Case Report

Treatment Outcomes of Locally Advanced Squamous Cell Carcinoma of the Ethmoid Sinus Treated with Anterior Craniofacial Resection or Chemoradiotherapy

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Keywords

Craniofacial resection · Squamous cell carcinoma · Ethmoid sinus · Cisplatin

Abstract

We retrospectively analyzed 14 patients with locally advanced squamous cell carcinoma of ethmoid sinus (LASCC-ES) for the feasibility of anterior craniofacial resection (ACFR). Ethmoid cancer treatment comprised alternating chemoradiotherapy (ALCRT; $n = 1$), concomitant radiotherapy and intra-arterial cisplatin (RADPLAT; $n = 4$) and ACFR ($n = 9$). The 3- and 5-year overall survival (OS) rates of patients were 47.6 and 39.6%, respectively. The 3-year local

control (LC) rates of chemoradiotherapy (CRT; ALCRT and RADPLAT) ($n = 5$) and ACFR ($n = 9$) groups were 0 and 66.7% ($p = 0.012$), respectively. The 3-year progression-free survival (PFS) rate of the CRT and ACFR groups were 0 and 55.6% ($p = 0.018$), respectively. The 3-year OS rate of the CRT and ACFR groups were 0 and 76.2% ($p = 0.005$), respectively. Postoperative pathological examinations confirmed positive margins in 3 (33%) of 9 cases. The 3-year LC and PFS rates of cases ($n = 3$) with positive surgical margins were significantly poorer than those of cases ($n = 6$) with negative surgical margins. Although ACFR for LASCC-ES is a feasible treatment, cases with positive surgical margins were more prone to local relapse. Therefore, surgical safety margins should be thoroughly assessed.

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Introduction

Sinonasal squamous cell carcinoma (SCC) is a rare form of head and neck malignancy, with an incidence of 3%, while SCC of the ethmoid sinus is even more infrequent with relatively few cases cited in the literature [1]. Since it is difficult to diagnose ethmoid cancer in the early stage of disease, most patients are diagnosed with locally advanced SCC of the ethmoid sinus (LASCC-ES). Ethmoid cancer easily extends into the anatomical structures around the ethmoid sinus, including the skull base plate, intracranial organs, facial skin, and orbital content. The general treatment for LASCC-ES is multidisciplinary consisting of surgery, radiotherapy (RT), or chemoradiotherapy (CRT). In our institution, anterior craniofacial resection (ACFR) has been performed for LASCC-ES patients in cooperation with plastic surgeons and neurosurgeons since 1984. Some LASCC-ES patients reject the option of ACFR because of the significant extent of anatomical damage that is often accompanied by facial deformation and/or visual impairment. Therefore, LASCC-ES patients who reject ACFR and require that organ anatomy and function should be preserved undergo alternating CRT (ALCRT) or concomitant RT and intra-arterial cisplatin (RADPLAT) as first reported by Robbins et al. [2] in 1992.

The aim of present study was to clarify the treatment outcome of ACFR and CRT (ALCRT and RADPLAT) for LASCC-ES and to evaluate the feasibility of ACFR.

Patients and Methods

Patients

We retrospectively analyzed the treatment outcomes of 14 patients with LASCC-ES who underwent ALCRT, RADPLAT, or ACFR at Kurume University Hospital between January 2000 and December 2013. The patient cohort consisted of 11 males and 3 females, with a median age of 60 years (range 41–82). The median observation period was 52 months (range 20–85). All patients had a World Health Organization performance status of 0–1. The tumor-node-metastasis stage classification was determined by the consensus of a head and neck surgeon and a radiation oncologist according to the 7th edition of the Union for International Cancer Control (UICC) staging system [3]. Patients with distant metastasis (M1) or palliation were excluded from the study. All patients were pathologically diagnosed as SCC. In the

study cohort, 1 primary tumor was classified as clinical T3, 9 as T4a, and 4 as T4b. There was 1 patient with metastasis to neck lymph nodes. One or 4 patients, who rejected ACFR, were treated with ALCRT or RADPLAT, respectively, and the others underwent ACFR. The institutional review board at Kurume University approved this retrospective study, and informed consent was obtained from all patients.

