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Title: Salvage surgery improves the treatment outcome of patients with residual/recurrent maxillary sinus cancer after superselective intra-arterial cisplatin infusion with concomitant radiation therapy

Authors:

Nayuta Tsushima, MD¹, Satoshi kano, MD, PhD¹, Takayoshi Suzuki, MD, PhD¹, Hiroshi Idogawa, MD¹, Daisuke Yoshida, MD¹, Koichi Yasuda, MD, PhD², Manami Otsuka, MD², Hidefumi Aoyama, MD, PhD², Akihiro Homma, MD, PhD¹

1. Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan
2. Department of Radiation Oncology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

Corresponding author: Akihiro Homma

Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan

Phone: +81-11-707-5958; Fax: +81-11-717-7566;

E-mail address: ak-homma@med.hokudai.ac.jp

Abstract

Purpose

We have performed superselective intra-arterial cisplatin infusion with concomitant radiotherapy (RADPLAT) for patients with maxillary sinus cancer. The promising treatment outcomes of this non-surgical treatment were reported in past studies. However, few clinical studies have been conducted to evaluate the outcome of salvage surgery following RADPLAT. The purpose of this study was to analyze the treatment outcomes of salvage surgery for patients with recurrent maxillary sinus cancer after RADPLAT.

Methods

We assessed 45 patients who had recurrence following RADPLAT between 1999 and 2017, and conducted a retrospective analysis. We excluded patients who did not complete RADPLAT. Patients were not considered to have completed RADPLAT if they underwent intra-arterial cisplatin less than three times or received a total radiation dose of less than 60 Gy. The primary endpoint was overall survival. The median follow-up period for surviving patients after recurrence was 5.1 years.

Results

Twenty-five of the 45 (56%) patients underwent salvage surgery. The 5-year overall survival rate was 68% in patients who underwent salvage surgery, while all patients who did not undergo salvage surgery died during the observation period.

Fifteen of 24 (63%) patients with local recurrence underwent salvage surgery. Eight patients did not undergo salvage surgery because of unresectable disease; five out of the eight patients had unresectable posterior extension. All nine patients with nodal recurrence underwent neck dissection.

Conclusion

Treatment outcomes of salvage surgery following RADPLAT were favorable enough for it to be generally recommended. To reduce unresectable recurrence, the posterior section should be eradicated by RADPLAT.

Keywords

maxillary sinus cancer, salvage surgery, intra-arterial, chemotherapy, radio therapy,

unresectable.

Declarations

Funding The authors did not receive support from any organization for the submitted work.

Conflicts of interest/Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This retrospective chart review study involving human participants was performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Hokkaido University Hospital approved this study (No. C-T2020-0152).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication not applicable.

Availability of data and material The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable

Abstract

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Introduction

The standard of care for maxillary sinus cancer is radical surgery and postoperative radiotherapy [1, 2]. However, this usually results, to a greater or lesser extent, in cosmetic problems and impairment of ocular function. Further, complete resection is difficult in very advanced tumors such as T4b. Patients with unresectable disease are usually treated with radiotherapy alone or intra-venous chemoradiotherapy. The reported 5-year overall survival rate of patients with unresectable maxillary sinus cancer is 15% when treated with such therapies [3]. We have been applying superselective intra-arterial cisplatin infusion with concomitant radiotherapy (RADPLAT) for patients with maxillary sinus cancer. The promising treatment outcomes of this non-surgical treatment were reported in previous studies [4, 5]. Salvage surgery is performed where possible in cases in which the tumor persists or recurs. However, few studies have been conducted to evaluate the outcome of salvage surgery [6]. Here, we analyze the treatment outcomes of salvage surgery for patients with residual/recurrent maxillary sinus cancer after RADPLAT. The primary outcome of this study is overall survival rate by various clinical factors.

Material and methods

Patients

Between January 1999 and December 2017, 110 patients with maxillary sinus cancer underwent RADPLAT at Hokkaido University Hospital. We excluded eight patients who did not complete treatment. Patients were not considered to have completed RADPLAT if they underwent intra-arterial cisplatin less than three times or the total radiation dose received was less than 60 Gy. Forty-five of 102 (43%) patients had recurrent disease and were eligible for this study (Fig. 1). The median follow-up period for surviving patients after recurrence was 5.1 years (range: 0.1-11.9 years). Patient characteristics are shown in Table 1. This study was approved by the Institutional Review Board at Hokkaido University Hospital (No. C-T2020-0152) and the study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Pretreatment

Clinical stage was evaluated by clinical examination, contrast-enhanced computed tomography (CT) imaging, magnetic resonance (MR) imaging and positron emission tomography, where possible. Precontrast CT or MR imaging was acceptable for patients unable to tolerate the contrast agent. Ultrasonography of the neck was used to evaluate lymph node metastasis, as required. For all patients, clinical stage was determined before

treatment by the cancer board consisting of head and neck surgeons, radiation oncologists, diagnostic radiologists, and medical oncologists.

