

Treatment outcome of maxillary sinus cancer

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Abstract

The standard treatment in the early stage of maxillary sinus cancer is surgical resection followed by postoperative radiation therapy. However, for locally advanced maxillary sinus cancer, a multimodality treatment approach is strongly recommended to improve the survival rate and quality of life of the patient. We determined the treatment outcomes of induction chemotherapy, concurrent chemoradiation therapy, and surgical resection for locally advanced maxillary sinus cancer. Forty-four patients with locally advanced maxillary sinus cancer, who had been treated between January 1990 and April 2008 at Kangnam St. Mary's Hospital, were retrospectively analyzed. The objective response rates were 70%, 53%, and 57% in the intra-arterial induction chemotherapy, intravenous induction chemotherapy, and concurrent chemoradiation therapy groups, respectively. The orbital preservation rates were 83%, 100%, and 75% in the intra-arterial induction chemotherapy, intravenous induction chemotherapy, and surgical resection groups, respectively. In seven of nine patients in whom the orbit could be preserved after induction chemotherapy, the primary tumors were removed completely. However, although the orbits were preserved in three patients who underwent surgical resection as a primary treatment, all three cases were confirmed to be incomplete resections. We found that active induction chemotherapy for locally advanced cancer of the maxillary sinus increased the possibility of complete resection with orbital preservation as well as tumor down-staging.

Introduction

Malignant tumors of the maxillary sinus are rare neoplasms that account for approximately

3% of head and neck cancers and 0.5% of all malignant diseases. The annual incidence of maxillary sinus cancer is 0.5-1.0 case per 100,000 of the population.¹ Squamous cell carcinoma is the most common histologic type, accounting for approximately 70-80% of the cancers. The other histologic types of maxillary sinus cancer include adenoid cystic carcinomas, adenocarcinomas, mucoepidermoid carcinomas, sarcomas, and lymphomas. Smoking and histories of chronic sinusitis are the most common risk factors for maxillary sinus cancer. In addition, occupational exposure to chemical substances, such as formaldehyde, chromium, nickel, and air pollution is associated with an increased risk for malignant tumors of the maxillary sinus.²

Most patients with maxillary sinus cancer have no symptoms in the early stage and, therefore, many of these patients are diagnosed in the advanced stage of the disease. The complexity of the anatomy and the proximity of the eyes, brain, and cranial nerves render complete surgical resection difficult, which leads to local recurrence, a major cause of treatment failure.³ The other issues pertaining to maxillary sinus cancer include the functional aspects of eyesight and the cosmetic aspects of facial contours, which make patients avoid surgical resection.

The standard treatment for maxillary sinus cancer has been surgical resection with or without orbital exenteration, followed by postoperative radiation therapy. However, in the advanced stages, tumor control and survival rate are still considered to be unsatisfactory, with a local control rate of 50-60% and a five-year disease-specific survival rate of 30-50%.^{3,4} Since the late 1970s, multimodality treatments have been investigated for the treatment of locally advanced maxillary sinus cancer, with the purpose of improvement in tumor control rate and reduction of functional impairment. Notably, induction chemotherapy (ICT) and concurrent chemoradiation therapy (CCRT) are the most common multimodality treatments for stages III and IV locally advanced maxillary sinus cancer. We investigated the treatment outcomes including orbital preservation, complete resection, pathologic down-staging, and relapse patterns in patients with locally advanced maxillary sinus cancer who underwent ICT, CCRT, and surgical resection.

Materials and Methods

Patients

Seventy-five patients who had been diagnosed with maxillary sinus cancer at Kangnam St. Mary's Hospital between 1 January 1990 and 30 April 2008 were reviewed. Among these patients, 10 received only palliative care owing

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to poor performance status, and seven patients with a history of prior surgery or chemotherapy were excluded. In addition, fourteen patients with malignant lymphomas or soft tissue sarcomas were excluded. Finally, 44 patients were analyzed and reviewed on the basis of their medical records, pathology slides and interpretation reports, and imaging studies. The following data were collected: age, gender, performance status, histopathologic diagnosis, tumor staging, orbital invasion, treatment modalities, recurrences, and survival rates.