Chemoradiation Methods

Regarding the RADPLAT method, intra-arterial cisplatin infusion was administered by a diagnostic radiologist using the Seldinger technique, which involved a transcatheter femoral insert. A microcatheter was intra-arterially inserted and selectively advanced to arteries feeding the tumors. Angiographic-assisted infusion of cisplatin via the internal maxillary artery branched from the external carotid artery was selected for all cases. The feeding arteries were identified by cone-beam computed tomography, and then cisplatin (80–100 mg/m²/week; with a total of 4 times) was intra-arterially administered at a flow rate of 0.3–1.0 mL/s with simultaneous intravenous administration of sodium thiosulfate (20–25 g) to neutralize the acidity of cisplatin and reduce systemic toxicity, renal dysfunction, and vessel damage. All patients received external beam radiation of 1.8 Gy/fraction/day 5 times/week from a 4-MeV X-ray beam linear accelerator using a three-dimensional method for a total radiation dose of 59.6–61 Gy.

Regarding the ALCRT, fluorouracil and cisplatin-based chemotherapy was performed intravenously before RT, and RT (1.8 Gy/fraction/day and 4-MeV X-ray) was then performed for 4 weeks beginning 2–3 days after the completion of chemotherapy, as previously reported [4].

Therapeutic evaluation of the response to RADPLAT or ALCRT was performed 6–8 weeks after the treatment by magnetic resonance imaging.

ACFR and Adjuvant Therapy after Surgery

Five of 9 patients underwent neoadjuvant chemotherapy (NAC) prior to ACFR. NAC was performed for chemoselection to preserve the eye bowl. If the tumor response to NAC was not a complete or partial response (PR), the extent of surgical resection was based on the extent of tumor invasion before NAC. After ACFR, radiation or cisplatin-based chemoradiation (final dosage, 60–65 Gy) therapy was administered to all cases regardless of the positive or negative surgical margin.

Statistical Analysis

Statistical analyses were performed using the JMP Pro 12 statistical software (SAS Institute, Inc., Cary, NC, USA). The Kaplan-Meier method was used to calculate local control (LC), progression-free survival (PFS), and overall survival (OS), which were evaluated from the beginning of treatment to disease relapse or death due to any cause. Comparisons of survival rates were performed using the log-rank test. A probability (*p*) value of <0.05 was considered to be statistically significant.

Results

Clinical Outcomes

For all 14 patients, the 3- and 5-year PFS rates were 35.7 and 35.7%, respectively, and these of OS rate were 47.6 and 39.6% (Fig. 1a). The 3-year LC rates of the CRT (ALCRT and RADPLAT) ($n = 5$) and ACFR groups ($n = 9$) were 0 and 66.7%, respectively, and the 5-year LC rate of the ACFR group was 66.7% (Fig. 1b). There was a statistically significant difference between the CRT and ACFR groups ($p = 0.012$). The 3-year PFS rates of the CRT and ACFR groups were 0 and 55.6%, respectively, and the 5-year PFS rate of the ACFR group was 55.6% (Fig. 1c). Statistically significant difference in PFS was noted between the CRT and ACFR groups ($p = 0.018$). The 3-year OS rates of the CRT and ACFR groups were 0 and 76.2%, respectively, and the 5-year OS rate of the ACFR group was 63.5% (Fig. 1d). There was a statistically significant difference in OS between the CRT and ACFR groups ($p = 0.005$).

