Long-Term Outcomes of Patients with Squamous Cell Carcinoma of the Temporal Bone after Concomitant Chemoradiotherapy

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Abstract

Objectives This article aims to clarify the long-term outcomes of patients with squamous cell carcinoma of the temporal bone who underwent concomitant chemoradiotherapy (CCRT).

Design and Setting The study design was a retrospective chart review.

Patients and Methods From December 2001 to June 2014, 23 patients with cancer of the temporal bone who were treated by CCRT at the Tohoku University Hospital and the Iwate Medical University Hospital were enrolled in this study. For advanced cancer of the temporal bone, a modified docetaxel, cisplatin, and 5-fluorouracil (TPF) regimen was used for CCRT. The long-term outcomes, including prognoses and late complications, were analyzed after CCRT of patients with cancers of the temporal bone.

Results The main long-term complications were stenosis of the external auditory canal and conductive hearing loss. No harmful late complications were observed in these patients. Disease-specific survival rates were 84.9% for all patients, 100% for patients of stage I, II, and III ($n = 10$), and 75.5% for patients of stage IV ($n = 13$) at 5 years.

Conclusions Our study showed that CCRT is an effective treatment choice for squamous cell carcinoma of the temporal bone. Furthermore, CCRT using the TPF regimen is a safe and effective initial treatment for patients with advanced cancers of the temporal bone.

Keywords

- squamous cell carcinoma
- external auditory canal
- chemoradiotherapy
- long-term prognosis
- adverse events
- complications

Introduction

Although treatment strategies for cancers of the temporal bone have been controversial, concomitant chemoradiotherapy (CCRT) is an effective choice of treatment, especially for advanced-stage disease.¹ Surgical treatment is effective for early-stage cancers of the temporal bone; however, once cancer cells invade the skull base and/or the surrounding extratemporal bone tissues, they are difficult

to manage surgically, and the prognosis of the patient becomes very poor.^{2,3} Although CCRT using the TPF regimen (docetaxel, cisplatin, and 5-fluorouracil) is a safe and effective initial treatment for patients with advanced cancers of the temporal bone,¹ the long-term outcomes of the patients are yet to be determined. Here, we report the long-term outcomes after CCRT, including prognoses and late complications of patients with cancers of the temporal bone.

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Patients and Methods

The study design was a retrospective chart review. From December 2001 to June 2014, 27 patients with cancer of the temporal bone were treated at the Tohoku University Hospital and the Iwate Medical University Hospital. Preoperative radiographic studies were performed on all patients, including computed tomography, magnetic resonance imaging, and 18-fluoro-2-deoxyglucose positron emission tomography. Patients were diagnosed and classified according to the University of Pittsburgh system,⁴ and none of the patients presented distant metastasis at the time of diagnosis. The T classification was as follows: T1, tumor limited to the external canal without bony erosion; T2, tumor limited to the external canal with bony erosion; T3, tumor eroding the middle ear and/or mastoid, or causing facial paralysis with limited soft tissue involvement; and T4, tumor eroding the cochlear, petrous apex, dura, or with extensive soft tissue involvement.

All but two patients had squamous cell carcinoma (SCC) that originated from the external auditory canal. There was one ceruminous gland adenocarcinoma and one adenoid cystic carcinoma. Three patients underwent surgery as initial treatment, and the reasons why these patients chose surgical

therapy included past history of irradiation after ipsilateral parotidectomy in a 74-year-old female (T1N0M0), advanced age in an 86-year-old male (T1N0M0), and histological type (adenoid cystic carcinoma) in a 52-year-old female (T2N0M0). We excluded these four patients who had tumors with extra-SCC and/or underwent surgery as initial treatment.