Chemotherapy and radiotherapy

The chemotherapy and radiotherapy procedures were described in detail in a previous report [5]. All patients received concurrent intra-arterial cisplatin and intravenous sodium thiosulfate infusions. Cisplatin was infused through a microcatheter administered at a dose of 100-120 mg/m², a median of 4 times weekly (range 3-7). The microcatheter was placed angiographically in the dominant blood supply of the tumor alone. Simultaneously, sodium thiosulfate (at a dose of 20-24g) was given intravenously to neutralize the cisplatin. All arterial catheterizations were accomplished transcutaneously through the femoral artery.

Radiotherapy was administered with high-energy photons by 4 or 6 MV X-rays. Until May 2006, the irradiation schedule was 65 Gy in 26 fractions over 6.5 weeks. After that time, it was changed to 70 Gy in 35 fractions over 7 weeks. For patients with neck metastasis, the ipsilateral neck was irradiated (40 Gy) and a 25-30 Gy boost was given to positive nodes. In patients without neck metastasis, no elective neck irradiation was performed.

Follow-up management

Patients were usually monitored monthly for recurrence during the first year, every two months during the second year, and every 3 to 6 months thereafter until death or data censoring. CT and MR imaging were routinely performed once every three months during the first year and every 3 to 6 months thereafter. Positron emission tomography was performed when needed. When persistent/recurrent disease was suspected, biopsy or fine needle aspiration cytology was attempted, where possible. Salvage surgery was recommended when the disease was regarded as resectable.

Types of recurrence

Each case of recurrence was categorized when it was first detected. Categories consisted of local recurrence, nodal recurrence, local and nodal recurrence, or recurrence with distant metastasis. We did not distinguish residual disease from local recurrence.

Patients who had combined local/nodal recurrence and distant metastasis were categorized as recurrence with distant metastasis. The prognosis of patients was assessed by the type of recurrence.

Salvage surgery

Salvage surgery was performed when the disease was evaluated as resectable.

Residual/recurrent local disease was resected by partial or total maxillectomy with or without orbital exenteration. The extent of resection was decided according to the residual/recurrent disease rather than the initial disease. Recurrent neck disease was treated by neck dissection unless it was unresectable. Usually, distant metastatic disease was treated by systemic chemotherapy. However, it was resected when it was a single, relatively slow growing lesion evaluated as resectable.

Statistics

The Kaplan-Meier method was used for the calculation of survival rates using JMP Pro 14.0.0 statistical software (SAS Institute, Cary, NC). Time of interest was the period from recurrence to death or failure. The log-rank test was applied to compare the survival rates between two groups. The level of statistical significance was set at $p < 0.05$.

Results

Clinical outcomes

Figure 2 shows the distribution of first recurrence sites. Twenty-four patients were

categorized with local recurrence and nine nodal recurrence. No patient had combined local and nodal recurrence. Eight patients had only distant metastasis. One patient with combined local and distant recurrences and three patients with combined neck and distant recurrences were categorized with recurrence with distant metastasis. In total, 12 patients were categorized with recurrence with distant metastasis.

Twenty-five of the 45 patients (56%) underwent salvage surgery. The treatment course of the patients by recurrent category is shown in Fig. 3a, b, c. Table 2 shows the types of salvage surgery. Fifteen of the 24 (63%) patients with local recurrence underwent salvage surgery. In 24 patients with local recurrence, six patients (27%) underwent partial maxillectomy, which was the most commonly performed salvage surgery (Fig. 4a, b, c). Meanwhile, nine of the 24 (38%) patients with local recurrence did not undergo salvage surgery. Eight patients had unresectable disease, and lung metastasis was detected in one patient before undergoing salvage surgery. Among these eight patients with unresectable disease, five had tumors with posterior extension and three with intracranial extension. Figure 4d, e show CT imaging of a case of local recurrence which was unresectable because of posterior extension. All nine patients with nodal recurrence underwent neck dissection. The most frequent nodal recurrence level was IIA (5/9) and three patients had parotid node metastasis. One patient with renal metastasis underwent nephrectomy. The

remaining 13 patients with distant metastasis did not undergo salvage surgery.

