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Salvage surgery for a locally persistent or recurrent tumour in maxillary cancer patients who have undergone radiotherapy and concomitant intra-arterial cisplatin: implications for surgical margin assessment

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Abstract. Limited information about salvage surgery is available for locally persistent and recurrent maxillary sinus cancers after the completion of chemoradiation therapy. Seventy-six maxillary sinus cancer patients who had undergone chemoradioselection using initial radiotherapy and concomitant intra-arterial cisplatin were screened retrospectively. Twenty-four of these patients who had a locally persistent or recurrent tumour were investigated. The 2-year overall survival rate of patients with maxillary sinus cancer of all types was 39.0% for those who underwent salvage surgery and 10.0% for those who did not. The 2-year overall survival rate of patients with maxillary sinus squamous cell carcinoma was 45.8% for those who underwent salvage surgery and 11.1% for those who did not. Furthermore, the 2-year local control and overall survival rates of patients with positive and negative surgical margins were 14.3% and 83.3% and 14.3% and 66.7%, respectively. There were significant differences in local control ($P = 0.004$) and overall survival ($P = 0.005$) regarding surgical margin status. Although salvage surgery for a locally persistent or recurrent maxillary sinus cancer is a feasible treatment, patients with positive surgical margins are more prone to local relapse. Therefore, surgical safety margins should be assessed thoroughly.

Key words: maxillary cancer; RADPLAT; salvage surgery; surgical margin.

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Maxillary sinus cancer (MSC) is a rare malignant tumour representing 6.4% of all head and neck cancers in Japan[1]. Recommended treatments for locally advanced squamous cell carcinoma (SCC) in the maxillary sinus according to the Practice Guidelines in Oncology v. 1.2016 of the National Comprehensive Cancer Network (NCCN) are surgical resection followed by postoperative radiotherapy (RT) (T3 and T4a) or chemoradiation therapy (CRT) (T4b)[2]. However, the results of such surgical treatments for advanced MSC may lead to facial deformation and dysfunction such as dysarthria or dysphagia, resulting in a decreased quality of life. Therefore, powerful and intensive treatments such as CRT are often selected[3–5].

In a paper published in 1992, Robbins et al. were the first to demonstrate the use of RT and concomitant intra-arterial cisplatin (RADPLAT) for organ and functional preservation in head and neck cancers[6]. Based on this method, chemoradioselection using RADPLAT has been performed at Kurume University Hospital since 1998[7]. However, for patients with a locally recurrent tumour after the completion of treatment, it is necessary that they undergo salvage surgery such as a maxillectomy or craniomaxillofacial resection. Limited information is available regarding salvage surgery for patients with MSC treated with CRT, and it appears that there is little or no information on therapeutic strategies assessed by the surgical safety margin. The aim of this study was to clarify the outcomes of patients with MSC treated with RADPLAT, and furthermore, to present a reasonable salvage surgery for patients with a locally persistent or recurrent tumour.

Materials and methods

Patients with MSC treated with chemoradioselection using initial RADPLAT (I-RADPLAT) followed by sequential RADPLAT (S-RADPLAT) or surgery in the departments of head and neck surgery and radiology at Kurume University Hospital, between 1998 and 2016, were analyzed retrospectively. The inclusion criterion was T2–T4 maxillary cancer. Patients with distant metastasis at the first diagnosis were excluded. Clinical staging was determined based on the seventh edition of the Union for International Cancer Control (UICC) staging system[8]. Chemoradioselection using I-RADPLAT was performed as reported previously[7]. Cisplatin was administered at a dosage of 80–100 mg/m^2 per week for a total of three to eight cycles. All patients underwent irradiation five times per week (1.8 Gy/fraction/day). Patients with a complete response or partial response underwent S-RADPLAT at a total radiation dose of 38–40 Gy. Patients who did not respond to I-RADPLAT (those with stable disease or progressive disease) underwent surgery such as a subtotal or total maxillectomy (Fig. 1).

Statistical analysis

The response to therapy was assessed in terms of disease recurrence, time to disease recurrence, and the site of disease recurrence (local, regional, or distant). Local control (LC), disease-free survival (DFS), and overall survival (OS) from the date of diagnosis were calculated using the Kaplan–Meier method. Survival rates were compared using a log-rank test. Probabilities less than 0.05 were considered statistically significant. All statistical analyses were conducted with JMP Pro 12 statistical software (SAS Institute, Cary, NC, USA).

