

Investigation of distant metastasis occurrence rates with different treatments: A comparison of superselective intra-arterial chemoradiotherapy and surgery

Toshiaki Oyama  | Wataru Kobayashi  | Ryohei Ito | Yoshihiro Tamura | Anna Satake | Haruka Fukuta

Department of Oral and Maxillofacial Surgery, Hirosaki University School of Medicine Graduate School of Medicine, Hirosaki, Japan

Correspondence

Toshiaki Oyama, Department of Oral and Maxillofacial Surgery, Hirosaki University School of Medicine Graduate School of Medicine, 5 Zaifu-cho, Hirosaki 036-8562, Japan.
Email: h15gm507@hirosaki-u.ac.jp

Abstract

Control of distant metastasis is an important factor in improving treatment outcomes for oral cancer. Superselective intra-arterial chemoradiotherapy (SSIACRT) has been reported to be effective for preservation of form and function, thus enabling a satisfactory outcome. However, there have also been reports of a high frequency of distant metastases with SSIACRT. The present study therefore aimed to clarify whether treatment method has any relationship with the onset of distant metastases. Of a total of 384 cases of oral cancer, 270 underwent surgery, 44 underwent surgery followed by radiotherapy, and 70 underwent SSIACRT, and distant metastases occurred in 42 cases. On multivariate analysis, only N classification was a significant risk factor ($P = .0001$, odds ratio = 1.848). This confirmed that the only risk factor for distant metastases is lymph node metastasis, there is no relationship to treatment method, and there are no grounds to say that SSIACRT promotes distant metastases.

KEYWORDS

distant metastasis, multivariate analysis, oral and maxillofacial surgery, oral cancer, superselective intra-arterial chemoradiotherapy

1 | INTRODUCTION

Medical advances in the treatment of head and neck carcinoma have led to good rates of local control, but prevention of distant metastasis is difficult and remains an unresolved problem. Control of distant metastasis is essential for improvement of oral cancer treatment outcomes. On the other hand, superselective intra-arterial chemoradiotherapy (SSIACRT) enables functional organ preservation and achieves the same outcome as surgical treatment while reportedly conferring a better prognosis.¹ A poor prognosis is associated with

distant metastasis (DM), which is the most common form of recurrence in patients with advanced head and neck carcinoma.^{2,3}

DM is believed to occur in 4%-26% of cases of typical head and neck carcinoma,⁴⁻⁸ and looking at DM occurrence rates, reports of DM appear to be more common with SSIACRT than with other therapies.⁹ A univariate analysis of DM of oral cancer using a small number of cases has been previously reported.¹⁰ In the present study, the aim was to investigate whether a higher incidence of DM occurred in SSIACRT compared with surgical therapies by examining more cases and using multivariate analysis.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. *Oral Science International* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Stomatological Society

2 | MATERIALS AND METHODS

This study was a retrospective analysis of samples derived from 384 patients with oral cancer who were treated at a university hospital in Japan between 2000 and 2015. The inclusion criteria were oral squamous cell carcinoma and a World Health Organization performance status between 0 and 1. The patients' characteristics are presented in Table 1.

At their initial examinations, patients underwent computed tomography (CT) from the primary region to the chest, oral and cervical magnetic resonance imaging, and whole body positron emission tomography (PET)-CT to determine the extent of tumor invasion and DM. Patients with DM at the first medical consultation and a history of other head and neck malignancies were excluded.

Surgical treatment was performed for all patients with operable oral cancer until 2003, after which SSIACRT was introduced as a radical treatment for advanced oral cancer. SSIACRT was preferred for cases where any surgical procedure, regardless of how ideally reconstruction was performed, could impair mastication and/or for inoperable cases.

The treatment procedures for SSIACRT were as follows: the primary tumor and all nodal areas were irradiated using 50 Gy in 25 fractions at five fractions/week over a period of 5 weeks, immediately followed by a boost of 16 Gy in eight fractions to all involved areas, including the primary tumor (total dose, 66 Gy). As reported

by Kobayashi et al, all patients received a concurrent intra-arterial docetaxel (DOC, 40 mg/m²) and nedaplatin (cis-diammine-glycolate platinum, 80 mg/m²) infusion every 4 weeks, repeated three times.¹¹

In contrast, surgical treatment was performed for resectable oral cancer for which excellent functional and cosmetic results could be obtained after concurrent reconstruction. In our department, excellent function was defined as good mastication by appropriate reconstruction in patients who had undergone subtotal or total glossectomy and were able to speak and swallow, but were not able to masticate, because, if the field of resection was greater than half of the tongue, the function of mastication could not be restored despite the existence of teeth.

