Intra-arterial Versus Intravenous Chemoradiotherapy for Maxillary Sinus Squamous Cell Carcinoma

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Research Article

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Abstract

Background

The surgical treatment of maxillary sinus cancer may be declined by patients from a functional and cosmetic point of view. Treatment methods other than surgery include intra-arterial and intravenous chemoradiotherapy. The purpose of this study was to evaluate the utility of intra-arterial chemoradiotherapy (RADPLAT) compared with that of intravenous chemoradiotherapy for patients with squamous cell carcinoma of the maxillary sinus (MS-SCC).

Methods

We retrospectively reviewed the records of 22 patients with MS-SCC histologically confirmed from January 2008 to January 2021. The patients underwent RADPLAT or intravenous chemoradiotherapy. Cumulative survival was analyzed using the Kaplan-Meier method; we specifically analyzed overall survival (OS), progression-free survival (PFS), and locoregional recurrence-free survival (LRFS).

Results

One patient (5%) was diagnosed with T2 disease, 5 (23%) with T3 disease, and 16 (72%) with T4 disease. The median follow-up time was 29.5 months. Seventeen patients underwent RADPLAT, and 5 patients underwent intravenous chemoradiotherapy with Cisplatin (CDDP). Nine patients each experienced grade 3 toxicity during the two treatments. The 3-year OS, PFS, and LRFS rates of patients who underwent RADPLAT were 82%, 65%, and 77%, respectively. The 3-year OS, PFS, and LRFS rates of patients who underwent intravenous chemoradiotherapy with CDDP were 60%, 20%, and 20%, respectively. Only the LRFS rate was statistically significant (p=0.029).

Conclusions

This study suggests that RADPLAT is more useful than intravenous chemoradiotherapy in terms of local control in treating MS-SCC patients who refuse surgery.

Background

Malignant tumors of the nasal cavity and paranasal sinuses are uncommon, accounting for 3% of malignant tumors of the head and neck (1). The maxillary sinus is the area most commonly affected in paranasal sinus carcinoma (2). The 5-year overall survival (OS) rate for maxillary sinus squamous cell carcinoma (MS-SCC) is low, about 49% (3).

Owing to the complexity of its structure and the need for organ preservation, surgery for MS-SCC has several limitations (4). Most advanced cases require radical surgery with or without complete resection of the orbital contents; however, this results in significant disfigurement and impairment of function (5). Therefore, some patients refuse surgical treatment and opt for intra-arterial or intravenous radiotherapy.
Primary tumor control has a strong influence on disease prognosis in patients with MS-SCC, as it reduces the risk of lymph node metastasis or distant metastasis, even in advanced disease stages (6). Intra-arterial chemotherapy with concomitant radiotherapy is a promising treatment for patients with advanced MS-SCC (5), (7). Although comparisons of intra-arterial and intravenous radiotherapy in the field of head and neck cancer have been reported, we are aware of no such reports for MS-SCC (8).

In this retrospective study, we aimed to compare intra-arterial and intravenous chemoradiotherapy in patients with MS-SCC in terms of OS, progression-free survival (PFS), and local recurrence-free survival (LRFS).

**Methods**

**Patients**

This single-center, retrospective study was approved by our institutional review board, which waived the requirement for written informed consent owing to the retrospective nature of the study. Twenty-two patients who had been diagnosed with MS-SCC and received initial treatment at the Department of Otolaryngology, Head and Neck Surgery at Kagoshima University from 2008 through 2021 were included in this study. Patients were classified according to the 8th edition of the American Joint Committee on Cancer tumor node metastasis (TNM) staging system (9).

**Clinical Evaluation**

Tumor and lymph node staging was performed based on physical examination, computed tomography (CT), and magnetic resonance imaging (MRI). The exclusion criteria were prior chemotherapy or distant metastases.

**Intra-arterial Chemotherapy**

Cisplatin (CDDP, 100 mg/m$^2$) was infused once a week for seven weeks, starting on the first day of radiotherapy. A microcatheter was percutaneously inserted through the femoral artery and CT angiography was used to identify the feeding artery. For tumors supplied by multiple blood vessels, CDDP was administered to each artery depending on tumor perfusion. CDDP was not administered to the metastatic lymph nodes. During CDDP administration, 10 g/kg bodyweight of sodium thiosulfate was administered for systemic drug neutralization.

**Intravenous Chemotherapy**

CDDP were administered as intravenous chemotherapy. CDDP was administered intravenously every three weeks at 200 mg/m$^2$ for a maximum of three doses.
Radiotherapy

Treatment was planned with a CT simulator and a three-dimensional dose calculation computer. Radiotherapy consisted of 70 Gy delivered in 35 fractions once daily for seven weeks using intensity-modulated radiotherapy. The dose to the spinal cord was maintained below 40 Gy in all patients without lymph node metastases, and patients with regional lymph node metastasis of the neck were treated with 70 Gy of radiotherapy.

Evaluation

Posttreatment evaluation was performed using CT, MRI, and 18F-fluorodeoxyglucose positron-emission tomography/CT fusion imaging 8 to 12 weeks after the end of treatment or when clinical symptoms worsened. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events, Version 3.0 [10].