RADPLAT and ALCRT Outcomes

Treatment modalities and clinical outcomes for patients treated with CRT (RADPLAT or ALCRT) are summarized in Table 1. Regarding the RADPLAT, the case with the tumor staining from an external carotid artery and an internal carotid artery was shown in Figure 2. To avoid central complications, the internal maxillary artery was selected for intra-arterial cisplatin infusion of a total 400–600 mg in all patients, and RT with a total dose of 59.6–61 Gy was concomitantly performed in 4 cases. In the clinical evaluation of the CRT group, complete response (CR) was observed in 4 cases, and the remaining 1 case showed a PR. In spite of the good response to CRT, local recurrence of the primary tumor resulted in the death of 4 patients within 15 months. The patient who showed PR died from recurrent metastasis to the neck lymph nodes and lung.

ACFR Outcomes

The surgical methods, adjuvant therapy, complications, and clinical outcomes of 9 patients who underwent ACFR are summarized in Table 2. According to the clinical T stage of these 9 cases, 1, 6, and 2 cases were classified as T3, T4a, and T4b, respectively. With respect to the facial incision method combined with ACFR, 5, 2, and 2 cases underwent midfacial degloving, lateral rhinotomy, and facial dismasking, respectively. Orbital removal was performed for 5 patients with intraorbital invasion. For skull base reconstruction, frontal musculopericranial flap (FMF) was performed for all patients, and a bone graft from iliac bone combined with FMF was performed for 3 patients, and a rectus abdominis flap combined with FMF was also performed for 2 patients. Postoperative adjuvant RT was performed for 8 patients, and CRT was performed for 1 patient. One patient, who had already undergone RT (45 Gy), received additional radiation (20 Gy) after ACFR. Although postoperative intracranial complications occurred in 4 patients (44%), which consisted of meningitis, brain herniation, and cerebrospinal fluid leak in 2, 1, and 1 patients, respectively, no mortality relative to ACFR was observed. Local recurrence occurred in 3 cases, 1 of which also had neck lymph node recurrence. Distant metastasis to the lung was observed in 1 case.

Postoperative Histopathological Examination

The results of pathological evaluations are shown in [Figure 3](#). There were no statistically significant differences in 3-year LC and PFS rates between cases with or without intraorbital invasion, whereas there was a significant difference in 3-year OS (60 and 75%, $p = 0.665$; 40 and 75%, $p = 0.307$; and 53 and 100%, $p = 0.046$, respectively). There were no statistically significant differences in 3-year LC, PFS, and OS rates between the cases with or without dural invasion (50 and 80%, $p = 0.378$; 50 and 60%, $p = 0.779$; and 50 and 75%, $p = 0.348$, respectively). There were statistically significant differences in 3-year LC and PFS rates between cases with positive or negative surgical margins (0 and 100%, $p = 0.002$; 0 and 83.3%, $p = 0.023$, respectively), and there was tendency of a better outcome in 3-year OS (33.3 and 100%, $p = 0.106$).

Discussion

In 1963, Ketcham et al. [\[5\]](#) first reported the effectiveness of ACFR for the removal of intracranial organs by en block resection of a paranasal tumor extending from the nasal cavity to skull base plate. Although we have performed ACFR since 1984, some patients refuse such an invasive procedure for fear of potentially fatal postoperative complications and instead opt for CRT.

In the previously reported outcomes of RT and CRT, Waldron et al. [\[6\]](#) reported that rates of 5-year OS, disease-specific survival, and PFS of ethmoid cancer patients treated with megavoltage photons were 39, 58, and 41%, respectively. Morimoto et al. [\[7\]](#) reported 3-year OS and PFS rates of 44 and 31%, respectively, among SCC cases with unresectable growths invading the skull base, which were treated with photon beam or heavy ion RT. Saito et al. [\[8\]](#) recently reported that CR and PR rates of T4b SCC patients treated with proton (with or without X-ray) therapy were 29% (2/7) and 71% (5/7), respectively, and only 1 case showed no evidence of disease. In our study, the 3-year LC, PFS, and OS rates of patients treated with ALCRT or RADPLAT were all 0%, which were markedly poorer than in previous reports [\[6, 7\]](#). Although a CR of local tumors was achieved in 4 of 5 cases and a PR in 1 case, local relapse to the intracranial site occurred in 4 cases. Cisplatin was administered via the internal maxillary artery in 4 cases treated with RADPLAT. In consideration of the anatomical site, ethmoid tumors were found to be most commonly fed by the internal maxillary artery branched from the external carotid artery and followed by the optic artery branched from the internal carotid artery. Because local relapse occurred in 3 of 4 cases, we thought that administration of cisplatin via the internal maxillary artery only was insufficient to cover an entire tumor extending into the skull base plate. Administration into the optic artery may lead to visual disorders or central complications, such as brain infarction, and subsequently worsen the quality of life [\[9\]](#). Therefore, we believe that RADPLAT should not be considered for LASCC-ES extending into the skull base plate or intracranial organs.