Operable patients underwent resection of the primary tumor with simultaneous neck dissection, and head and neck reconstructions were performed using various free flaps.

When pathologic staging showed a positive margin, multiple positive cervical lymph node metastases, and/or extracapsular (extranodal) spread (ECS), postoperative radiotherapy was administered. The primary tumor and all nodal areas were irradiated with 60-70 Gy. Patients without a positive margin, ECS, or multiple nodal metastases were not administered postoperative radiotherapy. Routine CT including oral, cervical, and lung was performed every 3 months after treatment up to 1 year and after 1 year every 6 months up to 3 years, subsequently once a year up to 5 years. PET-CT was performed when clinically indicated.

TABLE 1 Patients characteristics

		Total	DM (-)	DM (+)	Rate of DM (%)	P value
		384	342	42	10.9	
Age (y)		66.5 ± 12.5	66.6 ± 12.6	65.9 ± 11.6		<i>P</i> = .668*
Sex	Male	224	202	22	9.8	<i>P</i> = .21†
	Female	160	140	20	12.5	
T classification	T1	70	67	3	4.3	<i>P</i> = .109†
	T2	161	146	15	9.3	
	T3	46	39	7	15.2	
	T4	107	90	17	15.9	
N classification	N0	257	239	18	7	<i>P</i> = .006†
	N1	37	32	5	13.5	
	N2	89	70	19	21.3	
	N3	1	1	0	0	
Primary site	Tongue	144	127	17	11.8	<i>P</i> = .688†
	Floor of the mouth	54	49	5	9.3	
	Lower gum	88	77	11	12.5	
	Upper gum	54	50	4	7.4	
	Buccal mucosa	40	36	4	10	
	Other	4	3	1	25	
Treatment method	S	270	250	20	7.4	<i>P</i> = .02†
	S + R	44	36	8	18.2	
	SSIACRT	70	56	14	20	

Abbreviations: DM, distant metastasis; S, Surgery; S + R, Surgery followed by radiotherapy; SSIACRT, Superselective intra-arterial chemoradiotherapy.

*Mann-Whitney *U* Test.

† χ^2 test.

This study was approved by the ethics committee of the authors' institution, and informed consent was obtained from all patients for use of their data. The authors have read the Declaration of Helsinki and have followed the guidelines in this study.

2.1 | Statistical analysis

Differences between the groups with and without DM were evaluated using the Mann-Whitney and chi-squared tests. In addition, odds ratios with 95% confidence intervals (95% CIs) were calculated using multiple logistic regression analysis. To explore the risk factors for DM, a model was built with multivariate analysis using the stepwise method. In addition, factors affecting the survival rate were investigated using a Cox proportional-hazards model with treatment method, TN classification, age, presence or absence of DM, and tumor site as independent variables.

A P value of 0.05 was considered significant. SPSS for Mac (Ver. 24; IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. The survival rate was calculated as the disease-specific survival rate using the Kaplan-Meier method.

In this paper, advanced oral cancer means greater than Stage III.

3 | RESULTS

3.1 | Patients' characteristics

Of the 384 patients with oral cancer, 42 developed DM. There were no significant differences in age, sex, T classification, the site of the tumor, N classification, and the method of treatment between

patients with and without DM. In Table 1, the average age, sex, TN classification, number of primary sites, and the treatment methods of patients are shown.

Number of cases of each type, classified by treatment procedure, and their progress (Table 2).

Surgical treatment was provided to 270 patients, surgical treatment followed by radiotherapy was provided to 44 patients, and SSIACRT was used to treat 70 patients. In Table 2, TN classification by treatment procedure, and the median follow-up time (months) are shown.

3.2 | Organs affected and time of DM

DM involved the lungs alone in 34 patients, the lungs, liver, and other organs in four patients, bone in two patients, and other organs in two patients. The average times from initial diagnosis to DM in the surgery-alone group, the surgery group followed by radiotherapy, and the SSIACRT group were 23.9 months, 11.4 months, and 9.2 months, respectively (Tables 3 and 4).

3.3 | Multivariate analysis of risk factors for DM

Age, sex, T classification, N classification, and treatment methods were selected as independent variables, and logistic regression analysis using the stepwise method was used to identify risk factors for DM. N classification was the only significant risk factor for DM; treatment method was not a risk factor (Table 5).

