



HOKKAIDO UNIVERSITY

Title	Clinical outcomes of weekly cisplatin chemoradiotherapy for patients with pyriform sinus cancer
Author(s)	Sakashita, Tomohiro; Homma, Akihiro; Hatakeyama, Hiromitsu et al.
Citation	International Journal of Clinical Oncology, 20(6), 1081-1085 https://doi.org/10.1007/s10147-015-0821-8
Issue Date	2015-12
Doc URL	https://hdl.handle.net/2115/63715
Rights	The final publication is available at Springer via http://dx.doi.org/10.1007/s10147-015-0821-8
Type	journal article
File Information	manuscript.pdf



Title: Clinical outcomes of weekly cisplatin chemoradiotherapy for patients with ~~advanced~~ pyriform sinus cancer.

Author: Tomohiro Sakashita, Akihiro Homma, Hiromitsu Hatakeyama, Jun Furusawa, Satoshi Kano, Takatsugu Mizumachi, Satoshi Iizuka, *Rikiya Onimaru, *Kazuhiko Tsuchiya, *Koichi Yasuda, *Hiroki Shirato, and Satoshi Fukuda

Department of Otolaryngology- Head & Neck Surgery, Hokkaido University Graduate School of Medicine

*Department of Radiology, Hokkaido University Graduate School of Medicine

Running title: Outcomes of weekly cisplatin chemoradiotherapy for ~~advanced~~ pyriform sinus cancer.

Corresponding author: Akihiro Homma

Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine. 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

Background: Pyriform sinus squamous cell carcinoma (SCC) has one of the worst prognoses of all upper aerodigestive tract cancers. The improvement of clinical outcomes for patients with hypopharyngeal SCC has been particularly challenging for head and neck surgeons and oncologists.

Methods: We investigated 30 patients with pyriform sinus SCC to verify the effectiveness of weekly cisplatin chemotherapy with concurrent radiotherapy. Cisplatin was administered at a dose of 40mg/m^2 on weeks 1, 2, 3, 5, 6, and 7 during definitive radiotherapy with the aim of preserving the larynx.

Results: All 30 patients achieved definitive radiotherapy at a median dose of 70 Gy (range, 64 to 70 Gy). Cisplatin was administered concomitantly a median of five times (range, 2 to 6 times). Persistent or recurrent primary disease was observed in four patients (13%). Persistent or recurrent nodal metastasis was observed in five patients (17%). Nine salvage surgeries were performed for ten eight patients, of which seven survived without any evidence of disease. Post-operative complications were observed in two cases (22%). The five-year overall survival and locoregional control rates were 87% and 96%, respectively. The five-year laryngeal preservation rate was 74%.

Conclusions: The regimen of weekly cisplatin CRT may be effective for pyriform sinus SCC; however, there were problems with the strong selection bias in the current study due to the large number of T2 patients. Salvage surgery was safe and was able to improve the survival rate. This chemoradiation regimen was considered successful in preserving laryngeal function.

Keywords: Chemoradiation, hypopharyngeal cancer, laryngeal preservation

Introduction

Squamous cell carcinoma (SCC) of the hypopharynx carries one of the worst prognoses of all upper aerodigestive tract cancers, particularly for tumors arising in the pyriform sinus, the most frequent site of hypopharyngeal origin [1]. Extended radical surgery, such as total pharyngo-laryngectomy (TPL), followed by radiotherapy is considered to be the standard treatment. The use of combined chemoradiotherapy (CRT) in the treatment of advanced resectable diseases is known as the organ preservation approach [2]. The National Comprehensive Cancer Network (NCCN) guidelines (2014, version 2) state that CRT, or surgical treatment, or induction chemotherapy followed by CRT or surgery was recommended for patients with T2-3 hypopharyngeal tumors requiring pharyngectomy with total laryngectomy. These guidelines also state that surgical treatment was preferred for patients with T4a hypopharyngeal tumors [3].

We applied weekly cisplatin chemotherapy with concurrent radiotherapy for patients with hypopharyngeal cancer, as the efficacy and feasibility of this regimen were reported previously [4]. We then retrospectively evaluated the survival and laryngeal preservation rates to verify the effectiveness of this treatment for patients with pyriform sinus SCC.

Materials and methods

Patient eligibility. Patients with resectable pyriform sinus SCC who underwent weekly cisplatin CRT between August 2006 and January 2013 in our institution were regarded as eligible. Cases without any invasion to the prevertebral or deep cervical muscle or the carotid artery were defined as resectable cases.