A detailed assessment of the tumor extent was performed in all patients, based on CT scans and/or MRI including the maxillary sinus and skull base. The orbital invasion was determined on these findings: contact of the mass with the lamina papyracea, erosion or destruction of the medial and/or inferior orbital wall, and invasion of the periorbital soft tissue including the optic nerves and extraocular muscles. Tumor staging was done using the 2006 edition of the American Joint Committee on Cancer (AJCC) classification, and retrospective restaging was done in previously diagnosed patients. The performance status was evaluated according to Eastern Cooperative Oncology Group (ECOG) criteria.

Chemotherapy

One of four different treatment modalities, including intra-arterial (IA)-ICT, intravenous (IV)-ICT, CCRT, and surgical resection, was selected as a primary treatment based on the TNM stage, performance status, age, and comorbidity. ICT was administered through the IA or IV route. Superselective IA infusion of chemotherapeutic drugs was attempted via a

series of processes. The contrast-enhanced tumor mass and tumor feeding vessels were confirmed via diagnostic angiographic procedures of the internal and external carotid arteries by means of transfemoral access. The internal maxillary artery was superselected with a microcatheter, and then the chemotherapeutic drug was administered via a microcatheter into the tumor-supplying artery. The transfemoral catheter was removed on completion of the infusion. Cisplatin (100 mg/m²) was administered via a microcatheter into the internal maxillary artery over two hours on day 1, and then 5-FU (1000 mg/m²/day) was continuously infused from day 1 to day 5 over 120 hours through the IV route. A standard hydration and mannitol diuresis regimen were applied. The entire procedure was repeated 2-3 times every 3-4 weeks.

The IV-ICT was performed 2-3 times every four weeks as well. Cisplatin (100 mg/m²) was administered intravenously over two hours on day 1, and 5-FU (1000 mg/m²/day) was infused continuously from day 1 to day 5 over 120 hours through the IV route. All patients who received ICT were re-evaluated for tumor response with CT and/or MRI at least 4-6 weeks after the completion of ICT. The decision to perform surgery after ICT was based on the tumor response.

The chemotherapeutic agent used in the CCRT group was cisplatin. During radiation therapy, cisplatin (30 mg/m²) was administered by a weekly schedule on days 1, 8, 15, 22, 29, 36, 43, and 50, or cisplatin (100 mg/m²) was administered every 3 weeks on days 1, 22, and 43. All patients treated with CCRT were re-evaluated for tumor response, and then the next treatment modality, surgical resection or salvage chemotherapy, was determined. The periodic follow-up was done at least 6-8 weeks after the completion of radiation therapy.

Surgical resection and radiation therapy

In most cases, a total maxillectomy with orbital preservation was carried out. However, if the tumor mass extended to the lamina papyracea and invaded the orbit and muscles, an orbital exenteration with a total maxillectomy should be performed. The patients with metastatic cervical lymphadenopathy underwent a modified radical neck dissection. Three-dimensional conformal radiation therapy (3DCRT) was applied as an external radiation therapy technique. The total dose of 55-60 Gy with 1.8-2.0 Gy daily fractions five times per week was given to the clinical target volume (CTV) in postoperative adjuvant radiation therapy. In the case of CCRT, the total dose of 70-75 Gy in 35-40 fractions was given with a shrinking-field technique; 50 Gy was given to the CTV with daily fractions of 1.8 Gy five times per week, and followed by 20-25 Gy to the gross tumor volume (GTV).

