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ORIGINAL ARTICLE

Radiation with concomitant superselective intra-arterial cisplatin infusion for maxillary sinus squamous cell carcinoma

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Abstract

Purpose To assess the efficacy and prognostic factors after superselective intra-arterial chemoradiation (RADPLAT) for maxillary sinus squamous cell carcinoma (MS-SCC).

Materials and methods Prognostic significance of age, gender, T and N factors, gross tumor volume of the primary-site (GTV), total cisplatin dosage, and total cisplatin dosage per GTV (CDDP/GTV) for primary-site recurrence-free survival rate (PRFS) were analyzed. RADPLAT was administered to 27 patients. The median follow-up period was 42.1 months.

Results The 3-year rates of overall survival and PRFS were 59.2% and 53.9%, respectively. In univariate analysis, age, male, and total cisplatin dosage were significant factors for PRFS. In multivariate analysis, lymph node metastasis was significant factors for PRFS, and gender and total cisplatin dosage weakly influenced PRFS. In acute phase, no patient showed ≥ grade 3 hematologic toxicity, and grade 3 mucositis developed in 5 patients. Late toxicities were recognized in 3 patients (grade 2 phlegmon of the face, grade 3 maxillofacial osteonecrosis, and retinopathy). Twelve patients (44%) experienced recurrences. Of them, 8 patients showed recurrence at the primarysite.

Conclusion RADPLAT was effective for MS-SCC, with acceptable toxicity. Total cisplatin dosage is suggested to be important for primary tumor control.

Keywords RADPLAT · Maxillary sinus squamous cell carcinoma · Radiotherapy · Cisplatin per tumor volume · Prognostic factor

Introduction

Maxillary cancer is a rare disease representing only 3.3% of all head and neck cancers in Japan [1]. Most tumors are already advanced at the time of initial presentation, and these advanced cases require complete surgical resection, followed by radiotherapy sometimes with systemic chemotherapy [2, 3]. Although this results in significant facial deformity and impairment of facial function, the outcomes of survival and disease control in these maxillary cancer cases are bleak.

Intra-arterial targeted chemotherapy with concomitant radiotherapy has been reported as a promising treatment for patients with advanced maxillary sinus squamous cell carcinoma (MS-SCC) [4–8]. There are several different treatment methods using intra-arterial targeted chemotherapy techniques. Among them, radiation and concurrent superselective intra-arterial cisplatin infusion regimen (RADPLAT) has been reported to be effective for treating MS-SCC. However, in the original protocol comprising 4 courses of weekly administration of cisplatin, the rates of grade 4 and 5 toxicities at the experienced and inexperienced institutions were 14% and 0% vs. 47% and 4%, respectively [9]. Hence, when we introduced RADPLAT into clinical practice, superselective intra-arterial cisplatin was infused biweekly and 4 times during radiotherapy.

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Primary tumor control has a strong influence on disease prognosis for patients with MS-SCC because of slight lymph node metastasis or distant metastasis, even in advanced disease stages. Therefore, it is important to investigate the intensiveness of local treatment. In the current study, we assessed the efficacy of RADPLAT for patients with MS-SCC and analyzed the factors useful for primary tumor control.

Materials and methods

This study was approved by an institutional review board of our center (405–29,021) and was performed in accordance with the Declaration of Helsinki and the ethical guidelines for medical research concerning humans by the Ministry of Education, Culture, Sports, Science, and Technology, Japan [10]. All patients provided written informed consent for receiving RADPLAT treatment.

We conducted a retrospective chart review of patients with MS-SCC who were treated with RADPLAT between April 2008 and June 2016. The primary outcome of interest was primary-site recurrence-free survival rate (PRFS) for patients with MS-SCC and the prognostic factors of PRFS were analyzed. The secondary outcomes of interest were the overall survival rate (OS) and adverse events. The prognostic factors of OS were analyzed.

Superselective arterial cisplatin infusion

Cisplatin was infused biweekly 4 times and was administered on the day of initiation of radiaotherapy. A 3Fr guiding catheter and a 2Fr coaxial microcatheter were transcutaneously introduced through the femoral artery, and computed tomographic arteriography was used to accurately and carefully identify the feeding arteries in every treatment session. If the tumor was fed by the maxillary artery alone, cisplatin was administered through this artery. For tumors in which blood was supplied by 2 or 3 vessels (maxillary and facial or other artery), cisplatin was administered to each artery, according to the tumor perfusion. Embolization for arterial redistribution was not performed. Cisplatin was not administered to the metastatic lymph nodes. Immediately before and during cisplatin infusion, 10 g/body of sodium thiosulfate was intravenously dripped to neutralize cisplatin. In addition, 20 mL of 7% sodium bicarbonate solution was administered to reduce vessel damage by cisplatin.