An Eastern Cooperative Oncology Group performance status of 0-1 was required in addition to the following criteria: a white cell count of at least $4,000/\text{mm}^3$, a platelet count of at least $100,000/\text{mm}^3$, a hemoglobin concentration of at least 9.5 g/dL, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels of less than twice the upper limit of the normal range, a total bilirubin concentration of $<2.0 \text{ mg/dL}$, a serum creatinine concentration of $<1.5 \text{ g/dL}$, a blood urea nitrogen concentration of $<25 \text{ mg/dL}$, and a creatinine clearance of $>60 \text{ mL/min}$.

Approval for this study was obtained from the institutional review board at Hokkaido University. Completion of the survey was regarded as implied consent for participation.

Chemotherapy and concurrent radiotherapy. Cisplatin was administered at a dose of 40mg/m² on weeks 1, 2, 3, 5, 6, and 7 of the radiotherapy. Patients received prophylactic hydration and 5HT₃ antagonists plus dexamethasone and/or neurokinin-1 receptor antagonist for anti-emetic prophylaxis. The intended maximum dose of cisplatin was 240 mg/m². The cisplatin dose was modified on a case-by-case basis according to the level of adverse events.

The irradiation plan was 40 Gy in 20 fractions of 2 Gy over four weeks for the primary site and all nodal areas, immediately followed by a boost of 30 Gy in 15 fractions to the primary cancer and metastatic nodal area over an additional three weeks (total dose, 70 Gy).

Post-treatment evaluation. Initial post-treatment evaluation was performed within one month after the completion of initial treatment using laryngeal endoscopy. Computed tomography (CT) and/or magnetic resonance (MR) imaging were performed within two months after the completion of treatment. If persistent primary disease was observed, biopsy was attempted and salvage surgery was indicated by the presence of viable tumor cells. If persistent regional disease was observed, salvage neck dissection was indicated.

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. CT scans or MR imaging were routinely performed once every three months in the first year, and every 6 or 12 months thereafter. If recurrent primary disease was suspected, biopsy was attempted and, again, salvage surgery was indicated by the presence of tumor cells. If recurrent regional disease was observed, salvage neck dissection was indicated.

Salvage surgery. Salvage surgery was indicated for patients with recurrent primary disease. Salvage neck dissection was performed for patients with recurrent regional disease. Level II, III, IV lymph nodes on the involved side were dissected as a rule, with level I or V lymph nodes also dissected if involved.

Statistics. We defined cases receiving more than 200 mg/m² of total cisplatin during CRT as completed, with the completion rate calculated accordingly.

Toxicities during CRT and surgical complications were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0. Post-operative complications evaluated as grade 3 or 4 were recorded according to NCI-CTCAE Version 4.0, and the complication rate was calculated.

The Kaplan-Meier method was used for the calculation of survival and control rates using JMP 10.0.0 statistical software (SAS Institute, Cary, NC). Time of interest was the period from the start of treatment to death or failure. The Kaplan-Meier method was also applied to calculate the laryngeal preservation rate. Time of interest was the period from the start of treatment to death or surgery with total laryngectomy.

Results

Patient characteristics. We treated 40 patients with resectable pyriform sinus SCC by weekly cisplatin CRT. Of these, 10 patients undergoing induction chemotherapy followed by weekly cisplatin CRT were excluded. The remaining 30 patients were eligible for this study. Table 1 shows the detailed demographics of the 30 patients enrolled in this study. None of the 30 cases showed any invasion to the prevertebral or deep cervical muscle or the carotid artery and, therefore, all 30 were thought to be resectable cases. The observation period for survivals ranged from 8.3 to 93.7 months (median, 58 months).

Chemoradiotherapy and treatment compliance. All 30 patients achieved definitive radiotherapy at a median dose of 70 Gy (range, 64 to 70 Gy). One patient developed aspiration pneumonia (Grade 3) after an irradiation dose of 64 Gy, and radiation therapy was subsequently discontinued. Cisplatin was administered concomitantly a median of five times (range, 2 to 6 times). Thirty-five patients (87.5%) achieved a total dose of more than 200 mg/m² of cisplatin during CRT. One patient developed renal failure after cisplatin was administered twice, and chemotherapy was, therefore, discontinued. Chemotherapy was also discontinued in one patient after three doses of cisplatin due to severe mucositis (Grade 3), as well as in two patients after four doses of cisplatin due to hypokalemia (Grade 3) and dermatitis (Grade 3), respectively. A summary of these patients who did

not complete the definitive radiotherapy or chemotherapy is shown in Table 2. Table 3 shows the details of acute toxicity during CRT. Late complications were observed in one patient (3%). This patient with severe stenosis of the pharynx required TPL and free jejunal reconstruction 10 months after the completion of CRT.