Evaluation of treatment outcomes

The primary end point of our study was the response rate of the primary treatment modalities (IA-ICT, IV-ICT, and CCRT). For the evaluation of tumor response, a physical examination, nasal endoscopy, and CT or MRI were performed. Tumor response was assessed according to the RECIST criteria (version 1.0). An objective tumor response was defined as more than partial response (PR). When recurrence or distant metastasis was suspected, PET-CT and other imaging studies of suspicious lesions were performed and, if needed, confirmed by biopsy.

The secondary end points were the complete resection and orbital preservation rates in patients who underwent surgical resection after ICT and surgical resection as a primary treatment. Complete resection was defined as where there were no microscopic residual tumor cells on the resection margin, and incomplete resection was defined as where there were residual tumors on the resection margin, identified by gross and/or microscopic examination. Orbital preservation was defined as when a case underwent total maxillectomy without orbital exenteration, among the patients with the evidence of orbital invasion on physical examinations and/or imaging studies at the time of diagnosis.

The tertiary end points were overall survival, recurrence rate, and the toxicity profile. Overall survival was defined as from the date

of diagnosis to the date of death or date of last follow-up. The adverse events occurring during ICT and CCRT were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0).

Statistical analysis

For categorical outcomes, between-group comparisons were done using either the Fisher's exact test or a Chi-square test. The overall survival curve was estimated using the Kaplan-Meier method, and the log-rank test was applied to assess statistical significance. All statistical analyses were performed using the SPSS program (version 13.0) and a *p* value of <0.05 was considered as statistically significant.

Results

Patient characteristics

The clinical characteristics of the 44 patients are summarized in Table 1. The median age was 60 years (range 33-89 years) and 93% of patients were ECOG 0-1. The most common histopathologic subtype was squamous cell carcinoma (n=31; 70%). Of the 44 patients, 12 patients (27%) underwent surgical resection as a primary treatment, and among these patients there were six (50%) with stage III, five (42%) with stage IV, and one

Table 1. Patient characteristics.

Patient characteristics (n=44)	n (%)
Gender (male/female)	30(68)/14(32)
Median age (years, range)	60(33-89)
ECOG performance 0/1/2	17(39)/24(54)/3(7)
Histologic type	
Squamous cell carcinoma	31(70)
Adenoid cystic carcinoma	6(14)
Adenocarcinoma	4(9)
Myoepithelial carcinoma	1(2)
Undifferentiated carcinoma	2(5)
TNM stage II/III/IVa/IVb	1(2)/10(23)/10(23)/23(52)
Tstage T2/T3/T4a/T4b	1(2)/10(23)/10(23)/23(52)
Nstage N0/N1/N2	36(81)/5(11)/3(8)
Orbit invasion yes/ no	31(70)/13(30)
Treatment modalities	
[†] IA-ICT/ [‡] IV-ICT	10(23)/15(34)
[§] CCRT/Surgical resection	7(16)/12(27)

[†]IA-ICT: intra-arterial induction chemotherapy, [‡]IV-ICT: intravenous induction chemotherapy, [§]CCRT: concurrent chemoradiation therapy.

(8%) with stage II tumors. Eleven patients with stage III-IV tumors received postoperative adjuvant radiation therapy after surgical resection. Ten (23%), 15 (34%), and 7 (16%) patients received IA-ICT, IV-ICT, and CCRT, respectively. Of the 25 patients who received ICT, there were 21 (84%) with stage IV and 3 (16%) with stage III tumors. All patients treated with CCRT were stage IV. The median duration of follow-up was 16 months.

