

Maxillary Sinus Squamous Cell Carcinoma: A Clinical Study

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Abstract

We retrospectively analyzed the clinical characteristics and treatment outcomes of patients with maxillary sinus squamous cell carcinoma. The patients were 22 newly diagnosed cases of maxillary sinus squamous cell carcinoma who were treated at our institute between 2005 and 2016. There were 19 males and 3 females, ranging in age from 45 to 83 years (average age: 64.2 years). Our treatment protocol was as follows: All patients received chemoradiotherapy with weekly superselective intra-arterial administration of cisplatin (radiotherapy and concomitant intra-arterial cisplatin [RADPLAT]; 100–120 mg/body). Good responders at 30 to 40 Gy received additional radiotherapy (RADPLAT, ordinary chemoradiotherapy, or radiotherapy alone) until the total dose reached 72 Gy, whereas the other patients underwent radical surgery (partial maxillectomy, total maxillectomy, or extended total maxillectomy). The latter patients were given postoperative (chemo)radiotherapy up to a total dose of 72 Gy, when histopathological examination revealed insufficient resection or a positive surgical margin. The overall 5-year crude and disease-specific survival rates determined by the Kaplan–Meier method were 47.8 and 56.9%, respectively. The crude survival rate tended to be higher in T3 patients than in T4 patients (80.0 vs. 29.9%, $p = 0.077$). Seven patients died of the primary disease. The cause of death was distant metastasis in four patients, recurrence of the primary lesion in two patients, and cervical lymph node metastasis in one patient. These results suggest the importance of early detection and early treatment, and of the development of more effective treatment for advanced maxillary cancers, to further improve the survival rate.

Keywords

- ▶ maxillary sinus squamous cell carcinoma
- ▶ treatment outcome
- ▶ survival rate
- ▶ superselective intra-arterial chemoradiotherapy

Introduction

The paranasal cavity is anatomically situated in proximity to the esthetically important organs, such as visual organs and the face. Malignant tumors that develop in the paranasal cavity are often difficult to treat; it is also challenging to ensure an adequate safety margin while performing surgery. Other factors complicating treatment include the facts that (1) subjective symptoms are negligible in the early stage, (2) the disease highly advances in several patients even before a diagnosis is made, and (3) various histopathological types are presented. Generally, multi-

modal treatment combines surgery, radiotherapy, and (intra-arterial) chemotherapy. Moreover, newly developed chemotherapies, including molecular-targeting drugs and advancements in radiotherapy such as proton beam, baryon beam, and intensity-modulated radiotherapy (IMRT), have recently been reported. However, compared with oral, pharyngeal, and laryngeal cancers, few patients present with paranasal cavity cancer, and it is difficult to say that the treatment method is established. Here, we examined and reported the clinical characteristics and treatment outcomes of maxillary sinus squamous cell carcinoma observed in inpatients at our hospital.

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Materials and Methods

The study included 22 (males, 19; females, 3; age, 45–83 years [mean age, 64.2 years]) patients diagnosed with and treated for maxillary sinus squamous cell carcinoma at the Department of Otorhinolaryngology and Head and Neck Surgery, University of Occupational and Environmental Health School of Medicine during the 11-year period between January 2005 and 2016. Patients with recurrence and a treatment history at any other institution were excluded. The mean observation period was 34.3 months.

Disease stage was determined based on the Union for International Cancer Control tumor node metastasis (UICC TNM) classification (7th ed.), and treatment outcomes were evaluated according to overall and disease-specific survival. The Kaplan–Meier method was used to analyze the survival rate, and significant differences in survival rate were verified using log-rank test. $p < 0.05$ was considered statistically significant, and $p < 0.1$ was considered a trend.