Patient outcomes and salvage surgery. Persistent or recurrent primary disease was observed in four patients (13%) after weekly cisplatin CRT. These four patients underwent salvage surgery with total laryngectomy a median of 25.4 months (range, 6.6 to 54.7 months) after the completion of weekly cisplatin CRT. Of these four patients undergoing salvage surgery with total laryngectomy, three survived without any evidence of disease. The remaining patient died of primary disease at two months after the salvage surgery.

Persistent or recurrent nodal metastasis was observed in five patients (17%) after weekly cisplatin CRT. These five patients underwent salvage neck dissection. All five patients survived without any evidence of disease.

Post-operative complications were observed in two of the nine patients (22%) undergoing salvage surgery. Fistula formation (Grade 3) was observed in one patient after pharyngectomy with total laryngectomy. One case of neck numbness (Grade 3) was also observed after salvage neck dissection.

Distant metastasis was observed in one patient at 23.1 months after the completion of weekly cisplatin CRT. This patient died of lung metastasis at 32.8 months after the completion of weekly cisplatin CRT.

Overall survival and laryngeal preservation survival rates. In all participants, the five-year overall survival and locoregional control rates were 87% and 96%, respectively (Figure 1). The five-year laryngeal preservation rate was 74% for all participants. Figure 2 shows the laryngeal preservation curve. The five-year overall survival rates of T1, T2, T3, and T4a were 100%, 88%, 83%, and 100%, respectively. Those of N0, N1, N2a-c, and N3 were 81%, 100%, 89%, and 100%, respectively. Further, the five-year laryngeal preservation rates of T1, T2, T3, and T4a were 0%, 76%, 83%, and 100%, respectively, while those of N0, N1, N2a-c, and N3 were 73%, 100%, 65%, and 100%, respectively.

Discussion

Hypopharyngeal SCC has one of the worst prognoses among malignant neoplasms, with the five-year overall survival rate was reported to be 35% by the intensive surgical treatment, such as TPL [5]. Therefore, the improvement of clinical outcomes for patients with hypopharyngeal SCC has been particularly challenging for head and neck surgeons and oncologists. CRT has been used for patients with advanced hypopharyngeal cancer with the aim of preserving the larynx. Although tri-weekly high-dose ($100\text{mg}/\text{m}^2$) cisplatin (three cycles) and radiotherapy has been considered a standard regimen, this protocol is associated with significant acute and late toxicities [6-9]. Furthermore, the completion rate for this regimen is relatively poor [6-7]. Therefore, weekly cisplatin at a dose of $40\text{mg}/\text{m}^2$ has been used at our institution since 2006, and we have also applied this treatment for patients with advanced pyriform sinus SCC. The favorable outcomes of this protocol were clarified in the current study

For comparison, we also investigated the overall survival of 23 patients with advanced pyriform sinus SCC undergoing surgical treatment at the same time in our institution. The five-year overall survival and locoregional control rates of the surgical treatment group were 50.4% and 75.7%, respectively. The number of patients with T2, 3, and 4a in the surgical treatment group was 6, 4, and 13, respectively. The median age of the surgical treatment group was 72 years, which was older than the median age (62 years) of the CRT group. Due to the marked inequality between the CRT group and the surgical treatment group, it was difficult to compare the outcomes between two groups. We recognize that there was a strong tendency for the surgical treatment to be indicated for more advanced primary disease and older patients in comparison to those receiving CRT. Therefore, the effectiveness of weekly cisplatin CRT remains to be confirmed on larger populations of patients with more advanced primary tumors, and further studies are needed to prove clarify this efficacy.