Results

A total of 76 patients with MSC treated with chemoradioselection using I-RADPLAT followed by S-RADPLAT or surgery were analyzed. The clinical characteristics of the patients are shown in Table 1. Sixty patients with a complete response or partial

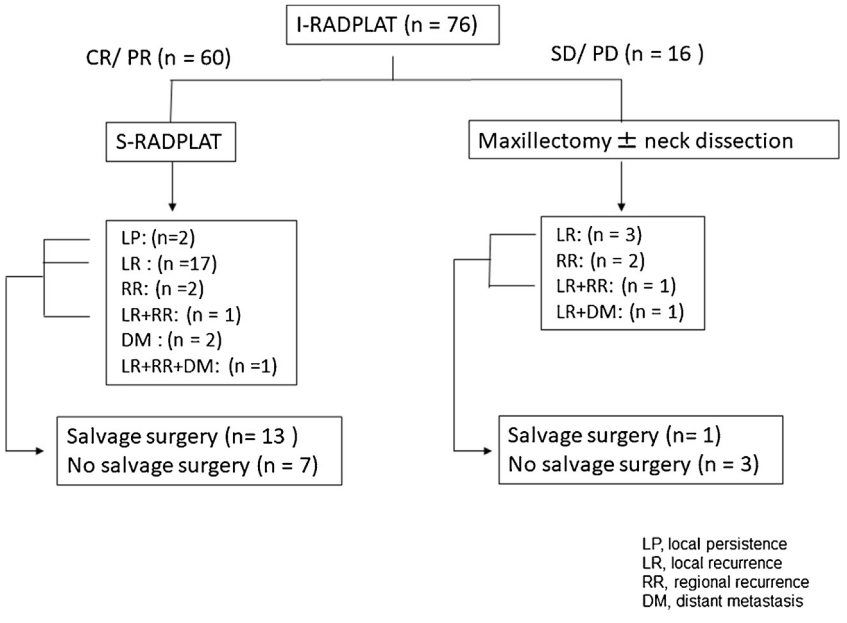

Fig. 1. Chemoradioselection by initial superselective intra-arterial cisplatin and concomitant radiation (I-RADPLAT). Responders (complete response/partial response) to I-RADPLAT underwent sequential RADPLAT (S-RADPLAT). I-RADPLAT non-responders (stable disease/progressive disease) underwent surgery. Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LP, local persistence; LR, local recurrence; RR, regional recurrence; DM, distant metastasis.

Table 1. Patient characteristics ($N = 76$).

Variables.	Total (%)
Age (years)	
Mean ± SD	66 ± 10
Sex	
Male	61 (80)
Female	15 (20)
T classification	
T2	2 (3)
T3	24 (31)
T4a	44 (58)
T4b	6 (8)
N classification	
N0	67 (88)
N1	6 (8)
N2b	1 (1)
N2c	2 (3)
Clinical stage	
II	2 (3)
III	24 (31)
IVA	44 (58)
IVB	6 (8)
Histopathology	
Squamous cell carcinoma	70 (92)
High grade mucoepidermoid carcinoma	2 (3)
Sarcomatoid carcinoma	2 (3)
Undifferentiated carcinoma	1 (1)
Spindle cell carcinoma	1 (1)
Follow-up (months)	
Median	60.9
Range	14.1–147.1
Total cisplatin dose (mg)	
Mean ± SD	563 ± 220
Total irradiation (Gy)	
Mean ± SD	60.5 ± 7.3

SD, standard deviation.