The basic policy for treating primary lesions followed by our department during the study period is presented in ►Fig. 1. First, preoperative superselective intra-arterial chemotherapy (radiotherapy and concomitant intra-arterial cisplatin [RADPLAT]) was administered. Intra-arterial infusion was administered in accordance with the Seldinger method, whereby a catheter was inserted via the right femoral artery and tumor-feeding vessels, such as the maxillary and facial arteries, were identified. Thereafter, cisplatin (CDDP) was administered via a microtube inserted into these blood vessels at a dose of 100 to 120 mg/body surface area (m^2) per week, total two to four times (mean doses, three). Radiation was given via the simple fractionated irradiation technique (2.0 Gy/fraction, 1 fraction/day), and when doses of 30 to 40 Gy were received, the primary lesion was evaluated according to the response evaluation criteria in solid tumors. In patients exhibiting good response in this interim evaluation (complete response [CR]:

Table 1 Number of patients according to each TN stage

T/N	N0	N1	N2	N3	Total
T1	0	0	0	0	0
T2	0	0	0	0	0
T3	4	0	2	0	6
T4	11 (1 ^a)	3	2	0	16
Total	15	3	4	0	22

^aPatients with distal metastasis are shown in parentheses.

disappearance or good partial response [good PR]: cicatrization) and in those unable to or refusing to undergo surgery, treatment was continued by either RADPLAT, chemoradiotherapy (CRT), or radiotherapy alone (RT) until 72 Gy. Among patients exhibiting other responses (PR:tumor reduction/stable disease [SD]:unchanged/progressive disease [PD]:exacerbation) and those who were able to undergo surgery, radical surgery by partial maxillectomy, total maxillectomy, or extended maxillectomy (\pm extensive skull base tumorectomy and reconstruction) was selected in accordance with the extent of progression of the primary lesion. Following surgery, based on the histopathology of the surgical specimen, CRT or RT was administered until a total dose of 72 Gy was reached.

Results

Patients' Clinical Characteristics and Treatment Outcomes

Clinical Staging

The number of patients chosen for each T and N classification is listed in ►Table 1. No patients exhibited T1 or T2 disease, 6 (21.4%) exhibited T3 disease, and 16 (72.7%) exhibited T4 disease. The staging classification was stage III in 4 patients

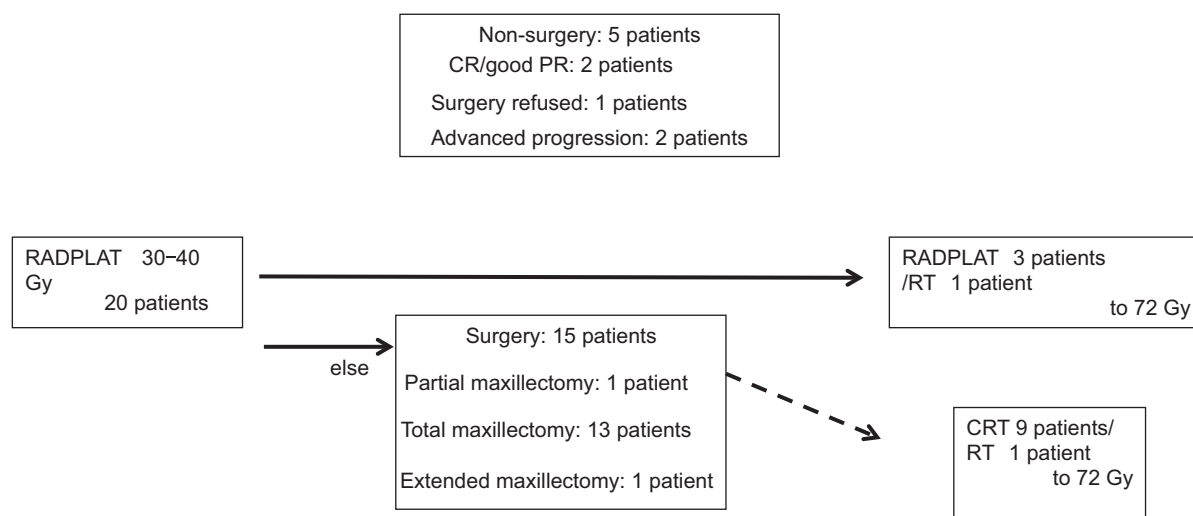


Fig. 1 Basic treatment policy for primary lesions of maxillary sinus squamous cell carcinoma followed at our department. RADPLAT, radiotherapy and concomitant intra-arterial cisplatin; RT, radiotherapy alone; CRT, chemoradiotherapy; Surgery, partial maxillectomy, total maxillectomy, and extended maxillectomy (\pm extensive skull base tumorectomy and reconstruction); CR, complete response and disappearance; good PR, good partial response and cicatrization.

and stage IV in 18 (IVA, 15 patients; IVB, 2 patients; and IVC, 1 patient), thus indicating that all patients were in the advanced disease stage.