Radiotherapy

All the patients received three-dimensional conformal radiotherapy. The patients were treated in the supine position using a thermo-plastic mask for immobilization. A slice thickness of 2.5 mm was selected for the planning computed tomography (CT). Gadolinium-enhanced magnetic resonance imaging (MRI) with a slice thickness of 3 mm was fused with the planning CT images to create reference images for delineation of the gross tumor volume (GTV) and clinical target volume (CTV). The median duration between MRI and treatment was 10 days (range, 3–20 days). ^{18}F-fluorodeoxyglucose positron emission tomography/CT was also referred if available. The CTV included the GTV with a 0.5cm margin and the ipsilateral maxilla, pterygopalatine fossa, and nasal cavity. The ethmoid sinus and orbital fossa were also included CTV depending on the extent of tumor spread. The planning target volume (PTV) for the CTV was defined as a 0.5cm margin around the CTV. The PTV was modified to meet the dose constraints for the normal tissues. The fields were shaped using multileaf collimators with 5 mm, and a modified 45-wedged pair technique was used, in which the beams were arranged at an adequate angle to reduce damage to normal tissues. Radiotherapy was delivered once a day, 5 times per week, using 2.0 Gy per fraction and an intended total dose of 60 Gy. After 40–50 Gy, the treatment volume was reduced to GTV. The maximum doses of spinal cord, optic nerves and chiasma w limited to less than 50 Gy. Dose constraints of eyeball, optic nerve and lense at involved site were not limited.

Evaluation

The initial response to treatment was evaluated between one and two months after treatment using computed tomography (CT) or magnetic resonance imaging (MRI) or both. Complete response (CR) was defined as the disappearance of all measurable or assessable lesions. Partial response (PR) was defined as $> 50\%$ decrease in the sum of the longest cross-sectional diameters of all measurable lesions. Stable disease (SD) was defined as $< 50\%$ reduction or $\leq 25\%$ increase in the sum of the longest cross-sectional diameters of all measurable lesions. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.0 [11].

Statistical analysis

PRFS was defined as primary-site recurrence or any death, and OS included death from any cause. The relationships between PRFS and the following factors were analyzed: age, gender, T and N factors, GTV, total dosage of cisplatin, and total dosage of cisplatin per GTV (CDDP/GTV).

Survival time was calculated from the beginning of treatment to any death and/or primary-site recurrence using the Kaplan–Meier method. Univariate and multivariate analyzes were performed using the Cox proportional-hazards model. The level of statistical significance was set at $p < 0.05$. All

statistical analyzes were conducted with EZR ver. 1.32 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [12].

Results

Patient characteristics

Patient characteristics are summarized in Table 1. A total of 27 participants, comprising 19 men and 8 women with a median age of 66 years (range 40–79 years) were included in the present study. All the patients were evaluated based on patient history, physical examination, and CT and/or MRI data. The body surface area (BSA) at beginning of the treatment was 1.15–2.04 m^2, and the median BSA was 1.58 m^2. The tumors were classified according to the 6th Edition of the Union for International Cancer Control (UICC) staging system.

Superselective arterial cisplatin infusion

The total cisplatin dosage was 305–730 mg, and the median dosage was 600 mg. The median total cisplatin dosage per BSA was 384.2 mg/m^2 (range 214.7–474.1 mg/m^2). Twenty-two patients were administered 100 mg/m^2 cisplatin, of which 20 patients were administered the same dose for all infusions, and 2 patients decreased cisplatin dosage at the fourth administration due to a decline in the creatinine clearance (< 40 mL/min). Five patients were administered 60–80 mg/m^2 cisplatin through all infusions because of advanced age (≥ 75 years).