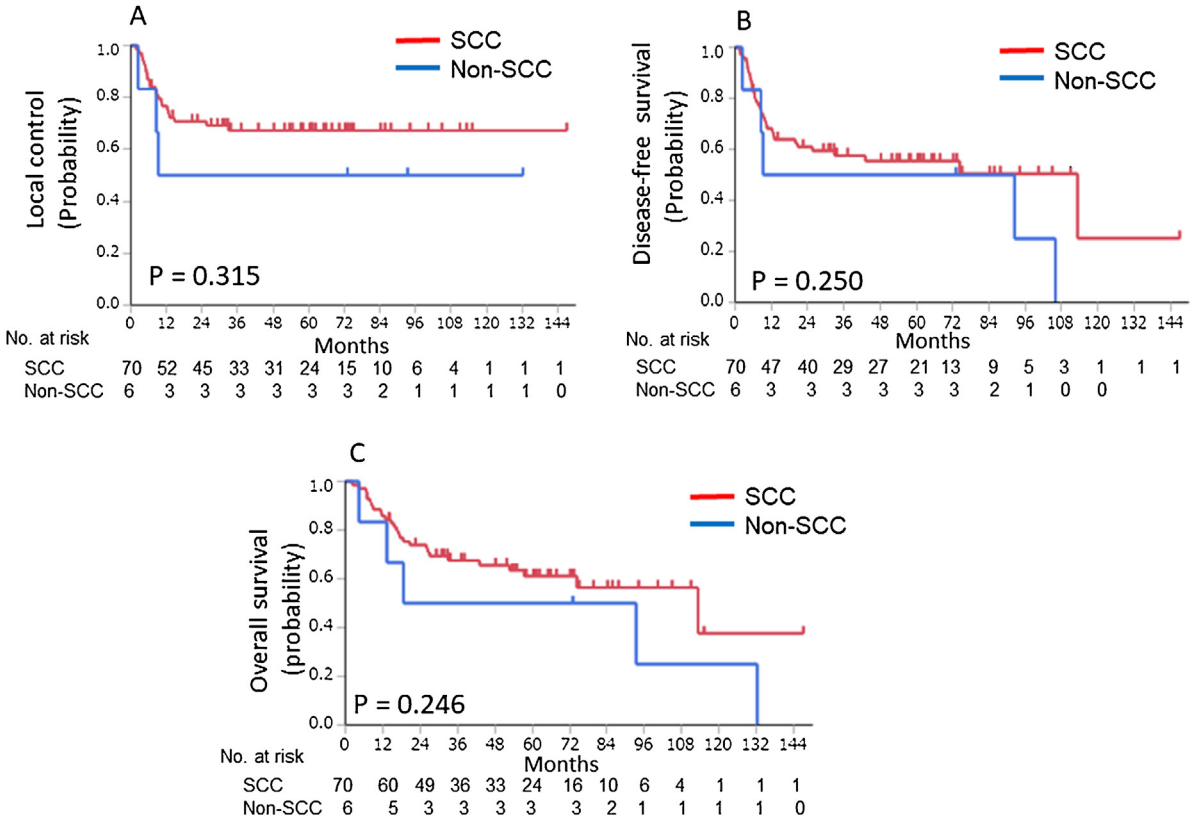

Fig. 2. Kaplan–Meier curves for (A) local control, (B) disease-free survival, and (C) overall survival, for patients with squamous cell carcinoma (SCC) and those with non-SCC who underwent RADPLAT.

response to I-RADPLAT underwent S-RADPLAT. Sixteen patients who did not respond to I-RADPLAT underwent surgery. In the S-RADPLAT group, two had a locally persistent tumour, 17 a locally recurrent tumour, two a regionally recurrent tumour, and one patient had locally and regionally recurrent tumours. Additionally, two patients had distant metastasis and one patient had local relapse with regional and distant metastases. In the surgery group, three patients had locally recurrent tumours, two patients had regionally recurrent tumours, and one patient had locally and regionally recurrent tumours. In addition, one patient had a local relapse with distant metastasis. All 24 patients with a locally or locally and regionally recurrent tumour without distant metastasis were examined in the present study regarding salvage treatment.

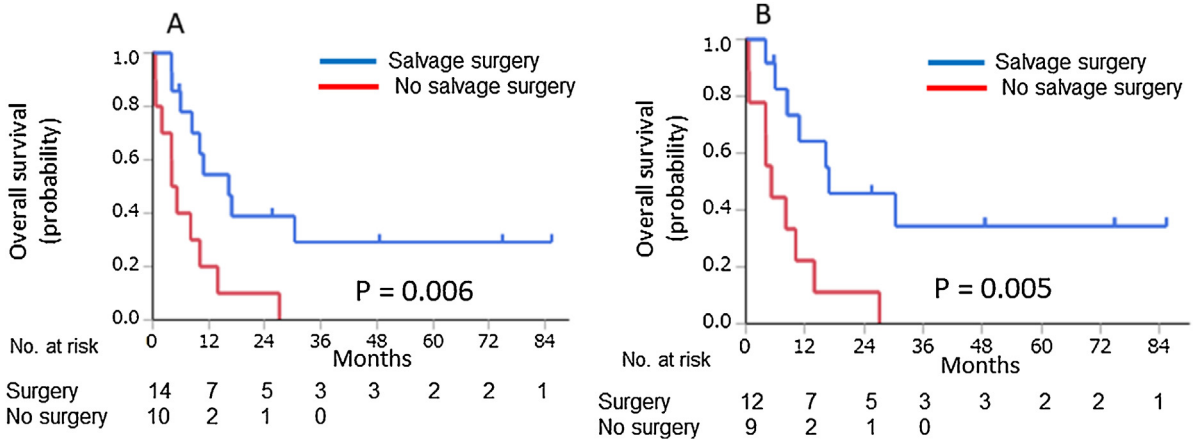

Fig. 3. (A) Kaplan–Meier curves for overall survival, for all patients who underwent salvage surgery (salvage surgery group) and those who underwent chemotherapy or palliative care (no salvage surgery group). (B) Kaplan–Meier curves for overall survival, for patients with squamous cell carcinoma who underwent salvage surgery (salvage surgery group) and those who did not (no salvage surgery group).