Tumor response and toxicity

The objective response rates of ICT and CCRT were 60% and 57%, respectively ($p=0.521$). The objective response rates of IA-ICT and IV-ICT were 70% and 53%, respectively ($p=0.311$) (Table 2). In the 10 patients who received IA-ICT, no complete response (CR) was achieved, seven patients (70%) had a PR, one patient had stable disease (SD), and one patient had progressive disease (PD). The intended chemotherapy was interrupted in one patient because of acute, severe toxicity. In the 15 patients treated with IV-ICT, two (13%) had a CR, six (40%) had a PR, three (20%) had SD, and three (20%) had PD. One patient was lost to follow-up. The most common acute toxicity associated with these treatment modalities was nausea and vomiting. The frequency of nausea and vomiting in the IA-ICT, IV-ICT, and CCRT groups was 70%, 87%, and 86%, respectively ($p=0.927$). The patients treated with IA-ICT experienced other adverse events: three patients had facial swelling, three had periorbital pain, one had severe mucositis, and one had transient dizziness.

Orbital preservation and complete resection rate

Seven (70%) of 10 patients in the IA-ICT group and seven (47%) of 15 patients in the IV-ICT group underwent surgical resection with curative intent. Of these patients, those in whom orbital invasion had been confirmed by imaging studies at diagnosis were six and four patients in the IA-ICT and IV-ICT groups, respectively. Orbital preservation was possible in five (83%) of six patients treated with IA-ICT and in all four (100%) patients treated with IV-ICT. On the other hand, orbital invasion was doubtful in four of 12 patients who underwent surgical resection as a primary treatment, and orbital preservation was possible in three (75%) of four patients. Therefore, there were no statistically significant differences in the orbital preservation rates between the ICT and surgical resection groups ($p=0.505$). Seven (78%) of nine patients with orbital preservation in the ICT group had complete resections. However, all three patients with orbital preservation in the primary surgical resection group had incomplete resections. Therefore, a higher complete resection rate

Table 2. Tumor response according to treatment modalities.

Treatment modalities	Tumor response			<i>p</i>
	¹ CR(n)	² PR(n)	³ ORR(%)	
Induction chemotherapy			60	0.521
IA-ICT	0	7	70	0.311
IV-ICT	2	6	53	
CCRT	1	3	57	

¹CR: complete response, ²PR: partial response, ³ORR: overall response rate.

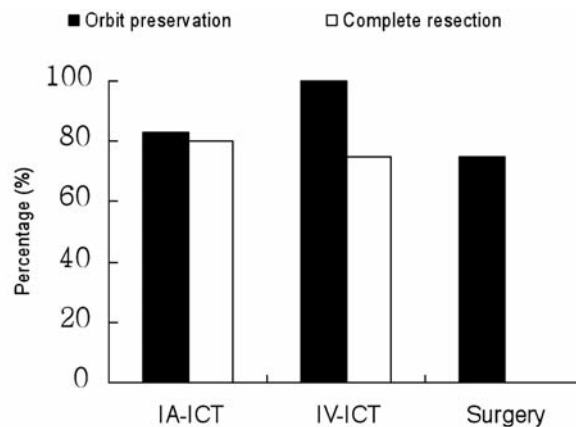


Figure 1. Orbital preservation and complete resection rate according to treatment modalities. IA-ICT: intra-arterial induction chemotherapy, IV-ICT: intravenous induction chemotherapy.

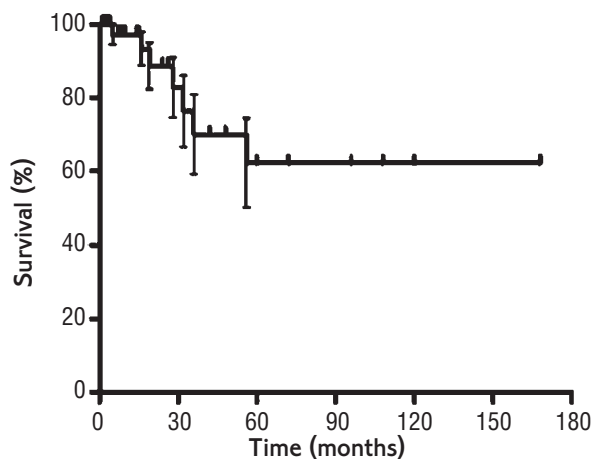


Figure 2. Overall survival curve of 44 patients with maxillary sinus malignancies by the Kaplan-Meier method.

was achieved in the patients who underwent surgical resection after ICT (Figure 1).