With respect to previously reported outcomes of craniofacial resection (CFR) for ethmoid cancers, Cantù et al. [\[10\]](#) reported that the 5-year OS rate of patients with SCC was 21% among 330 patients with ethmoid malignant tumors treated with CFR. Salvan et al. [\[11\]](#) reported a 5-year OS rate of 36% among 41 cases with ethmoid malignant tumors and 39%

in cases with adenocarcinomas. In the present study, the 5-year OS rate of LASCC-ES cases was 63.5%, which was considerably better than that in previous reports [10, 11]

In a report of 1,307 cases of skull base malignant tumors, Patel et al. [12] found that prognostic factors were dural invasion, brain invasion, and surgical cut end, whereas Howard et al. [13] found that prognostic factors among 308 sinonasal tumor cases treated with CFR were histological type, intraorbital invasion, and brain invasion. In the present study, there were no statistically significant differences in 3-year LC, PFS, and OS rates between the groups with intraorbital invasion or dural invasion. On the other hand, there were statistically significant differences in 3-year LC and PFS rates according to a positive or negative surgical margin, and such a significant difference was also reported by Patel et al. [12].

With respect to complications following CFR, it is necessary to pay attention to intracranial complications, because they may lead to high mortality. When CFR is performed, indigenous bacteria of the nasal cavity may infiltrate a sterile intracranial site, thereby increasing the risk of intracranial infection. Ganly et al. [14] reported intracranial complications of liquorrhea and meningitis following CFR in 16.2 and 4.7% of cases, respectively, and preoperative RT, dural invasion, and brain invasion increased the risk of intracranial complications. To prevent intracranial infection of CFR, it may be necessary to separate equipment used in the surgery of intracranial and nasal components. Administration of a standardized regimen of 3 different antibiotics, including vancomycin, following CFR as reported by Kraus et al. [15] should be considered. Indeed, intracranial infection has not been observed since the implementation of these preventative measures in our institution.

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Author Contributions

All authors have contributed and are in agreement with the content of the manuscript.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

This manuscript has not been published elsewhere and is not under consideration by another journal. There are no conflicts of interest to declare.

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Ono et al.: Treatment Outcomes of Locally Advanced Squamous Cell Carcinoma of the Ethmoid Sinus Treated with Anterior Craniofacial Resection or Chemoradiotherapy

Fig. 1. **a** The 3- and 5-year progression-free survival (PFS) or overall survival (OS) rates among all patients ($n = 14$) were 35.7 and 35.7%, and 47.6 and 39.6%, respectively. **b** The 3-year local control (LC) rate in patients ($n = 5$) treated with alternating chemoradiation (ALCRT) or concomitant RT and intra-arterial cisplatin (RADPLAT) was 0%, and the 3- and 5-year LC rates among patients ($n = 9$) treated with anterior craniofacial resection (ACFR) were 66.7 and 66.7%, respectively. **c** The 3-year PFS rate in patients ($n = 5$) treated with ALCRT or RADPLAT was 0%, and the 3- and 5-year PFS rates in patients ($n = 9$) treated with ACFR were 55.6 and 55.6%, respectively. **d** The 3-year OS rate in patients ($n = 5$) treated with ALCRT or RADPLAT was 0%, and the 3- and 5-year OS rates among patients ($n = 9$) treated with ACFR were 76.2 and 63.5%, respectively. CRT, chemoradiotherapy.