Table 1 Patient Characteristics ($n = 27$)

Age, years (median)	40–79 (66)
Gender (male/female)	19/8
TNM classification	
T3N0M0	6 (22%)
T3N2bM0	3 (11%)
T4aN0M0	13 (48%)
T4aN1M0	1 (4%)
T4bN0M0	4 (15%)
GTV (mL, median)	41.3–152.6 (70.8)
T3 ($n = 9$)	41.3–114.7 (65.6)*
T4a ($n = 14$)	42.8–152.6 (61.9)*
T4b ($n = 4$)	71.0–97.3 (80.8)*

GTV gross tumor volume at primarysite

*$p = 0.43$ by Kruskal–Wallis test

Radiotherapy

Radiotherapy was administered using 4- or 6-megavolt X-rays. All patients completed radiotherapy with 60 Gy. The median overall treatment time for radiotherapy was 44 days (range 40–51 days). The overall treatment time prolonged in 3 patients. Of them, 2 patients extended 4 days and 1 patient did 5 days. Two patients resulted from grade 3 mucositis and one patient without toxicities temporally refused the treatment.

Treatment outcome

The median follow-up period was 42.1 months from the start of radiotherapy, and ranged between 3.3 and 109.8 months. The initial response at the primarysite was evaluated in all patients. The CR, PR, and SD w obtained for 9 (33%), 17 (63%), and 1 (4%) patients, respectively. Of these 27 patients, 10 patients (4 patients with CR and 6 without CR) underwent salvage surgery. Among them, 7 patients (2 patients in CR and 5 in PR) underwent surgery following RADPLAT, and residual tumor cells were pathologically recognized in 2 patients with PR. The other 3 patients received surgery when obvious recurrences were recognized.

Among 4 patients with regional lymph node involvement, 2 patients were treated with radiation and 2 underwent surgery. In the absence of clinical and radiologic evidence of cervical lymph node involvement, no prophylactic treatment was administered to the neck for any patient.

Overall survival and primary-site recurrence-free survival

Figure 1 shows PRFS rates, which at the 3- and 5-year rates were 53.9% and 49.8%, respectively. The 3- and 5-year rates of OS were 59.2% and 55.0%, respectively (Fig. 2). Univariate and multivariate analyss of PRF are summarized in Table 2 according to variables of interest. In univariate analysis, age, gender, and the total cisplatin dosage showed significant associations with PRFS. In multivariate analysis, N factor showed significant associations with PRFS, and gender and total cisplatin dosage were found to weakly influence PRFS. Univariate and multivariate analyss of OS are summarized in Table 3 according to variables of interest. In univariate analysis, age, gender, the total cisplatin dosage and CDDP/GTV showed significant associations with OS. In multivariate analysis, age, gender and N factor showed significant associations with OS.

Toxicity

Toxicities occurring within three months after RADPLAT were considered acute, and those occurring 3 months or