First-Line Treatment

As the first-line treatment, RADPLAT was performed in 20 patients (90.9%), CRT in one patient who received concurrent treatment for hypopharyngeal cancer, and partial maxillectomy in one patient considering the general condition.

Among the 20 patients who received RADPLAT, radical surgery was performed in 15 (T3, 4 patients; T4, 11 patients; 70%). Surgery included total maxillectomy in 13 patients (65.0%), partial maxillectomy in 1 (5.0%), and extended total maxillectomy + extensive skull base tumorectomy and reconstruction in 1 (5.0%). Nonsurgery patients included two patients with CR/good PR on the interim evaluation, one (5.0%) who refused surgery, and two (10.0%) with highly advanced disease who were judged unable to undergo surgery (one patient with clivus invasion and another with invasion into the orbital apex).

Treatment Outcomes

Overall survival and disease-specific survival curves of maxillary sinus squamous cell carcinoma are presented in ►Fig. 2. For all patients, the 5-year overall survival rate was 47.8%, whereas the 5-year disease-specific survival rate was 56.9%. The overall survival and disease-specific survival curves according to T classification are presented in ►Figs. 3 and 4. The 5-year overall survival rate was 80.0% in T3 patients; however, this rate was significantly lower in T4 patients (29.9%; $p = 0.077$). The 5-year disease-specific survival rate was 80.0% in T3 patients and was lower at 42.3% in T4 patients; however, the difference observed was not significant ($p = 0.133$).

In the 20 patients who received RADPLAT, the 5-year overall survival rate was 47.9%, whereas the 5-year disease-

specific survival rate was 59.8%. Among the 15 patients who received RADPLAT and radical surgery, the 5-year overall survival rate was 59.4%, whereas the 5-year disease-specific survival rate was 71.8%.

During initial examination, seven patients had N+ disease. In the N- group, the 5-year overall survival rate was 53.2% and the 5-year disease-specific survival rate was 63.3%. In the N+ group, the 5-year overall survival rate and disease-specific survival rate were lower at 33.3%; however, the difference observed was not significant (overall survival rate, $p = 0.472$; disease-specific survival rate, $p = 0.397$).

Outcomes

Of the 22 patients, 9 patients died (7 cancer-specific deaths and 2 due to other causes). The cancer-specific deaths included T-related death in two patients, N-related death in one, and M-related death in four.

Discussion

The incidence of primary malignancy of the nasal and paranasal cavity is relatively rare, affecting 0.5 to 1.0 per 100,000 individuals; further, primary malignancy of the nasal and paranasal cavity is said to account for approximately 0.5% of all malignancies and 3% of head and neck cancers.¹ The incidence of maxillary sinus carcinoma is also low. Furthermore, while there is no clearly established evidence owing to very few prospective clinical treatment trials conducted worldwide, surgery-based treatment is recognized as the standard treatment in Europe and the United States. Surgery (total maxillectomy and extended total maxillectomy) is considered the standard treatment when resection is possible, and many patients receive postoperative radiotherapy. For overseas, patients in whom resection and surgery are not possible, CRT is generally administered.²