Twenty-three patients who underwent CCRT as an initial treatment were analyzed in our study (►Table 1), and no distant metastases were observed at the beginning of the treatment. There were 10 male patients and 13 female patients, and the average patient age was 66.0 years (range: 51–81 years). There were 12 tumors on the right side and 11 tumors on the left side. Treatments and the results of the patients were summarized in ►Table 2. Six patients with stage I tumors were treated by radiation therapy alone or with oral administration of S1.⁵ Three patients with stage II tumors were treated by radiation therapy concomitant with a weekly administration of low-dose docetaxel, i.e., 10 mg/m².^{2,6} Thirteen patients with stage III and IV tumors were treated by CCRT using the TPF regimen,^{7,8} which consists of continuous intravenous administration of 600 to 700 mg/m² 5-fluorouracil from day 1 through day 5, and a bolus injection of 50 mg/m² docetaxel and 60 mg/m² cisplatin on day 2. The other patient,

Table 1 Patient profiles

	Age	Sex	Side	Chief complaints	TNM	Extratemporal invasion
1	51	M	R	HI, otorrhea, otalgia	T4N1M0	Dura, JF
2	53	F	R	Otorrhea, FNP	T4N0M0	JF, VII, IX, X paralysis
3	56	F	R	Otorrhea	T4N2bM0	Parotid gland
4	59	F	L	Otorrhea	T4N0M0	ICA, MSB, skin
5	54	F	R	Otorrhea	T4N1M0	MSB, MJ
6	68	M	L	Tumor	T4N0M0	MJ, parotid gland
7	71	M	L	HI, otorrhea, otalgia	T4N0M0	PA, MJ
8	67	F	R	Otorrhea, otalgia	T4N2bM0	MSB, MJ, skin
9	58	M	L	Tumor	T4N2bM0	MJ, parotid gland, skin
10	77	F	L	Otorrhea, vertigo	T4N0M0	MSB
11	66	F	R	Otorrhea, fullness	T4N0M0	MJ
12	80	F	L	Otalgia	T4N0M0	MJ, parotid gland
13	71	M	L	Otalgia, otorrhea	T4N1M0	Parotid gland
14	66	F	L	Previous oto-surgery	T3N0M0	
15	58	F	R	Otorrhea	T2N0M0	
16	72	F	R	Otalgia	T2N0M0	
17	59	M	R	Otorrhea	T2N0M0	
18	72	M	L	Otorrhea	T1N0M0	
19	68	F	R	Tumor	T1N0M0	
20	71	M	R	HI, otorrhea	T1N0M0	
21	62	M	R	Bleeding	T1N0M0	
22	81	M	L	Not recorded	T1N0M0	
23	80	F	L	Itching	T1N0M0	

Abbreviations: F, female; FNP, facial nerve palsy; HA, hearing aid; HI, hearing impairment; ICA, internal carotid artery; JF, jugular foramen; L, left; M, male; MJ, mandibular joint; MSB, middle skull base; PA, petrous apex; R, right; TNM, tumor-node-metastasis.

Table 2 Treatment and results of the patients

	TNM	Chemo regimen	Response	RT (Gy)	Outcome	Notes
1	T4N1M0	TPF1 + 2	CR	70	NED	3M mastoidectomy, pathological CR
2	T4N0M0	TPFx2	CR	60	18M DOD	
3	T4N2bM0	TPFx2	CR	60	NED	RT cessation by dermatitis, S-1 orally after CCRT
4	T4N0M0	TPFx2	CR	70	13M DND	
5	T4N1M0	TPFx2	CR	66	NED	S-1 orally after CCRT
6	T4N0M0	TPFx1	PR	70	17M DOD	Refused second course of TPF
7	T4N0M0	TPFx1	CR	70	NED	Cessation of second course TPF by liver dysfunction
8	T4N2bM0	TPFx2	CR	70	NED	
9	T4N2bM0	TPFx2	CR	70	NED	9M salvage surgery
10	T4N0M0	TPFx2	CR	60	NED	
11	T4N0M0	TPFx2	CR	70	NED	
12	T4N0M0	CDDPiex4	CR	66	NED	
13	T4N1M0	TPFx2	PR	70	6M DOD	
14	T3N0M0	TPFx2	CR	68	NED	
15	T2N0M0	DOCx6	CR	70	NED	
16	T2N0M0	DOCx5	CR	70	NED	
17	T2N0M0	DOCx7	CR	60	NED	
18	T1N0M0	S-1	PR	70	NED	5M salvage surgery
19	T1N0M0	—	CR	60	NED	
20	T1N0M0	S-1	CR	70	NED	PH: Diabetes mellitus
21	T1N0M0	—	CR	70	NED	
22	T1N0M0	—	CR	CK	NED	
23	T1N0M0	—	CR	60	NED	