Table 2. Patients treated with salvage surgery.

No.	Age (years)	Sex	Histological type[a]	rTN classification	Surgical methods[b]	Orbital clearance	Reconstruction[c]	Complications
1	65	M	SCC	T3N0	SM	−	STSG + prosthesis	None
2	57	M	SCC	T3N0	TM	−	STSG + prosthesis	None
3	67	M	SCC	T4aN0	TM	−	STSG + prosthesis	Local infection
4	70	M	SCC	T3N0	TM	−	STSG + prosthesis	None
5	73	F	SCC	T2N0	TM	−	STSG + prosthesis	None
6	74	M	SCC	T4aN0	TM	−	STSG + prosthesis	None
7	59	M	SCC	T3N2b	TM + ND	+	STSG + prosthesis	None
8	48	M	SCC	T4aN2b	TM + ND	+	RAMF	Pneumonia
9	51	M	SpCC	T4bN0	CMFR	+	RAMF	Local infection Pneumonia
10	64	M	SCC	T4aN0	CMFR	+	RAMF	None
11	69	M	SCC	T4aN0	CMFR	+	RAMF	None
12	70	M	MEC	T4bN0	CMFR	+	RAMF	None
13	70	F	SCC	T4aN0	CMFR	+	RAMF	Local infection Fistula formation
14	73	M	SCC	T3N0	CMFR	+	RAMF	None

F, female; M, male.
[a] SCC, squamous cell carcinoma; SpCC, spindle cell carcinoma; MEC, mucoepidermoid carcinoma.
[b] SM, subtotal maxillectomy; TM, total maxillectomy; ND, neck dissection; CMFR, craniomaxillofacial resection.
[c] STSG, split thickness skin graft; RAMF, rectus abdominis musculocutaneous flap.

Disease control and survival in all 76 patients

The 5-year LC, DFS, and OS rates of all patients who underwent I-RADPLAT followed by S-RADPLAT or surgery were 65.9%, 55.2%, and 60.5%, respectively. The 5-year LC, DFS, and OS rates were 67.3%, 55.6%, and 61.2%, respectively, in patients with SCC, and 50.0%, 50.0%, and 50.0%, respectively, in those with non-SCC (Fig. 2). There was no significant difference in LC ($P = 0.315$), DFS ($P = 0.250$), or OS ($P = 0.246$) between the groups.

Treatment outcomes of patients with a locally persistent or recurrent tumour

Fourteen of 24 patients who had a locally persistent or recurrent tumour without distant metastasis underwent surgery (salvage surgery group) such as a subtotal maxillectomy ($n = 1$), total maxillectomy ($n = 7$), or craniomaxillofacial resection ($n = 6$). The remainder ($n = 10$) underwent chemotherapy or palliative care (no salvage surgery group) because they rejected salvage surgery. Among the patients who underwent chemotherapy ($n = 5$), two received tegafur/gimeracil/oteracil (TS-1), two received cisplatin and 5-fluorouracil (PF), and one received docetaxel, cisplatin, and 5-fluorouracil (TPF).

The 2-year OS rate was 39.0% in the salvage surgery group ($n = 14$) and 10% in the no salvage surgery group ($n = 10$) (Fig. 3). Additionally, in patients with SCC, the 2-year OS rate was 45.8% in the salvage surgery group ($n = 12$) and 11.1% in the no salvage surgery group ($n = 9$). There were significant differences in OS between the salvage surgery group and no salvage surgery group in all 24 patients ($P = 0.006$) and in patients with SCC ($P = 0.005$).

Patients who underwent salvage surgery

The histological types, recurrent TN classifications, surgical methods, orbital clearance, reconstructive methods, and complications of the 14 patients who underwent salvage surgery are summarized in Table 2. A subtotal or total maxillectomy was performed for one patient and seven patients, respectively; a neck dissection was also performed for two of the patients who had a total maxillectomy. Of the patients who had a maxillectomy, one or seven underwent reconstruction with a rectus abdominis musculocutaneous flap (RAMF) and a split-thickness skin graft (STSG), respectively. Craniomaxillofacial

Table 3. Tumour extension, surgical margin status, and clinical outcomes.