		S	S + R	SSIACRT	P value
Number of patients		270	44	70	
T classification	T1	70	0	0	$P < 0.0001^*$
	T2	131	18	12	
	T3	27	6	13	
	T4	42	20	45	
N classification	N0	231	10	16	$P < 0.0001^*$
	N1	21	4	12	
	N2a	0	0	2	
	N2b	15	25	21	
	N2c	3	5	18	
	N3	0	0	1	
Distant metastasis		20	8	14	$P = 0.003^*$
Uncontrolled disease (primary and/or neck)		26	11	12	$P = 0.006^*$
Median follow-up time (months)		61M (1-203)	75 (3-198)	63 (4-174)	NS [#]

*Chi square test.

[#]Kruskal-Wallis test. NS, not significant; S, Surgery; S + R, Surgery followed by radiotherapy; SSIACRT, Superselective intra-arterial chemoradiotherapy.

TABLE 2 Comparison by treatment methods

TABLE 3 Organs affected by distant metastasis

Organ	Number of cases
Lung	34
Lung, liver, other	4
Bone	2
Other	2

TABLE 4 Time from initial diagnosis to distant metastasis

	Number of patients	Months (average \pm SD)	P value
S	20	23.9 \pm 17.0	NS
S + R	8	11.4 \pm 4.3	
SSIACRT	14	9.2 \pm 6.4	
Total	42	16.2 \pm 13.8	

Note: Analysis of covariance adjusting (ANCOVA) for age and TN classification.

Abbreviations: NS, not significant; S, Surgery; S + R, Surgery followed by radiotherapy; SSIACRT, Superselective intra-arterial chemoradiotherapy.

TABLE 5 Logistic regression analysis to identify risk factors for distant metastasis

	B	P value	OR	95% CI
N classification	0.614	0.0001	1.848	1.311-2.605

Note: Logistic regression analysis (stepwise method).

Dependent variable: Presence or absence of distant metastasis.

Independent variables: sex, age, site of occurrence, T classification, N classification, treatment method, follow-up period.

Hosmer-Lemeshow: 0.848.

CI, confidence interval; OR, odds ratio.

TABLE 6 Multivariate analysis for the survival rate

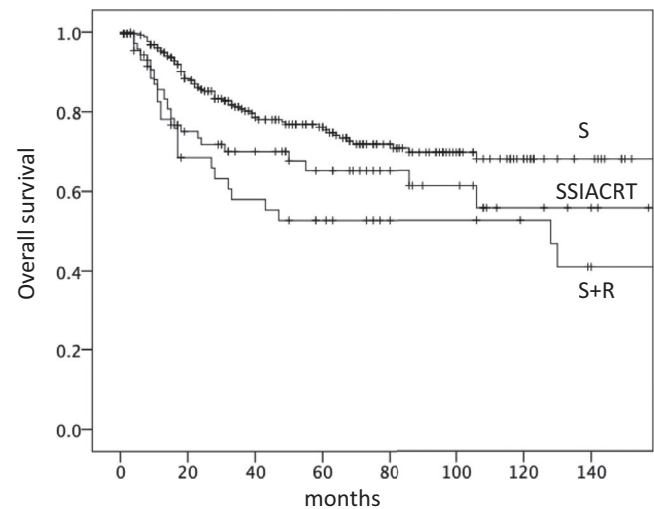
	P value	Hazard ratio	Hazard ratio 95% CI
N classification	0.009	1.416	1.092 1.835
Presence or absence of distant metastasis	0.001	6.285	3.655 10.806
Controlled state (primary and/or neck)	0.001	11.91	6.82 20.799

Note: Cox proportional-hazards analysis (stepwise method).

Independent variables: age, tumor site, T classification, N classification, treatment method, presence or absence of distant metastasis, presence or absence of local control.

3.4 | Overall survival rate for each treatment

The 5-year overall survival rates of the surgery-alone group, the surgery followed by radiotherapy group, and the SSIACRT group were 76.1%, 52.7%, and 66.2%, respectively. The median follow-up in the

**FIGURE 1** Kaplan-Meier estimates of overall survival. S: Surgery, S + R: Surgery followed by radiotherapy, SSIACRT: Superselective intra-arterial chemoradiotherapy

surgery-alone group, the surgery followed by radiotherapy group, and the SSIACRT group was 61 months, 75 months, and 63 months, respectively (Figure 1).

3.5 | Factors affecting the survival rate

The results of the Cox proportional-hazards model showed that N classification, presence or absence of DM, and controlled state (primary and/or neck) were factors affecting the survival rate (Table 6).