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using the chi-squared test or Fisher's exact test. The OS, PFS, and LRFS rates were calculated using the Kaplan-Meier method. The time to event was defined as the period from the date of confirmed diagnosis to that of the event, measured in months. Censoring was performed if the patients were alive at the follow-up cut-off date. OS was defined as the time from the date of initial diagnosis to the date of death. PFS was defined as the time from the start of treatment until the date of disease progression or death from any cause. LRFS was defined as the time from the start of treatment until the date of locoregional recurrence. If the tumor was never eradicated, the PFS and LRFS were zero. Kaplan-Meier and log-rank tests were performed to evaluate the OS, PFS, and LRFS rates. Values of $p < 0.05$ were considered statistically significant.

Results

Patient Characteristics

The patient characteristics are summarized in Table 1. Among the 22 patients, 18 were men and 4 were women, with a median age of 63.5 years (range, 37–79 years). One patient (5%) was diagnosed with T2 disease, 5 (23%) with T3 disease, and 16 (72%) with T4 disease. Nine patients (41%) were diagnosed with N0 disease, 3 (14%) with N1 disease, nine (41%) with N2 disease, and 1 (4%) with N3 disease. Seventeen (77%) patients underwent intra-arterial chemoradiotherapy (RADPLAT) and 5 (23%) underwent intravenous chemoradiotherapy. The median follow-up time was 29.5 months (range, 7–94 months).
Table 1
Patient characteristics (n = 22)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intra-arterial (n = 17)</th>
<th>Intravenous (n = 5)</th>
<th>p-value^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>63 (47–71)</td>
<td>58 (37–79)</td>
<td></td>
</tr>
<tr>
<td>Sex, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>4</td>
<td>0.904</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tumor depth^1), n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>0</td>
<td>1</td>
<td>0.168</td>
</tr>
<tr>
<td>T3</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>13</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lymph node metastasis^1), n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>7</td>
<td>2</td>
<td>0.232</td>
</tr>
<tr>
<td>N1</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TNM stage^1), n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>1</td>
<td>0.126</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>14</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

1) UICC 8th edition.

2) Chi-squared test or Fisher's exact test.

Toxicity

Acute toxicity was manageable in most patients (Table 2), and no patient died as a result of therapeutic toxicity. The most common toxicity was dermatitis, in 11/17 patients treated with RADPLAT and in 5/5 patients treated with intravenous chemoradiotherapy. Dermatitis was the most common grade 3 toxicity and was observed on the buccal skin. The second most common toxicity was mucositis. No difference was observed in the degree or occurrence of toxicity between RADPLAT and intravenous chemoradiotherapy.
### Table 2
**Number of patients by toxicity**

<table>
<thead>
<tr>
<th>Toxicity (Grade)</th>
<th>Intra-arterial (n = 17)</th>
<th>Intravenous (n = 5)</th>
<th>p-value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1 2 3 4</td>
<td>1</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6 1 3</td>
<td>3 1 1</td>
<td>0.829</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 1</td>
<td>1 0</td>
<td>0.576</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>5 6</td>
<td>1 3 1</td>
<td>0.245</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3 2</td>
<td>1 2</td>
<td>0.465</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2 5 2</td>
<td>1 2 2</td>
<td>0.772</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>2 2</td>
<td>0 2</td>
<td>0.221</td>
</tr>
<tr>
<td>Renal</td>
<td>4 3</td>
<td>2 1</td>
<td>0.778</td>
</tr>
</tbody>
</table>

1) Chi-square test or Fisher’s exact test.

All toxicities encountered during therapy were evaluated according to the Common Terminology Criteria for Adverse Events (version 3.0).

### Treatment

The median number of CDDP administrations in patients who underwent RADPLAT was 6 (range, 4–7). Intravenous chemotherapy was performed in 5 cases with CDDP. The average dose of radiotherapy was 69.2 Gy (range, 66–70 Gy). Intraorbital invasion was observed in 11/17 patients who underwent RADPLAT, but disappeared in all cases. Total maxillary resection was performed in 4 patients who requested surgery due to recurrence, but the eyeballs were preserved. Two patients had lymph node metastasis and underwent neck dissection. Recurrence of the primary tumor was observed in 4 out of 5 patients treated with intravenous chemotherapy, but in all cases the intraorbital tumor remained.

### Survival Analysis

The 3-year OS rate was 82% in patients who underwent RADPLAT, 60% in those who underwent intravenous chemoradiotherapy with CDDP (Fig. 1A); this was not significantly different (p = 0.195). The PFS rate was 65% in those who underwent RADPLAT and 20% in those who underwent intravenous chemoradiotherapy with CDDP (Fig. 1B), no significant difference (p = 0.085). The LRFS rate was 77% in those who underwent RADPLAT and 20% in those who underwent intravenous chemoradiotherapy CDDP (Fig. 1C), which were also significantly different (p = 0.029).
Discussion

In this study, we compared the therapeutic outcomes of RADPLAT and intravenous chemoradiotherapy in patients with MS-SCC. To the best of our knowledge, this is the first reported comparison of RADPLAT and intravenous chemoradiotherapy for the treatment of MS-SCC. We discovered that the survival rates in terms of LRFS were significantly higher in patients who underwent RADPLAT.