No.	Surgical methods[a]	Superior	Inferior	Anterior	Posterior	Outside	Superior-inside	Site of positive margin	Recurrence[b]	Outcome[c]
1	SM	Floor wall of orbit	Hard palate	Bone erosion	Bone erosion	Bone erosion	Middle nasal meatus	–	NER	NED
2	TM	Mucosa	Hard palate	Cheek skin	Mucosa	Mucosa	Middle nasal meatus	+ Cheek skin	Local	DOD
3	TM	Floor wall of orbit	Hard palate	Subcutaneous tissues	Inferior orbital fissure	Infratemporal fossa	Middle nasal meatus	+ Inferior orbital fissure	Local	NED
4	TM	Mucosa	Bone erosion	Mucosa	Bone erosion	Bone erosion	Mucosa	–	Local	DOD
5	TM	Floor wall of orbit	Hard palate	Bone erosion	Mucosa	Bone erosion	Middle nasal meatus	–	NER	NED
6	TM	Intra-orbit	Hard palate	Subcutaneous tissues	Pterygoid fossa	Infratemporal fossa	Mucosa	+ Infratemporal fossa + Pterygoid fossa	Local	DOD
7	TM + ND	Orbital apex	Bone erosion	Bone erosion	Sphenoid sinus	Mucosa	Ethmoid sinus	+ Ethmoid sinus + Orbital apex	Local	DOD
8	TM + ND	Intra-orbit	Hard palate	Subcutaneous tissues	Posterior bony wall	Infratemporal fossa	Middle nasal meatus	+ Infratemporal fossa	Local	DOD
9	CMFR	Skull base (dura) Intra-orbit	Bone erosion	Cheek skin	Sphenoid sinus	Infratemporal fossa	Frontal sinus	+ Intra-dural	Local Distant	DOD
10	CMFR	Orbital apex	Bone erosion	Cheek skin	Pterygoid process	Infratemporal fossa	Middle nasal meatus	–	Distant	DOD
11	CMFR	Floor wall of orbit	Hard palate	Subcutaneous tissues	Bone erosion	Infratemporal fossa	Ethmoid sinus	–	NER	NED
12	CMFR	Intra-orbit	Hard palate	Subcutaneous tissues	Cavernous sinus	Bone erosion	Ethmoid sinus	+ Intra-dural + Subcutaneous tissues	Local	DOD
13	CMFR	Intra-orbit	Bone erosion	Cheek skin	Inferior orbital fissure	Infratemporal fossa	Ethmoid sinus	–	NER	NED
14	CMFR	Floor wall of orbit	Bone erosion	Subcutaneous tissues	Pterygoid fossa	Bone erosion	Ethmoid sinus	–	NER	NED

[a] SM, subtotal maxillectomy; TM, total maxillectomy; ND, neck dissection; CMFR, craniomaxillofacial resection.
[b] NER, no evidence of recurrence.
[c] NED, no evidence of disease; DOD, died of disease.

resection was performed for six patients; these patients underwent a RAMF procedure. Although postoperative complications occurred in four patients (28.6%), no patient had a fatal complication.

Relationships between tumour extensions, surgical margins, and clinical outcomes

The tumour extension, surgical margin status, and clinical outcomes of the patients are shown in Table 3. A maxillectomy was performed for eight patients, two of whom had a tumour extending into the orbit. Craniomaxillofacial resection was performed for six patients; four of these patients had a tumour extending into the orbit and two had a tumour extending into the intra-cranial tissues.

The 2-year LC rate was 38.1% in patients with an intra-orbital extension and 57.1% in those without an intra-orbital extension, and the 2-year OS rate was 17.9% in patients with an intra-orbital extension and 57.1% in those without an intra-orbital extension (Fig. 4). Although patients without an intra-orbital extension tended to have favourable OS compared with patients with an intra-orbital extension, there was no significant difference between the two groups ($P = 0.051$).