Fig. 2. Angiography and cone beam computed tomography (CT) of the external carotid artery and internal carotid artery. **a** The tumor staining image from internal maxillary artery was observed in frontal view (white arrows). **b** The tumor staining image from the optic artery branched from the internal carotid artery was observed in lateral view (yellow arrows). Cone beam CT angiography of the external carotid artery in coronal (**c**) and sagittal view (**d**) could not identify the tumor stain extending into the skull base plate (yellow arrows).

Fig. 3. **a** The 3-year local control (LC), progression-free survival (PFS), and overall survival (OS) rates of patients with ($n = 5$) or without ($n = 4$) orbital invasion were 60 and 75%, 0 and 75%, and 53 and 100%, respectively. **b** The 3-year LC, PFS, and OS rates of patients with ($n = 5$) or without ($n = 5$) dural invasion were 50 and 80%, 50 and 60%, and 50 and 75%, respectively. **c** The 3-year LC, PFS, and OS rates of patients with positive ($n = 3$) or negative ($n = 6$) surgical margin were 0 and 100%, 0 and 83.3%, and 33.3 and 100%, respectively.

Table 1. Patients treated with chemoradiotherapy

Age, years	Sex	cTN	Treatment	Infusion artery	Total cisplatin, mg	RT, Gy	Clinical response	Recurrence	Follow-up, months	Outcome (cause)
66	M	T4bN0	RADPLAT	IMA	600	60	CR	Local	12	Death
67	F	T4aN0	RADPLAT	IMA	550	59.6	PR	Local	8.5	Death
82	F	T4aN0	RADPLAT	IMA	500	61	CR	Local	15	Death
75	M	T4bN0	RADPLAT	IMA	400	60	CR	Neck, lung	11	Death
44	M	T4aN2c	ALCRT	–	450	68.3	CR	Local	13	Death

cTN, clinical TN classification; RADPLAT, radiotherapy and intra-arterial cisplatin; ALCRT, alternating chemoradiotherapy; IMA, internal maxillary artery; RT, radiation therapy; CR, complete response; PR, partial response.

Table 2. Patients treated with anterior craniofacial resection

Age, years	Sex	cTN	Combined surgery	Orbital clear	Skull base reco	Adjuvant	Intracranial com	Recurrence	Follow-up, months	Outcome (cause)
59	M	T4aN0	LR	+	FMF+IB	RT 60 Gy	–	Local	10	Death
50	F	T4aN0	MD	–	FMF	CRT 50 Gy	–	–	53	Alive
56	M	T4aN0	MD	–	FMF	RT 61 Gy	–	–	85	Alive
70	M	T4aN0	FD	+	FMF+IB	RT 50 Gy	Meningitis	Local	25	Death
51	M	T4bN0	MD	–	FMF	RT 60 Gy	–	–	55	Alive
65	M	T3N0	MD	–	FMF	RT 60 Gy	Meningitis	Local + neck	42	Alive
41	M	T4aN0	LR	+	FMF+RAF	RT 60 Gy	Brain herniation	Lung	37	Death
58	M	T4aN0	MD	+	FMF+IB	RT 20 Gy	–	–	52	Alive
60	M	T4bN0	FD	+	FMF+RAF	RT 50 Gy	Cerebrospinal fluid leak	–	20	Alive

cTN, clinical TN classification; Orbital clear, orbital clearance; Skull base reco, skull base reconstruction; Intracranial com, intracranial complication; LR, lateral rhinotomy; MD, midfacial degloving; FD, facial dismasking; FMF, frontal musculoperi-cranial flap; IB, iliac bone; RAF, rectus abdominis flap; RT, radiation therapy; CRT, chemoradiotherapy.