Pathologic down-staging by ICT

Of the 14 patients who underwent ICT followed by surgical resection, the 10 patients with T4 tumors were available for pathologic tumor response. Nine (90%) of 10 patients were shown to have pathologic down-staging of the primary tumor after ICT. Among the 10 patients with clinical T4, five had pT3, three had pT1, and one had a pathologic CR (pT0). All cases with remarkable down-staging to pT1 and pT0 were observed in the IA-ICT group.

Overall survival and recurrence rate

The overall survival curve of the 44 patients is shown in Figure 2. The overall survival rate for these 44 patients was 60% at three years and 53% at five years.

The three-year survival rate was 57% and 50% in the IA-ICT and IV-ICT group, respectively ($p=0.665$). The most common cause of death was disease progression. Two of 10 patients in the IA-ICT group died; one patient owing to disease progression and the other patient because of infectious disease after relapse with lung metastasis. Five of 15 patients in the IV-ICT group died; three as a result of disease

progression and two owing to infectious disease accompanied by disease progression. Of the 12 patients in the surgical resection group, eight were still alive without recurrence for more than two years, but three of four patients with recurrences died of disease progression and one person was lost to follow-up.

The recurrence patterns were as follows: in seven patients who received IA-ICT followed by surgical resection, no local recurrences were identified except for one pulmonary metastasis. In nine patients who received IV-ICT followed by surgical resection, three local recurrences and two distant metastases were detected during the follow-up period. Hence, the recurrence rates were 17% and 56% in the IA-ICT and IV-ICT group, respectively. In the surgical resection group, local recurrences occurred in four (33%) of 12 patients.

In the ICT group, two patients with a positive resection margin died of local recurrence within two years. In contrast, one of seven patients with a tumor-free resection margin died of local recurrence, and the six remaining patients with squamous cell carcinoma had long-term disease-free survival. In the surgical resection group, one of three patients with a positive resection margin died of a local recurrence, and the remaining two patients with adenoid cystic carcinoma are alive still. Most recurrences occurred within the first two years after surgical resection or complete clinical response to ICT, and those who had no recurrences within the first two years had a long-term survival of more than five years.

Discussion

The prognosis of maxillary sinus cancer is disappointing, despite aggressive treatments. For successful treatment outcomes, it is necessary to acquire complete surgical resection and to secure adequate resection margins.

However, maxillary sinus cancers usually are diagnosed at advanced stages, and the proximity of important organs such as the eyes and cranial nerves makes complete surgical resection difficult. In addition, functional impairments after surgical resection are the major cause of a decreased quality of life. Therefore, surgical resection with a curative intent should be considered as a primary treatment only in the early stages of the disease. In the advanced stages, multimodality treatment strategies should be arranged for prolongation of survival and improvement in the quality of life.

CCRT is regarded as the more effective treatment because of the radiosensitizing efficacy of cisplatin compared with radiation therapy alone. Several studies have demonstrated that CCRT has a higher tumor control rate and survival rate in head and neck cancers than

