness of SBRT as a curative treatment for metastatic lung tumor has been growing. Norihisa et al. described the eligibility criteria of SBRT for oligometastatic lung tumor as follows: (1) one or 2 pulmonary metastases, (2) tumor diameter ≤ 4 cm, (3) locally controlled primary tumor, and (4) no other metastatic sites. In their report, the overall survival rate of the patients with oligometastatic lung cancer treated with SBRT including head and neck cancer at 2 years was 84.3% [23]. From these reports, SBRT will be effective for lung metastasis without other DM and local recurrence after SSIACRT. In order to improve prognosis, it is important to detect DM in early stage as oligometastasis because there is a possibility to perform a curative treatment for DM. As most DM occurred within 24 months, regular CT examination would be effective to detect DM.

In conclusion, same DM rate was observed between SSIACRT and surgical groups in our study and high DM rate is not restricted only to SSIACRT. Further effort to reduce the risk of DM is needed. In our opinion, induction chemotherapy prior to SSIACRT may be crucial. This study revealed that SSIACRT is superior to radical surgical management and we concluded that SSIACRT is an ideal treatment for advanced oral cancer.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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