Postoperative complications were found in four of 25 patients (16%) who underwent salvage surgery (Table 3). All patients who developed postoperative complications underwent salvage surgery for local recurrence. Two patients underwent total maxillectomy and the other two underwent extended total maxillectomy. No patients died during the perioperative period.

The 5-year overall survival rate of patients with residual/recurrent disease after RADPLAT was 39% (Fig. 5a). Figure 5b shows the overall survival rates of the patients with or without salvage surgery. The 5-year overall survival rate of patients undergoing salvage surgery was 68%. On the other hand, all patients who did not undergo salvage surgery died during the observation period. The overall survival rates by type of recurrence are shown in Fig. 5c. The site of recurrence was significantly associated with overall survival rate ($P=0.04$). The 5-year overall survival rate of the patients with local recurrence was 70% in those who underwent salvage surgery and 0% in those who did not (Fig. 5d). When salvage surgery was not performed, all patients with local recurrence died within 2 years.

The overall survival rates stratified by T classification are shown in Fig. 5e. T classification was significantly associated with overall survival rate ($P=0.0003$), with the

same trend observed for N classification (Fig. 5f), which was also significantly associated with overall survival rate (P=0.008).

Discussion

In the current study, the results of salvage surgery were favorable among patients with residual/recurrent disease who received RADPLAT for maxillary sinus cancer. The 5-year overall survival rate of patients undergoing salvage surgery was 68%. We consider that this rate would be sufficient to recommend salvage surgery. Twenty-four of 33 (73%) patients without distant metastasis underwent salvage surgery. Fifteen patients underwent surgery for residual/recurrent local disease and nine patients underwent neck dissection. The 5-year overall survival rate was 70% for local recurrence and 62% for nodal recurrence when salvage surgery was performed. These results indicate that surgery for either local or nodal recurrence should be considered when recurrent disease is detected.

The extent of resection was decided by the range of the recurrent disease rather than the initial disease in this study, although some surgeons might decide the extent of resection based on the initial disease. However, radical resection for maxillary sinus cancer results in cosmetic and functional problems. We resected only the existing disease

for RADPLAT and surgery was regarded as sequential therapy. Therefore, the most commonly performed salvage surgery for local recurrence was partial maxillectomy rather than total maxillectomy. The delivery of cisplatin to the entire tumor is sometimes difficult. When cisplatin is not delivered sufficiently to a part of the tumor, partial recurrence may result. In such cases of recurrence, we consider partial resection to be a valid approach. Four patients who developed postoperative complications underwent total maxillectomy or extended total maxillectomy. No postoperative complications were observed in patients undergoing partial maxillectomy. When patients underwent salvage surgery following RADPLAT, partial maxillectomy may reduce postoperative complications compared to total or extended total maxillectomy.

In the current study, 20 of the 45 (44%) patients did not undergo salvage surgery. Eight patients had unresectable disease; 5 had tumors with posterior extension and three with intracranial extension. The posterior section needed to be eradicated by RADPLAT because salvage surgery is difficult in this region. To perform RADPLAT and salvage surgery as sequential therapy, cooperation between the head and neck surgeon and interventional radiologist is important, as a surgical perspective is required to perform RADPLAT effectively.

T classification was significantly associated with overall survival rate. In patients

with T4b disease, the 2-year overall survival was 25%. That is to say, the prognosis was not satisfactory when residual/recurrent disease was detected in patients with very advanced tumors. All nine patients with nodal recurrence had resectable disease and underwent neck dissection. The role of prophylactic therapy for neck in maxillary cancer has not yet been established [7, 8]. The incidence of occult node metastasis was reported to be from 13.5% to 20% [1, 8, 9]. Some studies recommend elective neck irradiation for node-negative maxillary sinus cancer [9, 10], while it is reported that elective neck dissection for patients with T3/4 clinical N0 sinonasal cancer does not improve overall survival rate [1]. In the current study, three patients had parotid node metastasis. Elective neck irradiation including that of the parotid region would result in adverse effects such as xerostomia and osteoradionecrosis of the mandible. We think nodal recurrence could be identified at an early stage and controlled by close follow up. In consideration of the pros and cons, we have not performed elective neck irradiation.

We sought to reveal whether persistent or early recurrent disease affected the prognosis, but we were unable to achieve this as it was difficult to differentiate between radiographic changes related to the treatment and scar tissue from persisting tumors. The median time to persistent or recurrent disease was confirmed after the completion of RADPLAT to be 195 days. A previous study found that patients with a disease-free

interval of 6 months or less had worse survival outcomes after salvage surgery compared with those with an interval of more than 6 months [11]. Therefore, we compared the prognosis between these two groups. In the current study, the 5-year overall survival rate of patients with a disease-free interval of 6 months or less and that of patients with an interval of more than 6 months was 32% and 45%, respectively. Although this difference was not statistically significant ($P=0.14$), a shorter disease-free interval may also result in a deterioration of the survival rate in patients undergoing RADPLAT.