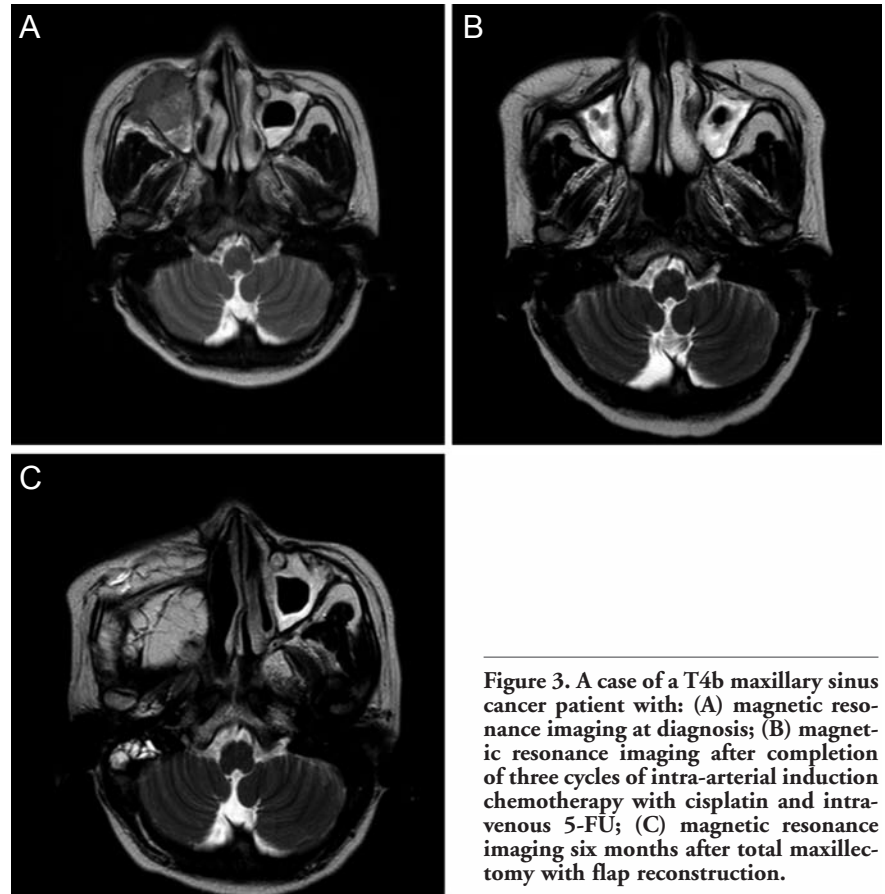


Figure 3. A case of a T4b maxillary sinus cancer patient with: (A) magnetic resonance imaging at diagnosis; (B) magnetic resonance imaging after completion of three cycles of intra-arterial induction chemotherapy with cisplatin and intravenous 5-FU; (C) magnetic resonance imaging six months after total maxillectomy with flap reconstruction.

radiation therapy alone.⁵ Harrison *et al.* reported a three-year local control rate of 78% and a three-year survival rate of 42% in 12 patients with paranasal sinus carcinomas treated with cisplatin-based CCRT.⁶ In this study, seven patients with stage IV maxillary sinus cancer received CCRT as a primary treatment, and the objective response rate was 57%. However, the assessments of recurrence and survival rate were impossible because of small sample size and loss to follow-up.

The most commonly used ICT in locally advanced head and neck cancer is IV cisplatin combined with a 5-FU continuous infusion. In several studies, ICT produced an objective response rate of 60-90% with a clinical CR of 20-50%.⁵ However, the antitumor efficacy of ICT did not lead to a prolongation in overall survival in every case.

To improve the antitumor efficacy, the addition of potent cytotoxic drugs such as docetaxel to a standard chemotherapy regimen or development of new drug delivery methods has been investigated actively. As one of the drug delivery methods, a superselective IA infusion of chemotherapeutic drugs has been proposed as an ICT in locally advanced head and neck cancers. Direct infusion of chemotherapeutic drugs to the feeding vessels exposed a high concentration of drug to the tumor cells; there-

fore, more potent antitumor efficacy with lower systemic toxicity was expected.⁷ IA chemotherapy may be more effective when it is administered as an initial treatment. Because prior surgery or radiation impairs the blood supply to the tumor bed, it makes local delivery of chemotherapeutic drugs difficult. Although the majority of head and neck cancers are diagnosed at advanced stages of the disease, distant metastases are rarely detected at the time of presentation. Moreover, maxillary sinus cancers are confined to the territory of the terminal branch of the internal maxillary artery; therefore, they are suitable for the local infusion of chemotherapeutic drugs.^{8,9}

