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**Title:** The incidence of late neck recurrence in N0 maxillary sinus squamous cell carcinomas after superselective intra-arterial chemoradiotherapy without prophylactic neck irradiation.

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## **ABSTRACT**

The efficacy of elective neck irradiation (ENI) for patients with N0 carcinoma of the maxillary sinus has been controversial. The purpose of our study was to investigate the incidence of late neck recurrence and the mortality rate from regional disease in patients with N0 maxillary sinus cancer after superselective cisplatin infusion and concomitant radiotherapy (RADPLAT) without ENI. We retrospectively analyzed 48 patients with N0 maxillary sinus cancer who underwent RADPLAT. Chemotherapy consisted of 100–120 mg/m<sup>2</sup> superselective intra-arterial cisplatin administered at a median rate of four times weekly. Concurrent radiation therapy was administered at a median dose of 65Gy without ENI. Late neck recurrence was observed in 8.3% (4/48). Three patients underwent salvage neck dissection and survived without any evidence of disease. The remaining patient did not undergo neck dissection due to coexistence with distant metastasis, and he died of regional disease. The mortality rate from regional disease was calculated to be 2% (1/48). The incidence of late neck recurrence was not frequent, and the mortality rate from regional disease was low. Salvage neck dissection was considered to be feasible for patients with late neck recurrence. When definitive radiotherapy and concomitant chemotherapy are applied, it is considered that ENI is not required for cases of N0 maxillary sinus cancer.

**Keywords:** maxillary sinus cancer, elective neck irradiation, intra-arterial chemotherapy, radiotherapy, regional recurrence

## INTRODUCTION

Carcinomas of the maxillary sinus are uncommon, comprising just 0.2-0.5% of all cancers, 3% of all head and neck cancers, and 80% of all paranasal sinus cancers [1]. Although nodal metastasis is uncommon in maxillary sinus cancer, many authors have advocated elective neck irradiation (ENI) based on the 10-29% rate of neck recurrence and the poor survival of patients with recurrent disease in the neck [2-3]. However, the role of ENI for patients with N0 maxillary sinus cancer remains controversial. In our institution, ENI has not been applied when patients with N0 maxillary sinus cancer undergo superselective cisplatin infusion and concomitant radiotherapy (RADPLAT). The purpose of our study was to investigate the incidence of late neck recurrence and the mortality rate from regional disease in patients with N0 maxillary sinus cancer after RADPLAT without ENI.

## METHOD

**Patients.** We retrospectively analyzed 49 patients with N0 maxillary sinus squamous cell carcinomas who underwent RADPLAT in Hokkaido University Hospital, Japan between September 1999 and July 2012. One patient, who died of primary disease within six months after the end of treatment, was excluded. The remaining 48 patients were eligible for our study. T and N stages were classified according to the American Joint Committee on Cancer (AJCC) staging system 2010. Table 1 presents patient demographics.

Approval for this study was obtained from the institutional review board at

Hokkaido University. Completion of the survey was considered to represent implied consent for participation.

**Radiotherapy.** The irradiation plan during the period 2006–2012 was 70 Gy in 35 fractions of 2 Gy over seven weeks for the primary site. Between 1999 and 2005, the primary site was irradiated with 65 Gy in 26 fractions of 2.5 Gy over 6.5 weeks. Elective irradiation of nodal area was not attempted.

**Chemotherapy.** Chemotherapy consisted of the administration of 100–120 mg/m<sup>2</sup> superselective intra-arterial cisplatin at a median rate of four times weekly (range, 2–5 times; mean, 3.7 times). At the same time, sodium thiosulfate was administered intravenously (24 g/body) to provide effective cisplatin neutralization.

**Monitoring management.** Patients were usually monitored monthly for recurrence in the first year, every couple of months in the second year, and every 6 or 12 months thereafter until death or data censoring. Ultrasonography and/or CT scan of the nodal area was routinely performed once every three months in the first year, and every 6 or 12 months thereafter. If late neck recurrence was observed, salvage neck dissection was indicated.

**Statistics.** The Kaplan-Meier method was applied for overall survival. The time of interest was the duration from the start of treatment to death or censoring. JMP Pro 10.0.2 statistical software (SAS Institute, Cary, NC) was used for the analysis.

## RESULTS

**Chemoradiotherapy.** Intra-arterial chemotherapy was performed a median 4 times

(range, 1-5 times). The median irradiation dose was 70 Gy. The irradiation dose ranged from 48Gy to 70Gy. Forty-five patients (93.7%) underwent a full course of irradiation (>65 Gy).

**Clinical outcomes of nodal status.** The median follow-up period for living patients was 69.5 months (range, 15.4-142.5 months). Late neck recurrence was observed in 8.3% (4/48) at a median 11 months (range, 1-32 months) after the completion of RADPLAT. Details of the four patients with late neck recurrence are given in Table 2. Neck dissection was performed in three of the four patients with late neck recurrence. These three patients survived without any evidence of disease. Neck dissection was not performed in the remaining patient due to coexistence with distant metastasis, and he died of regional disease two months after neck recurrence.

Five patients died of primary disease without any regional disease at a median 22 months (range, 8-46 months) after the completion of RADPLAT. Two patients died of other disease without any regional disease 11 to 43 months after the completion of RADPLAT. Another patient died of distant disease without any regional disease 6 months after the completion of RADPLAT. The mortality rate from regional disease was calculated to be 2% (1/48).

The 5-year overall survival rate of all 48 participants was calculated to be 78.2% by the Kaplan-Meier method (Figure 1).