We acknowledge several limitations to this study. First, this retrospective study had a low number of eligible patients (45). This may be acceptable as maxillary sinus cancer is a rare disease [12, 13] and the selected patients were treated by RADPLAT. We think that this number is adequate to evaluate treatment outcomes of salvage surgery following RADPLAT and that this study may serve as a guide for deciding whether salvage surgery should be performed. Second, patients who did not undergo salvage surgery had more advanced disease than those who did. Therefore, the prognoses of the patients who underwent salvage surgery were naturally better than those for patients who did not. However, we consider that the survival rate of the patients undergoing salvage surgery was sufficiently high for salvage surgery to be recommended.

Conclusion

Treatment outcomes of salvage surgery following RADPLAT were favorable enough for it to be generally recommended. We recommend the extent of resection for residual/recurrent local disease to be decided on the basis of the existing disease rather than on the initial disease. Neck dissection should be performed unless the disease is unresectable. To reduce cases of unresectable recurrence, the posterior section should be examined carefully when performing intra-arterial cisplatin infusion.

Disclosure statement: The authors declare no conflicts of interest associated with this manuscript.

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Figure Legends

Table 1. Characteristic of the eligible patients (n=45).

Table 2. Details of the salvage surgeries by recurrence category.

Table 3. Details of the four patients who developed postoperative complications. The severity of complications was graded using the Common Terminology Criteria for Adverse Events guidelines (CTCAE ver. 5.0) Abbreviation: IACDDP, intra-arterial cisplatin infusion

Fig. 1 Flowchart of patient screening

Fig. 2 Patterns of first recurrence in eligible patients. Twelve patients were categorized as recurrence with distant metastasis. * Combined pri and distant recurrences ** Combined nodal and distant recurrences

Fig. 3 Treatment course of the patients categorized as local recurrence (a), nodal recurrence (b), and recurrence with distant metastasis (c). Abbreviations: NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; DOOD, dead of other disease; BSC, best supportive care

Fig. 4 (a) Original disease filled the left maxillary sinus. (b) Recurrent local disease existed at the superior and medial wall of the maxillary sinus (arrow). (c) Partial

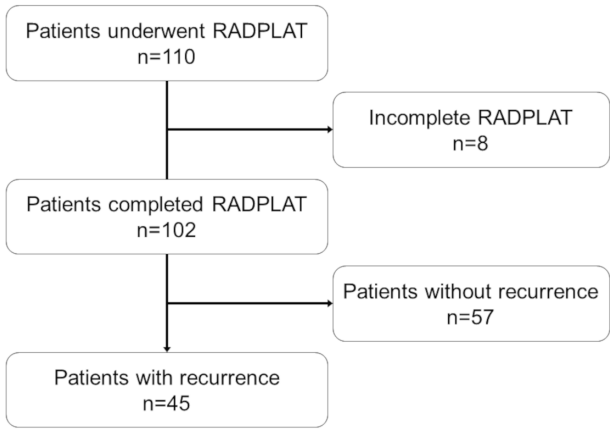
maxillectomy was performed with preservation of the hard palate. (d) Original disease extended to the posterior section of the right maxillary sinus. (e) Recurrent disease also extended to posterior section (arrow).

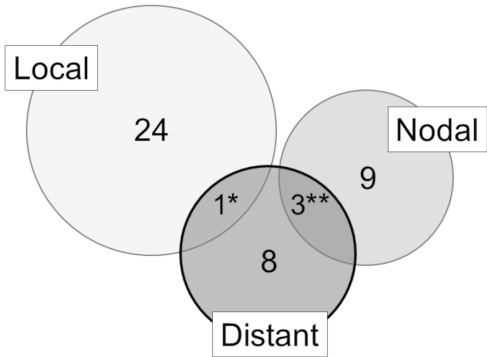
Fig. 5 Overall survival rates of (a) all eligible patients, (b) patients with or without salvage surgery, (c) patients by recurrence category, (d) patients with local recurrence with or without salvage surgery, (e) patients stratified by T classification, (f) patients stratified by N classification.