Regarding the surgical margin status, the 2-year LC and OS rates of patients with positive or negative surgical margins were 14.3% and 83.3% and 14.3% and 66.7%, respectively (Fig. 4). There were significant differences in LC ($P = 0.004$) and OS ($P = 0.005$) between the two groups. In patients who underwent maxillectomy, five of eight had positive surgical margins; the sites were the infratemporal fossa (two patients), cheek skin (one patient), ethmoid sinus (one patient), orbital apex (one patient), inferior orbital fissure (one patient), and pterygoid fossa (one patient). All patients with positive surgical margins experienced local relapse. In patients who underwent craniomaxillofacial resection, two of six patients had positive surgical margins; the sites were the intra-dural tissue (two patients) and subcutaneous tissue (one patient). These patients experienced local relapse, whereas no local relapse was observed in the four patients with negative surgical margins. A comparison of the surgical resection lines on computed tomography (CT) images between patients who underwent a total maxillectomy and those who underwent craniomaxillofacial resection is shown in Fig. 5.

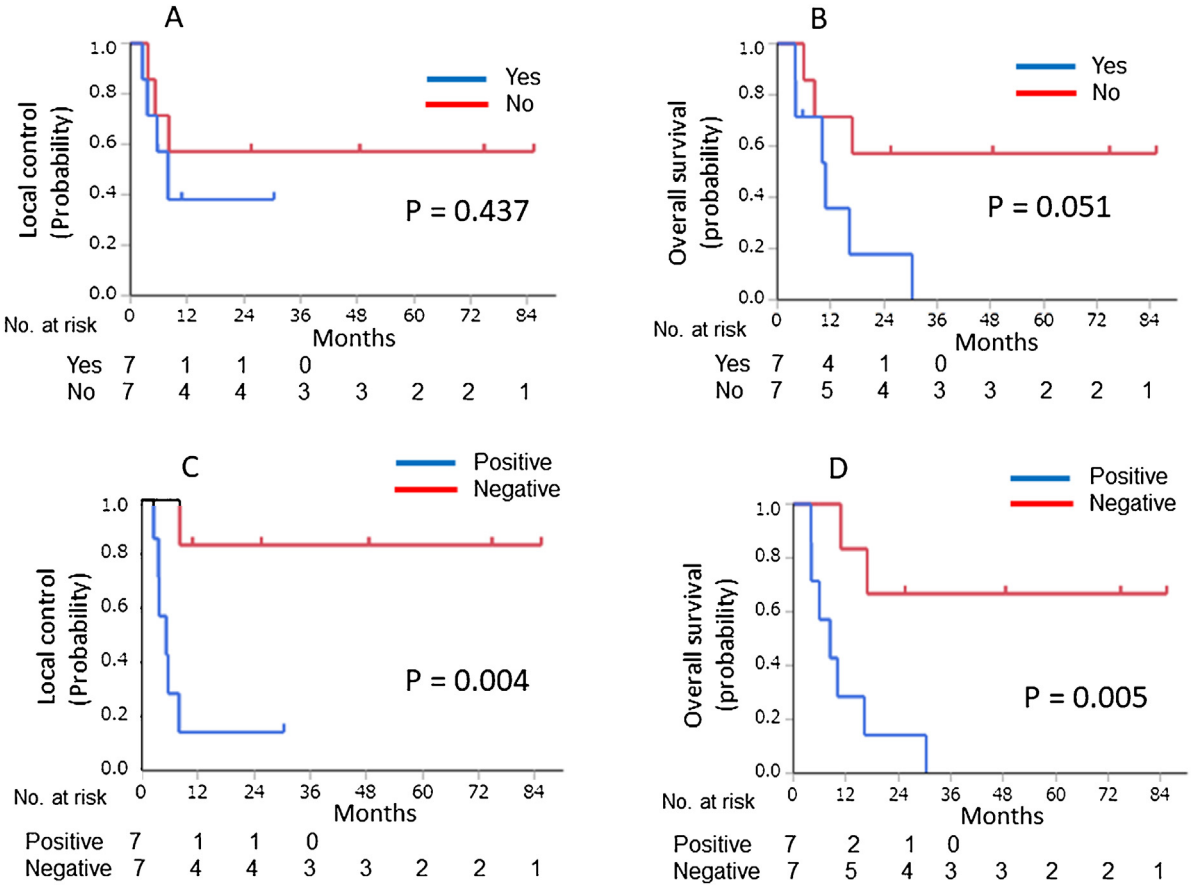

Fig. 4. Kaplan–Meier curves for (A) local control and (B) overall survival, according to the presence or absence of orbital invasion in patients who underwent salvage surgery. Kaplan–Meier curves of (C) local control and (D) overall survival, according to the presence of positive or negative surgical margins in patients who underwent salvage surgery.