**Salvage Neck Dissection.** Salvage neck dissection was performed in three patients. In one of these three patients, radiotherapy and chemotherapy were suspended at an irradiation dose of 50 Gy as an allergic reaction was observed after the second

intra-arterial administration of cisplatin. Although salvage surgery for persistent primary disease was planned, the presence of late neck recurrence was observed one month after the end of initial treatment. Therefore, salvage neck dissection was performed simultaneously with the primary tumor resection.

Although the extent of neck dissection varied, the lymph nodes in the upper and middle jugular chain areas were dissected in all three patients. The patient with metastasis of the intra-parotid lymph node underwent total parotidectomy associated with neck dissection of the upper and middle jugular chain areas. Submandibular nodes (level Ib) were dissected in two patients. The definitive pathological results of the lymph nodes revealed viable tumor cells in all three patients undergoing neck dissection. No post-operative complications were observed in any patient.

Two patients (case 1 and 3) did not undergo any adjunctive treatment after salvage neck dissection. One patient (case 4) underwent adjunctive chemotherapy consisting of oral uracil-tegafur (UFT) for a year after salvage neck dissection.

## **DISCUSSION**

In 1980s, most authors did not advocate ENI for patients with N0 maxillary sinus cancer because of the general belief that nodal metastasis was uncommon in tumors without extensive lymphatic involvement [4-6]. The overall nodal recurrence rate without ENI was reported to be 38% for squamous cell and undifferentiated carcinomas from the MD Anderson Cancer Center [7]. Based on this finding, researchers at the same institution began to advocate ENI for most patients with

carcinomas of the maxillary sinus, with the exception of those with T1 lesions. Following this report, many authors advocated ENI based on the high rate of late neck recurrence and the poor survival of patients with neck recurrence in 1990s-2000s [2-3]. However, the efficacy of ENI remains controversial due to the fact that there have been few reports indicating the incidence of late neck recurrence in patients with N0 maxillary sinus cancer treated by definitive radiotherapy and chemotherapy without ENI.

ENI has not been used for patients with N0 maxillary sinus cancer when definitive radiotherapy and concomitant superselective intra-arterial chemotherapy were applied in our institution. Our results indicate both a low mortality rate from regional disease (2%) and a low incidence of late neck recurrence (8.3%). Based on our uniformed treatment, these results can be considered reliable. The rate of late neck recurrence in our institution was considerably lower than that of recent reports. The reason for the low recurrence rate in our study is speculated to be that intra-arterially injected cisplatin targeting the primary tumor has a beneficial effect on subclinical metastatic lymph nodes. It has been reported that intra-arterially injected cisplatin can pass, via lymph flow, into the lymph nodes in patients with tongue cancer [8-9]. These reports appear to support our hypothesis. Further, Jang et al. reported that the incidence of late neck recurrence was 3.3% in patients with T3-4 N0 maxillary sinus cancer, who underwent definitive radiotherapy without ENI [10]. As 66% of all participants received induction chemotherapy and 10% of them received concurrent chemotherapy in this report, it might be that systemic drug application has the capacity to eliminate occult

micrometastases in regional lymphatics to a degree, comparable to that of ENI or surgery.

Approaching this subject from a different perspective, Brown et al. investigated the efficacy of elective neck dissection in the management of maxillary sinus cancer. They concluded that elective neck dissection did not contribute to an improved rate of neck control [11]. In terms of surgical treatment, prophylactic intervention for subclinical regional disease was also ineffective.

Patterns of late neck recurrence appear to be varied. It was reported that the most common site of neck recurrence was in level Ib and IIa nodes [2,12]. Our patients included two with nodal metastasis involving in level IIa, and one involving in level Ib nodes, as well as one patient with an intra-parotid metastatic node. Although nodal metastasis in the intra-parotid area was not common, frontal wall and skin invasion might cause nodal metastasis in this area.

## **CONCLUSIONS**

We showed both a low mortality rate from regional disease (2%) and a low incidence of late neck recurrence (8.3%) for patients with N0 maxillary sinus cancer, who were treated by RADPLAT. Therefore, it is considered that ENI does not have a significant role in treatment in cases in which definitive radiotherapy and concomitant chemotherapy are applied.

## **Conflict of interest statement**

None declared.

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### **Figure legends**

Figure 1. The overall survival curve of all 48 patients with N0 maxillary sinus cancer after intra-arterial cisplatin infusion with concomitant radiotherapy.

Table 1. Patient Demographics

Characteristic	No. of patients (%)
Total	48
Gender	
Male	38 (79%)
Female	10 (21%)
Age, years	
Median	60.5
Range	35-73 (Ave. 58.7)
Follow-up period, months	
Median	69.5
Range	15.4-142.5 (Ave. 62.1)
T classification	
T2	1 (2%)
T3	14 (29%)
T4a	23 (48%)
T4b	10 (21%)

Table 2. Details of the four patients with late neck recurrence

Case	Age	Sex	T classification	Radiation dose	Chemotherapy (No. of times)	Extent of primary disease	Recurrent nodal area	Treatment for subsequent nodal metastasis	Outcome (Observation period after recurrence)
1	45	F	4a	65	4	Infra-temporal fossa	Ila	Neck dissection	NED (9 years)
2	41	M	4b	65	4	Orbital apex	Ila	Palliative treatment	Dead of regional disease (2 months)
3	67	M	4a	50	2	Infra-temporal fossa and oral mucosa	Ib	Neck dissection associated with resection of the primary tumor	NED (5.7 years)
4	37	M	4a	70	4	Frontal wall and skin	Intra-parotid	Neck dissection	NED (5.5 years)

NED: no evidence of disease