Characteristic	
Age, years	
median (range)	70 (29-77)
Sex	
Male	37
Female	8
Follow-up period, years	
Median (range)	5.1 (0.1-11.9)
Histological type	
Squamous cell carcinoma	37
Undifferentiated carcinoma	4
Adenoid cystic carcinoma	1
Poorly differentiated carcinoma	1
Spindle cell carcinoma	1
Angiosarcoma	1
T classification	
T2	1
T3	15
T4a	17
T4b	12
N classification	
N0	35
N1	7
N2b	3

Recurrence category	Type of salvage surgery	
Local recurrence (n=24)	Frontal craniotomy	1
	Extended total maxillectomy	3
	Total maxillectomy	5
	Partial maxillectomy	6
	No salvage surgery	9
Nodal recurrence (n=9)	Neck dissection	9
Distant metastasis (n=12)	Nephrectomy	1
	No salvage surgery	11

Case	age	sex	classification		Radiation dose (Gy)	Cycles of IACDDP	Recurrence category	Type of surgery	Complications
			T	N					
1	73	M	4a	1	64	4	Local	Extended total maxillectomy	Wound infection (grade 3) Sepsis (grade 3) Venous thrombosis (grade 3)
2	51	M	3	0	70	4	Local	Total maxillectomy	Wound infection (grade 2)
3	61	M	3	0	70	4	Local	Extended total maxillectomy	Wound infection (grade 3)
4	61	M	4a	0	70	4	Local	Total maxillectomy	Wound infection (grade 3)





Local recurrence
n=24

Salvage surgery
n=15

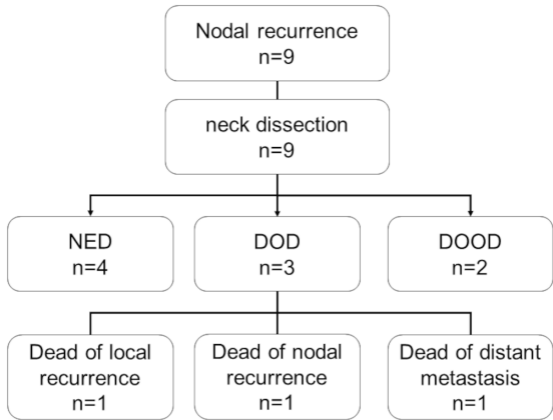
No salvage surgery n=9
Systemic therapy n=5
BSC n=4

NED
n=7

AWD
n=4

DOD
n=4

DOD
n=9



Distant metastasis
n=12

Systemic therapy
n=7

BSC
n=4

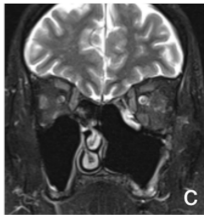
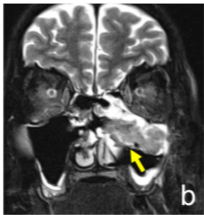
Salvage surgery
n=1

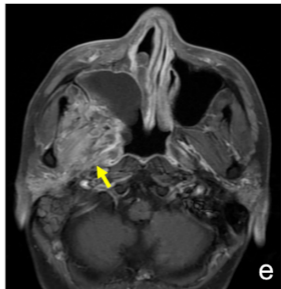
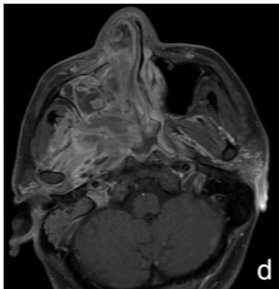
DOD
n=6

AWD
n=1

DOD
n=4

NED
n=1





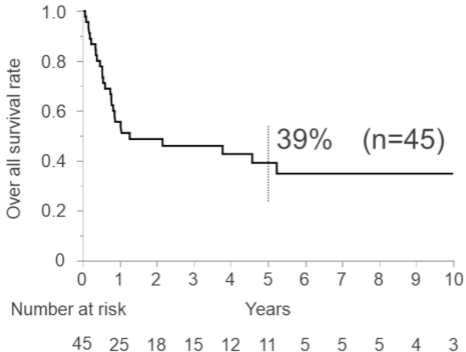
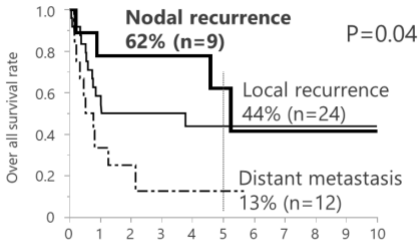


Fig. 5c



	Years										
Number at risk	0	1	2	3	4	5	6	7	8	9	10
Nodal	9	7	7	6	5	4	3	2	2	2	2
local	24	14	9	8	6	6	3	3	3	1	1
distant	12	4	2	1	1	1	0	0	0	0	0