Discussion

RT, CRT, and bioradiation therapy have been performed for head and neck cancers as options for organ and functional preservation[9–11]. However, despite aggressive treatment combinations of RT and chemotherapy or biotherapy, about 30% of patients will have a locally recurrent and/or regionally recurrent tumour[12]. Salvage surgery is considered to be the only method able to provide a complete recovery in locally persistent or recurrent head and neck cancers, although a high complication rate and low salvage rate remain after salvage surgery[13–16]. Several sources of information are available regarding salvage surgery for laryngeal, hypopharyngeal, oropharyngeal, and oral cancers[17–20]; however, information regarding salvage surgery following RT and CRT in paranasal cancers is limited[21,22].

In a study involving patients undergoing salvage surgery after failed radiation for paranasal sinus malignancy, Curran et al. reported 2 and 5-year OS rates of 54% and 35%, respectively[21]. In patients with recurrent sinonasal malignancy undergoing salvage surgery ($n = 42$), Kaplan et al. reported OS rates at 6 months, 12 months, and 5 years after surgery of 83.3%, 69%, and 47.6%, respectively; they also reported that the 5-year OS rate with maxillary recurrence was 45.5%[22]. Additionally, in patients with locally persistent or recurrent cancer after RADPLAT, Sakashita et al. reported that the 5-year OS in the salvage surgery group was 61% and that the group had a statistically favourable OS compared with the no salvage surgery group[23]. The 5-year OS rates of patients who did and did not undergo salvage surgery were 29.2% and 0%, respectively, in the present study. Furthermore, the 5-year OS rates of patients with SCC who did and did not undergo salvage surgery were 34.8% and 0%, respectively. The salvage rate in this study exhibited an unfavourable outcome compared with those in recent reports.

Previous studies on sinonasal cancers have demonstrated that specific factors affect the prognosis, such as intracranial invasion, orbital extension, and the surgical margin status[24–27]. Of the 14 patients in the present study who underwent salvage surgery, two patients who underwent craniomaxillofacial resection had histopathologically positive surgical margins with intra-cranial invasion. These patients had local recurrence and distant metastasis in the short term. Regarding orbital extension, several studies have shown that patients with an intra-orbital tumour extension have unfavourable outcomes compared with patients without an intra-orbital extension[22,24–26]. The present study showed no significant difference in LC or OS between patients with and without an intra-orbital extension, although there was a tendency towards unfavourable OS for patients with an intra-orbital extension.

Regarding surgical margin status, previous studies have reported that this was a strong prognostic factor affecting LC and survival[24,27]. The present study showed that patients with positive surgical mar-