Abbreviations: CCRT, concomitant chemoradiotherapy; CK, cyberknife; CR, complete response; DOD, dead of disease; DND, dead not of disease; NED, no evidence of disease; PH, past history; PR, partial response; RT, radiotherapy; TNM, tumor-node-metastasis; TPF, docetaxel, cisplatin, and 5-fluorouracil regimen.

who was an 80-year-old female, underwent intra-arterial infusion of Cisplatin as a concomitant chemotherapy.⁹ Radiation therapies were performed using a 4 MeV linear accelerator and an equally divided protocol. Patients received 2 Gy/fraction radiation therapy every weekday (five fractions per week), and the total dose was 70 Gy.

Statistical analyses were performed using the Kaplan–Meier method for patient survival rates, and a log-rank test was used to examine significant differences.

Results

Adverse Events

The acute adverse events (AEs) that were experienced by patients who received CCRT with the TPF regimen ($n = 13$) are summarized in ►Table 3. A grade 4 AE that involved leukocyte count was observed in one patient (7.7%), and AEs involving granulocyte count were observed in four patients (31%). Grade 3 AEs that were related to bone marrow suppression were also observed, which involved leukocyte count in three patients, neutrophil count in one patient, lymphocyte count in nine patients, hemoglobin level in one

patient, and platelet count in one patient. The following grade 3 AEs were observed: glutamic oxaloacetic transaminase (GOT) in one patient, hypokalemia in one patient, and hyponatremia in two patients. One patient (case 6), for whom the second course of TPF was canceled, showed liver dysfunction (GOT, grade 3). Radiotherapy at the dose of 62 Gy was also canceled in one patient (case 3) because of radiation dermatitis (►Table 2).

A comparison of acute AEs is shown in ►Table 4. AEs that were experienced by the patients were compared with those experienced by 16 patients with stage IVA hypopharyngeal SCC who underwent CCRT using the TPF regimen during the same period. Although grade 3 or 4 leukocyte counts were observed in 76% of the patients with hypopharyngeal cancer, such counts were only observed in 30.7% of the patients with temporal bone cancer. Moreover, although grade 3 or 4 neutrophil counts were observed in 75% of the patients with hypopharyngeal cancer, only 38.7% of the patients with temporal bone cancer presented grade 3 or 4 neutrophil counts. These results indicate that CCRT using the TPF regimen showed less bone marrow suppression in patients with cancer of the temporal bone.

Table 3 Acute adverse events of the patients who underwent CCRT using TPF

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes		5	3	1
Neutrophils	2	2	1	4
Lymphopenia	1	3	9	
Hemoglobin	7	5	1	
Platelets	5		1	
Bilirubin	3			
Alkaline phosphatase	4	1		
g-GTP	1	2		
GOT (AST)	6	1	1	
GPT (ALT)	3	4		
Albumin	8	2		
Creatinine	2			
Hyponatremia	5		2	
Hyperkalemia	3	1		
Hypokalemia	3		1	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CCRT, concomitant chemoradiotherapy; GOT, glutamic oxaloacetic transaminase; g-GTP, gamma-glutamyl transpeptidase; GPT, glutamic pyruvic transaminase; TPF, docetaxel, cisplatin, and 5-fluorouracil regimen.

Long-term complications primarily included stenosis of the external auditory canal and conductive hearing loss. The stenosis of the external auditory canal was observed in more than half of the patients, some of whom showed conductive hearing loss. Two patients also showed sensorineural hearing loss whose averages of threshold of bone conduction were reduced around 10 dB after CRT.

Table 4 Comparison of the acute adverse events

	Cancer of the temporal bone (n = 13)		Cancer of the hypopharynx (n = 16)	
Adverse events	Grade 3	Grade 4	Grade 3	Grade 4
Leukocytes	23	7.7	31	25
Neutrophils	7.7	31	25	50
Lymphopenia	69		100	
Hemoglobin	7.7		13	19
GOT (AST)	7.7		6.3	
GPT (ALT)			6.3	
Hyponatremia	15		38	
Hyperkalemia			6.3	
Hypokalemia	7.7		6.3	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase

Note: Numbers are indicated by %.