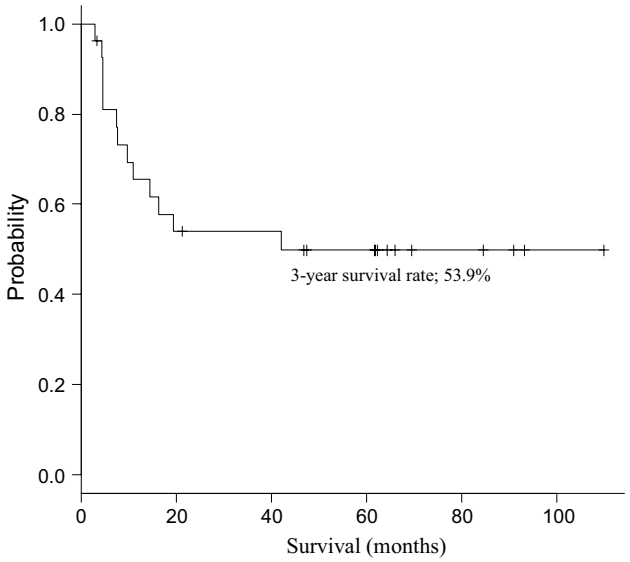

Fig. 1 Kaplan–Meier curves for primary-site recurrence-free survival

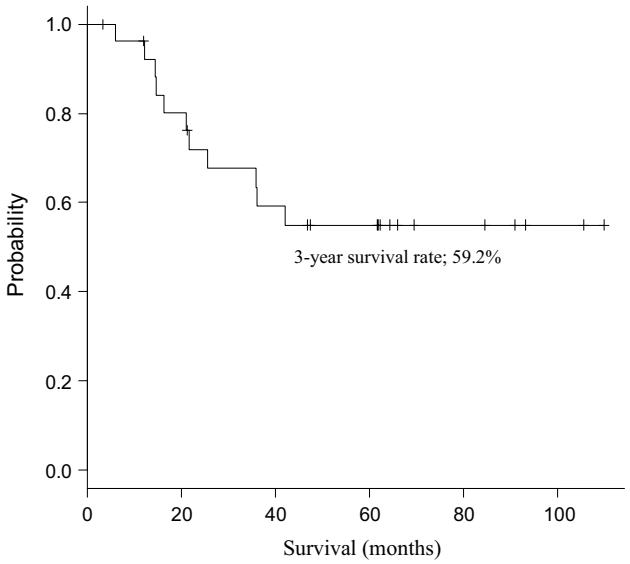

Fig. 2 Kaplan–Meier curves for overall survival

more after treatment were defined as late. In acute phase, no patient showed grade 3 or worse hematologic toxicity. Grade 1, 2, and 3 mucositis developed in 7, 15, and 5 patients, respectively. Of them, 22 patients showed no creatinine elevation and 5 patients showed slight elevation (grade 1). Three late toxicities were recognized as follows: grade 2 phlegmon of the face, grade 3 maxillary osteonecrosis, and retinopathy. Maxillary osteonecrosis occurred in the patient involving the maxilla. D1cc of the maxilla, which was the maximum dose delivered to 1 cm^3 of the organ was 66.8 Gy and D5cc of that was 59.4 Gy. Retinopathy occurred in the patient involving the orbital floor. D1cc and D5cc of eyeball were 64.7 Gy and 60.0 Gy, respectively.

Patterns of recurrence

Recurrences were recognized in 12 patients (44.4%) as follows: primary-site recurrence (P) in 8 patients; regional node (N) recurrence in 1 patient; distant metastasis (M) recurrence in 1 patient; N and M recurrence in 1 patient; and P, N, and M recurrence in 1 patient.

Discussion

In this study, we aimed to determine the efficacy and prognostic factors after RADPLAT for MS-SCC and found that N factor w significant for PRFS, and total cisplatin dosage weakly influenced PRFS. Dose-finding study (JCOG1212), in which 100 mg/m^2 of cisplatin was administered intra-arterially weekly with concomitant radiotherapy (70 Gy), was safe and welltolerated at 7 cycle of cisplatin [13]. Total cisplatin dosage of JCOG1212 is more than that of the current study. The patient who meets the inclusion criteria of JCOG1212 should be considered administration of 7 cycle of cisplatin. Because resistance to cisplatin can be circumvented through high concentration doses [14, 15], we hypothesized CDDP/GTV could predict the primary-site control. However, CDDP/GTV did not show prognostic significance. One of the possible reasons is that cisplatin distribution in the tumor was guessed to be inhomogeneous although cisplatin was administered according to the tumor perfusion using computed tomographic arteriography.

Homma et al. reported the efficacy of RADPLAT in 54 patients with MS-SCC and determined the 5-year OS rate and local progression-free survival rate as 65.8% and 67.9%, respectively, for all patients [8]. The disease outcomes found in the present study seem to be inferior to those found in the study by Homma et al. A factor that may have contributed to the difference in results is differing schedules of intra-arterial cisplatin infusion. Our RADPLAT regimen consisted of biweekly intra-arterial cisplatin infusions, while Homma et al. administered weekly treatments. The total radiation doses in our study were less than those in the study by Homma et al. (65–70 Gy). Finally, the median age of our patients was 7 years more than that of patients included in the study by Homma et al. This difference of age may strongly affect survival outcomes. In the present study, age was significant for PRFS and OS.

The results of the present study are comparable to those of studies in which the treatment consisted of surgery followed by radiation, which is considered to be the standard strategy for MS-SCC treatment. Ogawa et al. analyzed the treatment results of patients with MS-SCC who received

Table 2 Univariate and multivariate analysis of primary-site recurrence-free survival rate according to variables

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.08	1.01–1.17	0.03	1.06	0.94–1.21	0.34
Gender	0.30[a]	0.10–0.90	0.03	0.25[a]	0.06–1.10	0.07
T factor	1.01	0.22–4.57	0.99	1.01	0.08–12.73	0.99
N factor	2.35	0.64–8.60	0.20	23.18	2.43–221.00	0.006
GTV	1.01	0.99–1.03	0.56	1.04	0.98–1.11	0.19
CDDP	1.00	0.990–0.999	0.02	0.99	0.98–1.00	0.07
CDDP/GTV	0.87	0.72–1.05	0.15	1.22	0.67–2.20	0.52