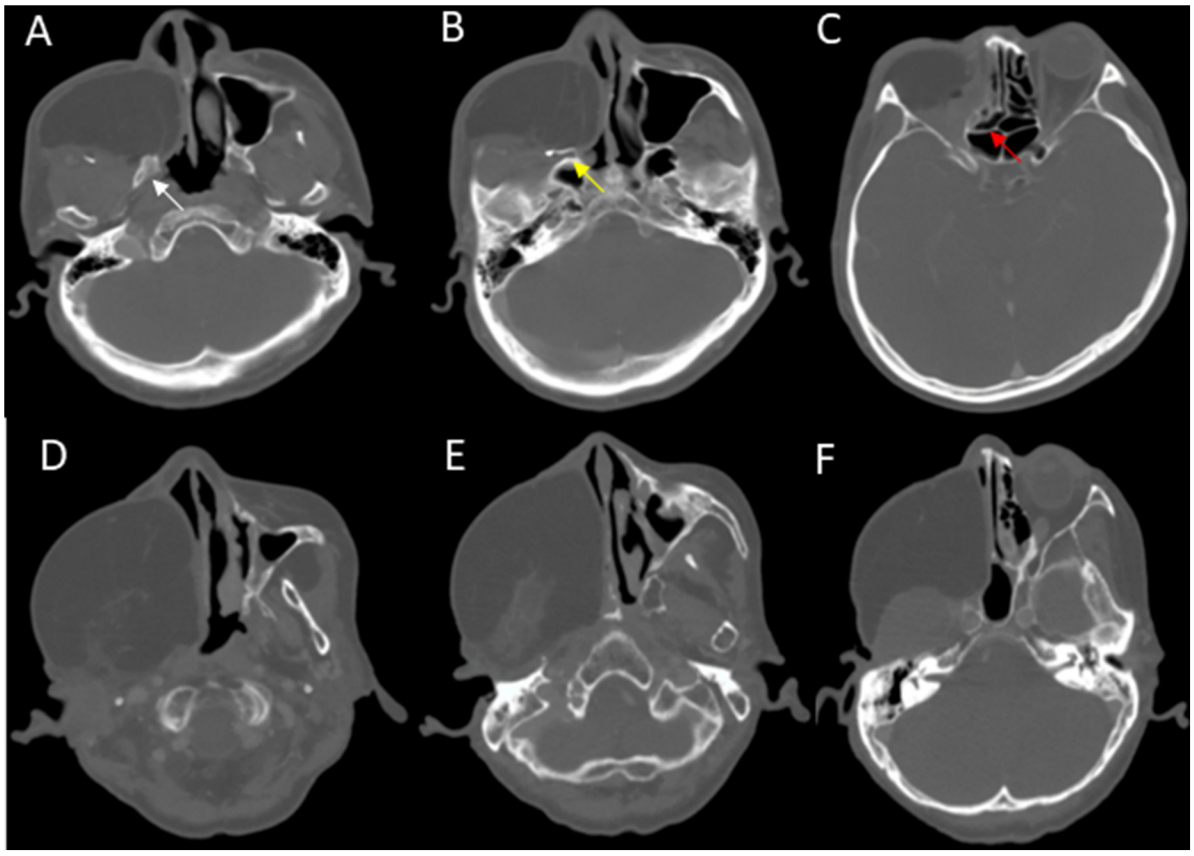

Fig. 5. Differences in resection lines between total maxillectomy (A–C) and craniomaxillofacial resection (D–F). In total maxillectomy, the pterygoid process (white arrow), pterygopalatine fossa (yellow arrow), inferior orbital fissure, and ethmoidal air cells (red arrow) are removed incompletely. In the craniomaxillofacial resection approach, the anterior-middle fossa floor is drilled along the lines from the cribriform plate to the superior wall of the sphenoid sinus, optic canal, foramen rotundum, foramen ovale, and mandibular fossa. The infratemporal fossa, pterygopalatine fossa, inferior orbital fissure, and orbital components including the orbital apex and ethmoid sinus are removed completely without involving the surgical margins.

gins had significantly worse LC and OS compared with patients with negative surgical margins. Furthermore, the median survival time of patients who underwent salvage surgery with positive surgical margins was 8.3 months and that of patients who did not undergo salvage surgery was 4.0 months ($P = 0.300$; data not shown). Thus, it is believed that if surgical safety margins cannot be assessed for local tumour extension, a surgical approach should not be selected because of the inability to perform postoperative definitive irradiation as an adjuvant therapy. Therefore, it is important to carefully assess the surgical safety margin.

As can be seen, locally recurrent maxillary cancer conveys poor survival because of diagnostic difficulty at the time of local recurrence, an advanced-stage tumour at the time of diagnosis, and difficulty in the assessment of surgical safety margins due to the complex anatomy.

In this study, the anatomical sites of the extensions and positive surgical margins of the locally recurrent tumours were analyzed retrospectively (Table 3). Considering the resection lines shown in Fig. 5, if recurrent tumours do not extend into the frontal sinus, ethmoid sinus, pterygopalatine fossa, inferior orbital fissure, orbital apex, or infratemporal fossa, a total maxillectomy without intracranial processing can be adapted to the case. However, in cases in which a recurrent tumour extends into or beyond these sites, craniomaxillofacial resection using an intracranial approach should be selected to secure surgical safety margins. Patients with invasion into the cavernous sinus, internal carotid artery, or beyond the dura may not be appropriate candidates for a surgical approach because of the extremely poor prognosis and high mortality reported previously[28].

Regarding salvage surgery in head and neck cancers, a correlation between CRT and postoperative complications has been reported, and complications rates of 24–42% and mortality rates of 2.0–5.2% have been reported[13,29,30]. Furthermore, complication rates in salvage surgery of 24% for sinonasal cancers and 18% (2/11 patients) for maxillary cancers have been reported[21,23]. The complication and mortality rates in the present study were 28.6% and 0%, respectively. Therefore, it is believed that salvage surgery after intensive CRT to local sites, such as RADPLAT, is acceptable and feasible.

This study has several limitations. First, it used a small, retrospective cohort. Second, the categorizations of patients who underwent salvage surgery, chemotherapy, and palliative care were not made by therapeutic criteria but by whether the patient accepted or refused the surgery. This fact may have resulted in a selection bias.

In conclusion, salvage surgery for locally persistent or recurrent MSC after

RADPLAT or surgery is considered to be feasible and safe. However, it is important to assess the surgical safety margins and it should be decided whether an intracranial approach is needed for negative surgical margins.

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Competing interests. There are no competing interests.

Ethical approval. This study was conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of Kurume University Hospital (Ref. 17013).

Patient consent. Not required.

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