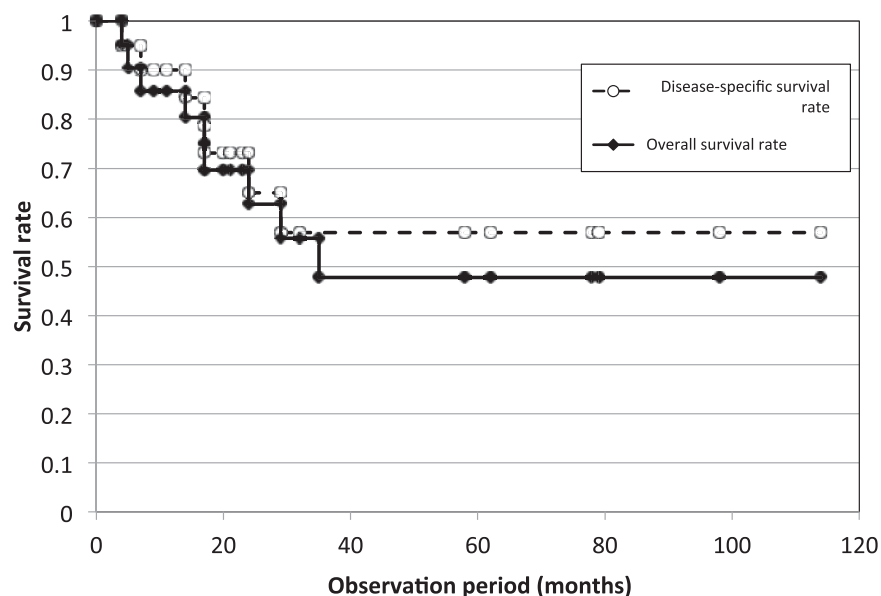


Fig. 2 Overall survival and disease-specific survival for maxillary sinus squamous cell carcinoma. The 5-year overall survival was 47.8%, whereas the 5-year disease-specific survival was 56.9%.

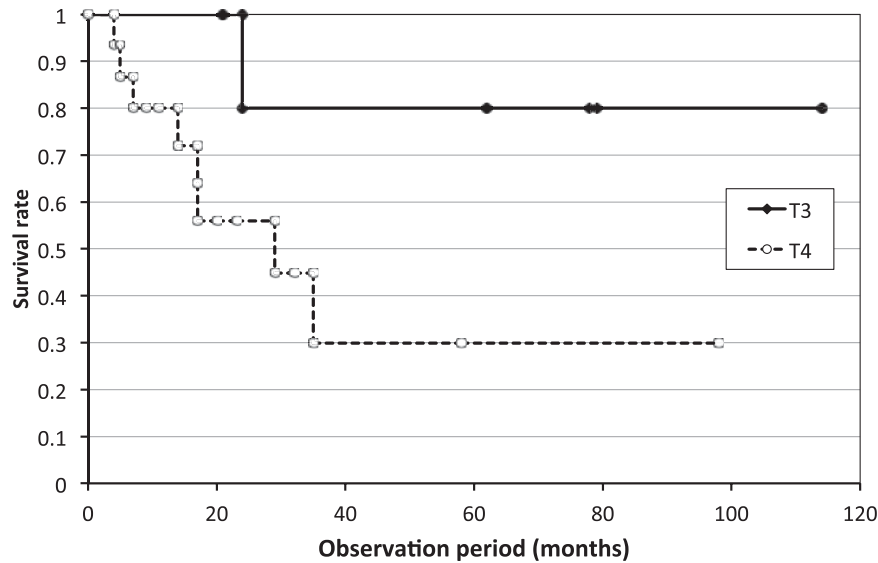


Fig. 3 Overall survival rate according to T-staging of maxillary sinus squamous cell carcinoma. The 5-year overall survival was 80.0% in T3 patients and 29.9% in T4 patients ($p = 0.077$).

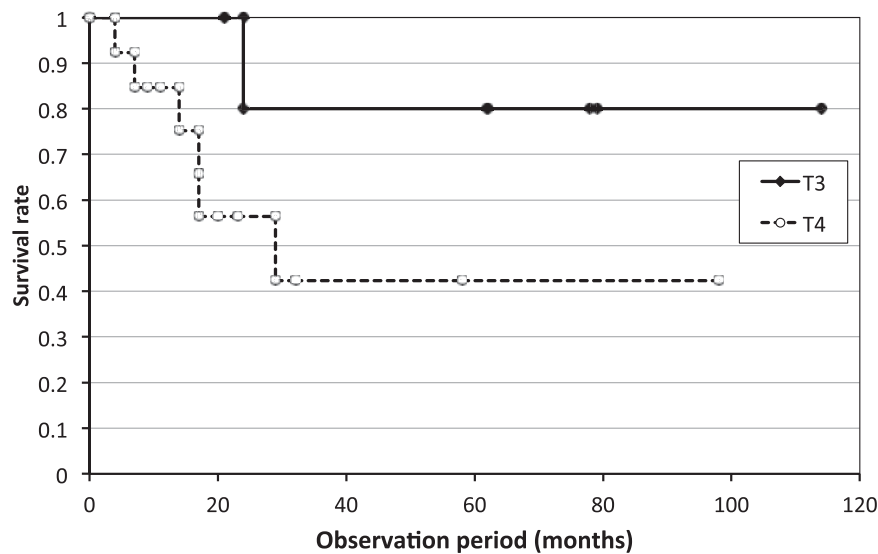


Fig. 4 Disease-specific survival rate according to T-staging of maxillary sinus squamous cell carcinoma. The 5-year overall survival was 80.0% in T3 patients and 42.3% in T4 patients ($p = 0.133$).