HR hazard ratio, *CI* confidence interval, *T factor* comparison between T3/4a and T4b, *N factor* comparison between negative and positive, *GTV* gross tumor volume at primarysite, *CDDP* the total dosage of cisplatin

[a]Male is favorable

Table 3 Univariate and multivariate analysis of overall survival rate according to variables

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.13	1.04–1.24	0.006	1.43	1.06–1.93	0.02
Gender	0.18[a]	0.05–0.60	0.006	0.007[a]	0.0001–0.29	0.009
T factor	1.03	0.22–4.80	0.97	0.05	0.001–2.51	0.14
N factor	1.63	0.35–7.55	0.54	3.10e+04	33.37–2.88e+07	0.003
GTV	1.01	0.99–1.03	0.25	1.07	0.92–1.25	0.38
CDDP	0.99	0.989–0.999	0.01	1.00	0.97–1.03	0.97
CDDP/GTV	0.73	0.54–0.97	0.03	0.43	0.04–4.76	0.49

HR hazard ratio, *CI* confidence interval, *T factor* comparison between T3/4a and T4b, *N factor* comparison between negative and positive, *GTV* gross tumor volume at primarysite, *CDDP* the total dosage of cisplatin

[a]Male is favorable

postoperative radiotherapy following partial or total maxillectomy, and the 5-year OS rate was found to be 48% [2]. Bristol et al. reported that the 5-year OS rate of patients with MS-SCC who were treated surgically, followed by radiotherapy was 49% [3]. RADPLAT has the advantage that patients can avoid major surgery, which results in significant facial deformity and impairment of facial function.

A randomized phase III trial showed that cisplatin-based intra-arterial chemoradiation was not superior to intravenous chemoradiation for advanced stage IV head and neck cancer with regard to locoregional control and survival [16]. However, this trial targeted squamous cell carcinoma of the oropharynx, oral cavity, or hypopharynx, and did not include maxillary sinus carcinoma. Moreover, 58% of patients treated with intra-arterial chemoradiation received double-sided infusion with the same total dose of cisplatin. Unplanned subgroup analysis revealed a significantly higher local and locoregional control rate for the intra-arterial treatment group for large (> 30 mL) lateralized tumors. These findings suggest that intra-arterial chemoradiation plays a role in the treatment of large lateralized tumors amenable to unilateral infusion. Maxillary sinus cancer shares these features, viz., it is usually lateralized and is mostly fed by the internal maxillary artery.

The findings of this study show that there is still room for improvement of disease prognosis. It is important to intensify local therapy for further improvements in disease prognosis, because primary-site recurrence is the major failure pattern found in this study. Not only cisplatin but also radiation dose should be escalated. Intensity-modulated radiotherapy (IMRT) improves dose delivery to the tumor while sparing normal tissues, particularly critical organs such as the spinal cord, optic nerve, and eyeball. Postoperative IMRT for MS-SCC results in improved outcomes [17, 18]. IMRT can be used for MS-SCC to escalate radiation dose for the tumor and to decrease radiation dose for normal tissues, if necessary. Patients with lymph node involvement had worse outcomes compared to those without lymph node involvement, which agrees with the results of previous studies [19, 20]. Improving the prognosis of patients with lymph node metastasis is challenging. Surgical resection is considered the main therapy for regional lymph node metastasis. Postoperative (chemo-) radiotherapy is indicated for patients with extracapsular extension, closed margin, and multiple diseases. Elective nodal irradiation is not always applicable

for all patients with MS-SCC because of low incidence of nodal failure.

This study has several limitations. First, this study is a single-institution experience and the small sample size might be insufficient for the results to be conclusive. Second, adverse events could not be fully assessed and are likely to be underestimated because of the retrospective nature of the study. Furthermore, the optimal total cisplatin dosage was not determined because infusion frequency and cisplatin dosage less than previous studies.

In conclusion, RADPLAT comprising biweekly cisplatin infusion was effective for MS-SCC, with acceptable acute and late toxicity, and comparable to surgery followed by radiation. The total cisplatin dosage was suggested to be important to improve primary-site tumor control. Therefore, it is necessary to evaluate the efficacy of RADPLAT for MS-SCC by conducting prospective studies, some of which are currently ongoing in Japan (the efficacy confirmation phase of JCOG1212).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the present study were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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