Fig. 1 Survival curves of the patients. Overall survival rates were calculated by the Kaplan–Meier method. The 5-year survival rate of all patients was 80.6% (open circles), of patients who were T1–3 was 100% (closed circles), and of patients who were T4 and stage IV was 69.2% (closed squares).

Responses and Prognoses

We investigated the responses of the primary tumors to CRT. There were 23 objective lesions, of which complete response (CR) was obtained in 20 cases and partial response (PR) in three, resulting in a 100% response rate (RR) and 87% CR rate. As for regional lymph node metastases, there were seven objective lesions, and CR was obtained all seven cases, resulting in 100% RR and CR rates.

We calculated the survival rates of the patients by the Kaplan–Meier method. The mean and median observation times were 59.5 and 57 months, respectively. The overall survival rates were 80.6% for all patients, 100% for patients of stage I, II, and III, and 69.2% for patients of stage IV at 5 years (→**Fig. 1**). There were no significant differences among these three groups of patients in terms of overall survival rates. The disease-specific survival rates were 84.9% for all patients, 100% for patients of stage I, II, and III, and 75.5% for patients of stage IV at 5 years (→**Fig. 2**). There were no significant

Fig. 2 Survival curves of the patients. Disease-specific survival rates were calculated by the Kaplan–Meier method. The 5-year survival rate of all patients was 84.9% (open circles), of patients who were T1–3 was 100% (closed circles), and of patients who were T4 and stage IV was 75.5% (closed squares).

differences among these three groups of patients in terms of disease-specific survival rates.

Discussion

The TPF regimen has been widely used as induction chemotherapy for patients with head and neck SCC (HNSCC), and the usefulness of this regimen has been analyzed and reported elsewhere.^{10,11} On the other hand, CCRT has been recognized as a standard treatment for HNSCC, and its efficacy has been proven in many clinical studies.¹² However, CCRT using the TPF regimen is not widely used because physicians and medical oncologists are concerned about the toxicity of the TPF regimen, using standard doses of the individual agents. Therefore, we used modified doses of these agents. We also performed a phase I trial of CCRT using the TPF regimen for patients with HNSCC and estimated the recommended doses of docetaxel and cisplatin (Shiga et al, in preparation). Another trial reported by Katori and Tsukuda et al⁸ recommended doses that are in agreement with our results.

With respect to acute toxicity, AEs that were experienced by our group of patients were less toxic than those experienced by patients with tumors in the hypopharynx (►Table 4). Also, the main long-term AEs included stenosis of external auditory canal and hearing impairment due to the long-term effects of radiation therapy. We concluded that CCRT using the TPF regimen was tolerable and had minimum influence on the quality of life of patients with SCC of the temporal bone.

The patients who underwent CCRT displayed very good responses, and all but three patients obtained CR, although some patients showed PR after finishing CCRT. The reason for not obtaining CR seemed partially due to the TPF chemotherapy course number. Two patients who showed PR after CCRT with the TPF regimen displayed poor prognoses, one patient refused the second course of TPF chemotherapy and therefore only underwent one course of TPF. This result suggested that the overall dose of TPF, i.e., docetaxel, cisplatin, and 5-fluorouracil, and at least two courses of TPF, determine CR against the T4 tumor of the temporal bone.

Several studies have reported the treatment of cancers of the temporal bone. Essig et al¹³ reported that lateral temporal bone resections achieved good results when negative margins were obtained during surgery for advanced SCC of the temporal bone. Sinha et al¹⁴ also reported that achieving a negative margin was difficult during lateral bone resection surgery and that lymph node metastases correlated with poor prognoses. Morita et al¹⁵ concluded that T1–2 tumors were well controlled by surgery, but recommended for T3–4 tumors to be treated by CRT. Shinomiya et al¹⁶ reported the results of CCRT using the TPF regimen for advanced SCC of the temporal bone. Furthermore, Takenaka et al¹⁷ performed a meta-analysis of CRT for SCC of the external auditory canal.