4 | DISCUSSION

The frequency of DM in patients with head and neck carcinoma is considered to be 4%-26%.⁴⁻⁸ Recently, the 5-year survival rate for patients with advanced oral cancer (stages III and IV) treated using SSIACRT reached 70%,¹ which is better than that for surgically treated patients. Even if DM has occurred in many patients after SSIACRT, the complete response rate of the primary site was over 80%,¹¹ and a good survival rate has been obtained.

Prevention of DM is essential to further improve treatment outcomes. The DM rate with SSIACRT at our department is greater than 20%, prompting us to ask whether DM may be unintentionally promoted by SSIACRT.

The mechanism of invasion and metastasis of cancer cells within the body is believed to be a process whereby cells first detach from the primary lesion and infiltrate the surrounding tissue, disrupting it and invading blood vessels and lymph ducts. Cancer cells adhere to vascular endothelial cells of the target organ, where they escape from the vessel and engraft and regrow in the target organ.¹² While DM depends in part on the malignancy of the primary tumor, it follows from the foregoing that the longer the cancer-bearing condition, the greater the potential for DM. There is therefore an inescapable possibility that,

with cancers having the same characteristics, DM may occur more readily with radiotherapy, in which the cancer is present in the body for a longer time before its elimination, than with surgical treatment, in which the cancer is removed at an early stage. In the present study, a statistical analysis was therefore performed to determine whether the frequency of DM occurrence was greater with SSIACRT than with surgical treatment. SSIACRT was started at this department in 2003 so that there were more cases of surgical treatment of advanced cancer prior to 2003. This means that the post-treatment time was longer in cases with surgical treatment than with SSIACRT, and there were concerns that this may have increased the incidence of DM seen with surgical treatment. However, DM almost always occurs within 2 years, and there are practically no new cases of DM after 10 years, so it is probably safe to assume that there was no bias. Nonetheless, length of follow-up was included as a confounding factor.

On univariate analysis, N classification and treatment type showed significant correlations with the rate of DM occurrence. However, the choice of subjects may be biased because advanced oral cancer is generally treated using SSIACRT. In the present study, logistic regression analysis was used to adjust for this confounding factor. On multivariate analysis, there was no significant difference by therapy; rather, N classification was found to be a crucial factor affecting DM. Numerous reports have cited the presence of positive nodes as a risk factor for DM.^{13,14} Doweck et al also reported cervical lymph node metastasis as a risk factor in SSIACRT.⁹

The most probable reason for the high incidence of DM in the SSIACRT group was its inclusion of not only advanced cases of the T classification but also advanced cases of the N classification.

Next, factors affecting the survival rate were investigated. Simply comparing survival rates by treatment method would be meaningless because of differences in the stage of the cancers. Therefore, a multivariate analysis using a Cox proportional-hazards model was performed to clarify the factors affecting the survival rate. The results showed that degree of advancement of the tumor (T classification, N classification), presence or absence of DM, and age had a significant relationship with the survival rate, and treatment method had no relationship. This result also shows that prevention of DM is the most effective way to improve patients' prognosis.

Prior to this study comparing SSIACRT and conventional surgical treatment for the first time, no report had demonstrated that SSIACRT did not promote DM in oral cancer.

Whatever the treatment option, the most important factor in improving the prognosis for oral cancer is to resolve the problem of controlling DM. The systemic concentration of cisplatin, as reported by Robins et al in 1992,¹⁵ was very low in RADPLAT because cisplatin was neutralized by sodium thiosulfate, a neutralizing agent for cisplatin. On the other hand, because hematological toxicity as an adverse event was observed in most cases, and because nedaplatin was not neutralized in this study, the systemic concentration of anticancer agents was high.¹¹

However, adjuvant chemotherapy is not considered effective because DM sometimes occurs during SSIACRT. Generally, the standard treatment for DM is systemic chemotherapy. In our procedure of SSIACRT, the complete response rate of the primary site was over 80%, the treatment effect was believed to be sufficiently satisfactory, and the dose of the anticancer agent was considered appropriate.¹¹

When the target of treatment is a DM organ, the dosage of the anticancer drug may be low. Considering the severe oral mucositis that occurred in all cases in our regimen of chemotherapy, it would have been challenging to increase the dosage of the anticancer drug.

Several chemotherapy regimens have been tried as neoadjuvant chemotherapy for the prevention of DM, but an effective chemotherapy regimen has not yet been found.