Robbins *et al.* reported a higher objective response rate of 92%, with a CR of 88% in 76 patients with head and neck cancers treated with IA cisplatin and concomitant radiation therapy.¹⁰ In another study, a five-year survival rate of 53% was reported, with a local recurrence rate of 15% in 19 patients with locally advanced paranasal sinus cancers who underwent surgical resection after IA chemotherapy combined with concomitant radiation therapy. Orbital preservation was possible in three of four patients with orbital invasion.⁴ Lee *et al.* presented their clinical experiences with superselective IA cisplatin combined with IV 5-FU in advanced paranasal sinus cancers.¹¹

Forty-three percent of 21 evaluated patients had a CR and 48% of the patients had a PR, with an objective response rate of 91%. In our study, either IA-ICT or IV-ICT was performed as an ICT. The objective response rate in the IA-ICT group was 70%, which was similar to previous results, and the objective response rate in the IV-ICT group was 53%. There were no statistically significant differences in the response rate and toxicities between the two groups.

The orbital preservation rates in the patients with paranasal sinus tumors, who received the ICT followed by surgical resection or CCRT, have been reported to be approximately 50-70%.^{12,13} In this study, orbital preservation was possible in five of six patients in the IA-ICT group and all four patients in the IV-ICT group. Although orbital preservation was possible in three of four patients who underwent surgical resection as a primary treatment, incomplete resection with a positive resection margin was finally ascertained in these three patients. On the other hand, in nine patients who underwent ICT followed by surgical resection with orbit preservation, incomplete resection was confirmed in only two patients. Most of the patients with a positive resection margin experienced a local recurrence during the follow-up, which led to a disease progression and then death.

A case of a patient with locally advanced maxillary sinus cancer is shown in Figure 3. This patient was diagnosed with T4b maxillary sinus cancer with orbital invasion in May 2007. She received three cycles of IA-ICT with cisplatin and IV 5-FU, and then underwent total maxillectomy with orbital preservation and flap reconstruction. On the pathologic reports, the tumor was removed nearly completely but close to a margin. She received postoperative radiation therapy. She has remained disease free to date.

Several studies have demonstrated that a pathologic CR has a closer relationship than a clinical CR with survival.¹⁴ In the current study, the pathologic down-staging of the primary tumor in the patients treated with ICT followed by surgical resection was evaluated. In 10 cases of T4 tumors, pathologic down-staging after the ICT was identified in nine cases with one pathologic CR. In addition, IA-ICT was more effective with respect to pathologic tumor down-staging compared with IV-ICT. It is thought that the first-passage effect and exposure to higher local concentrations during IA cisplatin have a major role in effective down-staging.^{15,16} There were no statistically significant differences in survival rate between the

IA-ICT and IV-ICT groups. However, the local recurrence rate was lower in the IA-ICT group than in the IV-ICT group.

The limitation of this study is that it is a retrospective, relatively small sample size evaluation. Additionally, a discrepancy in clinical characteristics between groups existed. Patients diagnosed with a more advanced staged tumor or orbital invasions were more likely to receive ICT than surgery; therefore, comparing survival according to treatment modalities was difficult. However, clinical characteristics between the IA-ICT and IV-ICT groups were comparable and the comparison of these two groups may bear significance.

Conclusion

From our study we conclude that ICT in locally advanced maxillary sinus cancers increased the possibility of tumor down-staging and complete resection with orbital preservation. Although there were no significant differences in response rate and toxicity profile between the two groups of ICT, IA-ICT was superior to IV-ICT with respect to tumor down-staging and local tumor control. In the future, a large-sized, prospective randomized study to compare ICT followed by surgical resection with surgical resection alone is warranted clinically as a primary treatment for locally advanced maxillary sinus cancers.

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