Because this study included a small number of patients with cancers of the temporal bone, a randomized control study is required to gather more information and to validate the efficacy of CCRT as a treatment for cancers of the temporal bone.

Conclusions

Our study showed that CCRT is an effective choice of treatment for SCC of the temporal bone. Especially, CCRT using the TPF regimen is safe and effective to be used as the initial treatment for patients with advanced cancers of the temporal bone. No harmful complications were observed in the patients after long-term follow-up. Our treatment strategy seems to be the best approach and should be a standard method for treating patients with SCC of the temporal bone.

Conflict of Interest

None.

References

- Shiga K, Ogawa T, Maki A, Amano M, Kobayashi T. Concomitant chemoradiotherapy as a standard treatment for squamous cell carcinoma of the temporal bone. *Skull Base* 2011;21(03):153–158
- Lewis JS, Page R. Radical surgery for malignant tumors of the ear. *Arch Otolaryngol* 1966;83(02):114–119
- Prasad S, Janecka IP. Efficacy of surgical treatments for squamous cell carcinoma of the temporal bone: a literature review. *Otolaryngol Head Neck Surg* 1994;110(03):270–280
- Arriaga M, Curtin H, Takahashi H, Hirsch BE, Kamerer DB. Staging proposal for external auditory meatus carcinoma based on pre-operative clinical examination and computed tomography findings. *Ann Otol Rhinol Laryngol* 1990;99(9 Pt 1):714–721
- Niibe Y, Nakayama M, Matsubayashi T, et al. Effectiveness of concurrent radiation therapy with UFT or TS-1 for T2N0 glottic cancer in Japan. *Anticancer Res* 2007;27(5B):3497–3500
- Akimoto T, Nonaka T, Kitamoto Y, et al. Radiation therapy for T2N0 laryngeal cancer: a retrospective analysis for the impact of concurrent chemotherapy on local control. *Int J Radiat Oncol Biol Phys* 2006;64(04):995–1001
- Schrijvers D, Vermorken JB. Role of taxoids in head and neck cancer. *Oncologist* 2000;5(03):199–208
- Katori H, Tsukuda M. Comparison of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (TPF) followed by radiation vs concurrent chemoradiotherapy with TPF in patients with locally advanced squamous cell carcinoma of the head and neck. *Clin Oncol (R Coll Radiol)* 2005;17(03):148–152
- Shiga K, Yokoyama J, Hashimoto S, et al. Combined therapy after superselective arterial cisplatin infusion to treat maxillary squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2007;136(06):1003–1009
- Vermorken JB, Remenar E, van Herpen C, et al; EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med* 2007;357(17):1695–1704
- Posner MR, Herschock DM, Blajman CR, et al; TAX 324 Study Group. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 2007;357(17):1705–1715
- Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. *Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet* 2000;355(9208):949–955
- Essig GF, Kitipornchai L, Adams F, et al. Lateral temporal bone resection in advanced cutaneous squamous cell carcinoma: report of 35 patients. *J Neurol Surg B Skull Base* 2013;74(01):54–59

- 14 Sinha S, Dedmon MM, Naunheim MR, Fuller JC, Gray ST, Lin DT. Update on surgical outcomes of lateral temporal bone resection for ear and temporal bone malignancies. *J Neurol Surg B Skull Base* 2017;78(01):37–42
- 15 Morita S, Homma A, Nakamaru Y, et al. The outcomes of surgery and chemoradiotherapy for temporal bone cancer. *Otol Neurotol* 2016;37(08):1174–1182
- 16 Shinomiya H, Hasegawa S, Yamashita D, et al. Concomitant chemoradiotherapy for advanced squamous cell carcinoma of the temporal bone. *Head Neck* 2016;38(Suppl 1):E949–E953
- 17 Takenaka Y, Cho H, Nakahara S, Yamamoto Y, Yasui T, Inohara H. Chemoradiation therapy for squamous cell carcinoma of the external auditory canal: a meta-analysis. *Head Neck* 2015;37(07):1073–1080