There was no significant difference in survival rates between patients who underwent surgery after cisplatin and 5-fluorouracil (PF) chemotherapy and those who underwent surgery alone.¹⁶ An evaluation of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (TPF) followed by surgery and postoperative radiotherapy versus upfront surgery and postoperative radiotherapy demonstrated that there was no significant difference in the overall survival rate.¹⁷

5 | CONCLUSION

The results of the present study demonstrated that SSIACRT did not promote DM in oral cancer; instead, the high incidence of DM in the SSIACRT group was attributed to the inclusion of cases with advanced node involvement. The occurrence of DM is, therefore, neither attributable to nor a disadvantage of SSIACRT. We believe that SSIACRT should be recommended as an option for advanced oral cancer because of its higher survival rate and functional organ preservation.

CONFLICT OF INTEREST

The authors have no conflicts of interest directly relevant to the content of this article.

ORCID

Toshiaki Oyama  <https://orcid.org/0000-0001-7882-2686>

Wataru Kobayashi  <https://orcid.org/0000-0001-7255-6030>

REFERENCES

1. Kobayashi W, Kubota K, Ito R, Sakaki H, Nakagawa H, Teh BG. Can superselective intra-arterial chemoradiotherapy replace surgery followed by radiation for advanced cancer of the tongue and floor of the mouth? *J Oral Maxillofac Surg*. 2016;74:1248–54.
2. León X, Quer M, Orús C, del Prado Venegas M, López M. Distant metastases in head and neck cancer patients who achieved loco-regional control. *Head Neck*. 2000;22:680–6.
3. Kumagai A, Mikami T, Takeda Y, Sugiyama Y. Multiple distant organ metastases from squamous cell carcinoma of the lower gingiva that followed a rapid course: an autopsy case report. *Oral Sci Int*. 2018;15:68–72.

4. Lindberg R. Sites of first failure in head and neck cancer. *Cancer Treat Symp.* 1983;2:21–31.
5. Vikram B, Strong EW, Shah JP, Spiro R. Failure at distant sites following multimodality treatment for advanced head and neck cancer. *Head Neck Surg.* 1984;6:730–3.
6. Hong WK, Bromer RH, Amato DA, Shapshay S, Vincent M, Vaughan C, et al. Patterns of relapse in locally advanced head and neck cancer patients who achieved complete remission after combined modality therapy. *Cancer.* 1985;56:1242–5.
7. Bhatia R, Bahadur S. Distant metastasis in malignancies of the head and neck. *J Laryngol Otol.* 1987;101:925–8.
8. Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2001;51:571–8.
9. Doweck I, Robbins KT, Vieira F. Analysis of risk factors predictive of distant failure after targeted chemoradiation for advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2001;127:1315–8.
10. Kobayashi W, Teh BG, Narita N, Ito R, Saito Y, Furudate K, et al. Comparative study of superselective intra-arterial chemoradiotherapy versus radical surgery on distant metastasis for advanced oral cancer. *J Oral Oncol.* 2014;2014:7.
11. Kobayashi W, Teh BG, Sakaki H, Sato H, Kimura H, Kakehata S, et al. Superselective intra-arterial chemoradiotherapy with docetaxel-nedaplatin for advanced oral cancer. *Oral Oncol.* 2010;46:860–3.
12. Weinberg RA, Weinberg RA. *The biology of cancer.* New York: Garland Science, 2007.
13. Ellis ER, Mendenhall WM, Rao P, Parsons JT, Spangler AE, Million RR. Does node location affect the incidence of distant metastases in head and neck squamous cell carcinoma? *Int J Radiat Oncol* Biol* Phys.* 1989;17:293–7.
14. Alvi A, Johnson JT. Development of distant metastasis after treatment of advanced-stage head and neck cancer. *Head Neck.* 1997;19:500–5.
15. Robbins KT, Storniolo AM, Kerber C, Seagren S, Berson A, Howell SB, et al. Rapid superselective high-dose cisplatin infusion for advanced head and neck malignancies. *Head Neck.* 1992;14:364–71.
16. Licitra L, Grandi C, Guzzo M, Mariani L, Vullo SL, Valvo F, et al. Primary chemotherapy in resectable oral cavity squamous cell cancer: a randomized controlled trial. *J Clin Oncol.* 2003;21:327–33.
17. Zhong LP, Zhang CP, Ren GX, Guo W, William WN, Sun J, et al. Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. *J Clin Oncol.* 2013;31:744–51.

How to cite this article: Oyama T, Kobayashi W, Ito R, Tamura Y, Satake A, Fukuta H. Investigation of distant metastasis occurrence rates with different treatments: A comparison of superselective intra-arterial chemoradiotherapy and surgery. *Oral Sci Int.* 2021;18:56–61. <https://doi.org/10.1002/osi2.1080>