At our department, the 5-year overall survival rate was 47.8% and the disease-specific survival rate was 56.9% for all patients with maxillary sinus squamous cell carcinoma. Several Japanese studies reported the 5-year survival rate to be 44.0 to 57.0%,³⁻⁵ and our results corroborated with those reported in these studies.

The histopathological types of nasal and paranasal cavity malignancies are more varied compared with those of laryngeal and pharyngeal malignancies; however, most instances are of squamous cell carcinoma. This is attributable to the fact that the mucosa of the nasal and paranasal cavities consists of ciliated pseudostratified columnar epithelium, which develops into squamous epithelium where cancer develops.⁶ Squamous cell carcinoma responds relatively well to CRT; therefore, multimodal treatment is administered.

Regarding the degree of progression of the primary lesion in maxillary sinus carcinoma, several studies reported to date indicate that T3 disease or greater is common.⁷⁻⁹ In our reports also, all patients had T3 disease or greater. T-staging has the greatest impact as a prognosticator of maxillary sinus carcinoma,¹⁰ and reportedly, prognosis is significantly worse in patients with T4 disease than with T3 or lesser.^{4-6,8,9} In the present study, the 5-year overall survival rate in T3 patients was 80.0%; however, the rate reduced to 29.9% in patients with T4 disease. Maxillary sinus carcinoma with the tumor limited to within the sinus (T1/T2) presents no symptoms or symptoms that barely differ from those of sinusitis; further, it is difficult to detect T1/T2 early-stage maxillary sinus carcinoma. By the time specific symptoms, such as foul-smelling nasal discharge, buccal pain, dental

pain, and buccal redness and swelling, are observed, many patients would have had already developed T3/T4 disease. It is common for patients to observe and ignore symptoms such as nasal congestion and nasal flow; further, when buccal pain and swelling appears, many patients consult a dentist thinking it is a tooth-related problem. From a physician's perspective, general nasal symptoms should not be neglected; particularly, when the symptoms are unilateral, image examination such as computed tomography should be proactively performed. To detect maxillary sinus carcinoma well in advance, we believe it is important to educate the society in general and provide information to not only departments of otorhinolaryngology but also to medical departments of adjacent areas, such as the department of dentistry and ophthalmology.

The incidence of N+ disease at the initial examination is reported to be 6 to 22% in maxillary sinus carcinoma, and our result of seven patients (31.8%) is somewhat higher than the usual. In the process of evaluating prognosis according to the presence or absence of cervical lymph node metastasis, Maeda et al⁸ reported that the 5-year disease-specific survival rate is 63% in N- patients and 18% in N+ patients, thereby indicating poorer prognosis in N+ patients. By contrast, Asakura et al¹¹ reported that the survival rate does not depend on cervical lymph node metastasis and that control of the primary lesion is more important. Our results indicated that the 5-year overall survival rate was lower in N+ patients; however, this difference was not statistically significant. In the future, an ongoing follow-up survey should be conducted with a larger number of samples.

The basic treatment method for maxillary sinus squamous cell carcinoma at our department, as shown in ►Fig. 1, is preoperative RADPLAT combined with surgery. A comparative study conducted in Holland¹² revealed that RADPLAT is not superior to CRT; therefore, administration of RADPLAT has recently ceased in the West.¹³ On the contrary, RADPLAT is generally used to treat maxillary sinus carcinoma in Japan. Similar to that performed at our institution, Koike et al administered preoperative RADPLAT using the Seldinger method combined with surgery and reported a 5-year disease-specific survival rate of 100% in T3 patients and 84.7% in T4 patients, indicating good outcomes.¹⁴ Shiga et al administered RADPLAT via superselective intra-arterial chemotherapy for maxillary sinus squamous cell carcinoma and reported no difference in survival in the group with surgery compared with in the group without surgery and radiation therapy up to the curative dose; further, they reported good outcomes in both groups and improved prognosis in stage IV patients.^{7,15} Based on these reports, we can adequately infer that RADPLAT has a certain effectiveness.