MS-SCC is a relatively rare neoplasm (1). MS-SCC is the most common pathological type of MS-SCC, and nearly 80% of MS-SCC are diagnosed at advanced stages because of the tumor location and the lack of early symptoms, resulting in poor local control and survival (11), (12). In this study, 73% (16/22) of patients had stage IV disease and 23% (5/22) had stage III disease. RADPLAT was performed in 77% (17/22) of the cases and was more commonly selected for more advanced than for less advanced cancer cases.

According to widely adopted guidelines, surgery followed by adjuvant chemoradiotherapy is highly recommended for resectable MS-SCC (T1-T4a) (13), (14). Although the treatment for MS-SCC is well developed, the relatively high local recurrence rate after treatment and the 5-year OS rate remain unsatisfactory (15), (16). Moreover, the functional and cosmetic results after surgical treatment of MS-SCC (particularly T4) are unsatisfactory from the patient's point of view (17). Therefore, some patients refuse surgical treatment and opt for radiotherapy (17). The patients in this study refused postoperative cosmetic procedures and eyeball removal, opting for radiotherapy. Radiotherapy is the first choice in such cases; however, the therapeutic effect should be optimized.

RADPLAT for head and neck cancer has yielded favorable results in many clinical trials with the development of advanced angiography technology that enables super-selective administration of drugs to tumor-feeding arteries (18). Although intra-arterial chemotherapy is sometimes considered dangerous owing to the risks of catheter-related problems and cerebrovascular accidents (19), in this study, there were no serious complications. In addition, similar to intravenous chemoradiotherapy, it is a relatively safe treatment with a similar frequency of occurrence of toxicity and complications of grade 3 or higher.

RADPLAT allows patients with advanced sinus cancer to improve survival and avoid surgery (20). In this study, the 3-year OS rate was 82% in patients who underwent RADPLAT and 60% in those who underwent intravenous chemoradiotherapy. We used CDDP, but RADPLAT with docetaxel and nedaplatin may also be used, as it previously yielded a very high 5-year OS rate (84.6%) (21). In contrast, in a study of 98 patients with MS-SCC, the 5-year OS rate was 40.6% for the 65 who underwent surgery and 26.5% for the 33 who underwent radiotherapy (22). These results suggest that RADPLAT may improve survival compared with surgical treatment. Furthermore, if the tumor spreads to the intraorbital fat or muscle tissue, eyeball enucleation must be performed, whereas RADPLAT is a treatment method that can be used to avoid eyeball enucleation (23). In this study, ocular preservation was possible in all cases in which RADPLAT was performed. This suggests that RADPLAT may have a therapeutic effect even in cases requiring eyeball enucleation.
Local control is important in the treatment of MS-SCC (24), and complete resection is of the essence in surgical treatment (25). In addition, if cervical lymph node metastasis occurs, the prognosis is poor (26). In this study, the PFS and LRFS rates were 65% and 77% for patients who underwent RADPLAT. Wang et al. reported a disease-free survival rate of 32.8% in the surgical group (19). Based on those results, RADPLAT may be more promising than surgical treatment for local control and metastasis.

This study had an important limitation. As it was a small, single-center, retrospective study, it was prone to various sources of bias, including selection bias. Consequently, a larger retrospective analysis and multi-institutional clinical trials are required for a more detailed analysis of this rare malignant tumor and its optimal treatment.

**Conclusions**

RADPLAT is expected to increase the local control rates of patients with MS-SCC.

**Abbreviations**

CDDP  
Cisplatin  
CT  
computed tomography  
LRFS  
locoregional recurrence-free survival  
MRI  
magnetic resonance imaging  
MS-SCC  
squamous cell carcinoma of the maxillary sinus  
OS  
overall survival  
PFS  
progression-free survival  
RADPLAT  
intra-arterial chemoradiotherapy  
TNM  
tumor node metastasis

**Declarations**

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.
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Contributions

Conceptualization, H.I.; Methodology, H.I., M.Y.; Formal Analysis, H.I., M.H.; Data Curation, H.I., S.T.; Writing—Original Draft Preparation, H.I., J.O.. All authors have read and agreed to the published version of the manuscript.

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Ethics approval and consent to participate

This study was approved by the Kagoshima University Hospital Medical Science Research Ethics Committee and was performed in accordance with the Declaration of Helsinki. The need for informed consent was waived by the Medical Science Research Ethics Committee of Kagoshima University Hospital, because of the retrospective design of the study.

Consent for publication

Not applicable.

Competing interests

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


Figures
Figure 1

A; Overall survival, B; Progression-free survival, C; Locoregional recurrence-free survival

There was no significant difference in overall survival and progression-free survival between intra-arterial chemoradiotherapy (RADPLAT) and intravenous chemoradiotherapy (CCRT). The locoregional recurrence-free survival rate was significantly higher in patients who underwent intra-arterial chemoradiotherapy (RADPLAT) (log-rank, p=0.029).