Among the patients at our department, long-term survival was achieved in two patients with ongoing RADPLAT without surgery. In the interim evaluation, good PR was observed in one patient with T3 disease and one with T4b disease who was unable to undergo surgery. Currently, both these patients are alive and recurrence free. While it is hard to draw a conclusion owing to the small sample size, we believe that continuing using RADPLAT for patients who

responded well to RADPLAT based on the interim evaluation might be sufficient to preserve the maxilla and achieve long-term survival. Particularly, it should be noted that CR was achieved in a patient with T4b disease, which corroborates with the finding reported by Shiga,⁷ thus indicating that RADPLAT monotherapy should be considered in the treatment of advanced maxillary sinus carcinoma.

The dose/CDDP infusion using the original method reported by Robbins et al is 150 mg/m²;^{2,16} however, CDDP is often administered at a dose of 100 mg/m² in Japan. Yoshizaki et al compared the outcomes achieved with CDDP doses of 100 and 150 mg/body surface area and observed that the outcomes were better with the latter dose; furthermore, they discussed the need for high-dose CDDP administration because maxillary sinus carcinoma has a greater tumor volume compared with that of laryngeal or hypopharyngeal cancer.¹⁷ Moreover, the Japan Clinical Oncology Group conducted a multicenter, prospective clinical trial of maxillary sinus carcinoma in Japan and reported that RADPLAT was effective for localized advanced maxillary sinus squamous cell carcinoma and that cisplatin administered at a dose of 100 mg/m² for seven cycles is safe and stable.¹⁸ To date, at our department, we have mainly administered CDDP arterial infusion at a dose of 100 mg/body surface area; however, for localized, highly advanced patients, we believe that increasing the CDDP dosage will ease further examination. On the contrary, a certain incidence of severe adverse events of RADPLAT including cerebrovascular accidents, central nervous system disorder, and respiratory stenosis, as well as late adverse events including osteonecrosis, brain necrosis, and severe visual impairment, which are irreversible adverse events that decrease quality of life, has been reported.¹⁹ Among all the patients at our department, one patient had temporary visual impairment and another had facial nerve paralysis; however, there was no occurrence of the abovementioned severe adverse events. Both these patients recovered; we believe that in the future, the possibility of the onset of late adverse events should be recognized and careful follow-up observation should continue over a long period.

The outcomes observed via the current treatment, which combined RADPLAT with surgery, used at our department were generally good for maxillary sinus carcinoma up to the T3 disease. However, in highly advanced patients (T4), the disease is often difficult to control, and more treatment methods need to be developed. Upon examining fatal cases, the most common cause of death was found to be M-related, followed by T-related deaths. As presented in ►Table 1, patients with distal metastasis (+) at the time of initial examination were in the T4 stage; in advanced patients, appropriate intervention via systemic chemotherapy might be needed from the time of initial treatment. Therefore, a more effective chemotherapy regimen needs to be established in the future. Noronha et al²⁰ achieved certain outcomes by treating patients with localized advanced cancer with systemic chemotherapy followed by surgery and radiotherapy. Furthermore, the first-line treatment is important for improving the primary lesion control rate. Because the center of the face is adjacent to the orbit and the cranium, and particularly in advanced maxillary sinus carcinoma, performing surgery while ensuring an adequate safety margin is often

functionally and esthetically difficult, which we believe leads to T-related death. To improve the localized control rate, we believe it might be useful to examine the use of surgery-assisting tools, such as endoscopy and navigation systems, which have made remarkable advancements recently, as well as the concomitant use of advanced radiotherapies, such as IMRT and particle beam radiotherapy.

Conclusion

We examined 22 patients with maxillary sinus squamous cell carcinoma who underwent first-line treatment at our department. The 5-year overall survival and disease-specific survival rates were 47.8 and 56.9%, respectively. The survival rate was good up to the T3 disease stage and then declined in the T4 disease stage. In fatal cases, the most common cause of death was M-related, followed by T-related death. We believe that improving the survival rate in the future involves early detection and treatment, establishing improved treatment methods for advanced cancer, and, in particular, controlling the metastatic lesions and the primary lesion.

Conflict of Interest

None declared.

Note

This study was approved by the Ethics Committee of the University of Occupational and Environmental Health.

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