Long before the turn of the century, various CRT regimens were investigated for patients with hypopharyngeal cancer with the aim of preserving the larynx. Yoon et al. reported the outcomes of high dose cisplatin ($100\text{ mg}/\text{m}^2$) CRT for 28 patients with locally advanced hypopharyngeal cancer [10]. The three-year overall survival and locoregional control rates were 54% and 52%,

respectively. Prades et al. presented the outcomes of carboplatin CRT for 46 patients with pyriform sinus carcinoma [11], with a two-year overall survival rate of 53-58%. Tai et al. investigated 42 patients with advanced hypopharyngeal cancer who were treated by CRT consisting of cisplatin and 5-FU with and without induction chemotherapy [12]. The three-year overall survival rate was reported to be 50%. A comparison with these previous reports shows that the five-year overall survival and locoregional control rates (78.8% and 89.2%) in current study were superior to those of other regimen. We speculated the advantage of the weekly cisplatin regimen is that it enables an adequate total dose of cisplatin to be administered during concurrent radiotherapy. It was confirmed that over than 80% of all participants achieved this regimen, with this high completion rate considered to lead to improved outcomes.

In the current study, local or regional recurrence was observed in eight patients. Of these, all eight patients underwent salvage surgery. Seven patients (87.5%) survived after salvage surgery without any evidence of disease. The post-operative complication rate (22%) was also acceptable. These reasonable salvage and complication rates encouraged us to perform salvage surgery after weekly cisplatin CRT. We considered that salvage surgery could contribute the improvement of overall survival and locoregional control for patients with persistent or recurrent locoregional disease.

The favorable laryngeal preservation rate (74%) achieved in our current study confirmed that weekly cisplatin chemotherapy with concurrent radiotherapy was effective in preserving laryngeal function.

Conclusions

The regimen of weekly cisplatin CRT may be effective for pyriform sinus SCC; however, there were problems with the strong selection bias in the current study due to the large number of T2 patients. The high completion rate of weekly cisplatin CRT together with appropriate salvage surgery could contribute favorable outcomes. Further, we confirmed the safety and efficacy of salvage surgery following CRT. These combined therapies could improve the overall survival for patients with pyriform sinus SCC.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Young Scientists (B) Number 26861352 from the Ministry of Education, Culture, Sports, Science and Technology of Japan, by a Health and Labour Sciences Research Grant for Clinical Cancer Research (H26-141) from the Ministry of Health, Labour and Welfare of Japan and the National Cancer Center Research and Development Fund (26-A-4) of Japan.

References

1. Pingree TF, Davis RK, Reichman O, et al. (1987) Treatment of hypopharyngeal carcinoma: a 10-year review of 1,362 cases. *Laryngoscope* **97**:901-904.
2. Koch WM, Lee DJ, Eisele DW, et al. (1995) Chemoradiotherapy for organ preservation in oral and pharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* **121**:974-980.
3. National Comprehensive Cancer Network guidelines version 2.2014 on web site http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
4. Homma A, Inamura N, Oridate N, et al. (2011) Concomitant Weekly Cisplatin and Radiotherapy for Head and Neck Cancer. *Jpn J Clin Oncol* **41**:980-986.
5. Lefebvre JL, Chevalier D, Lubinski B, et al. (1996) Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst* **88**:890-899.
6. Forastiere AA, Goepfert H, Maor M, et al. (2003) Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* **349**: 2091-2098.
7. Adelstein DJ, Li Y, Adams GL, et al. (2003) An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* **21**:92-98.
8. Machtay M, Moughan J, Trotti A, et al. (2008) Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol* **26**: 3582-3589.

9. Al-Sarraf M, LeBlanc M, Giri PG, et al. (1998) Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* **16**: 1310-1317.
10. Yoon MS, Chung WK, Ahn SJ, et al. (2008) Concurrent chemoradiotherapy with cisplatin and fluorouracil for locally advanced hypopharyngeal carcinoma. *Acta Otolaryngol* **128**:590-596.
11. Prades JM, Schmitt TM, Timoshenko AP, et al. (2002) Concomitant chemoradiotherapy in pyriform sinus carcinoma. *Arch Otolaryngol Head Neck Surg* **128**:384-388.
12. Tai SK, Yang MH, Wang LW, et al. (2008) Chemoradiotherapy laryngeal preservation for advanced hypopharyngeal cancer. *Jpn J Clin Oncol* **38**:521-527.

Figure legend

Figure 1. Kaplan-Meier estimation of overall survival and locoregional control rates among 30 patients with advanced pyriform sinus squamous cell carcinoma.

Figure 2. Kaplan-Meier estimation of the laryngeal preservation rate among 30 patients with advanced pyriform sinus squamous cell carcinoma.

Table 1. Patient Demographics

Table 2. A summary of the five patients who did not completed weekly cisplatin chemoradiotherapy

Table 3. Acute toxicity of weekly cisplatin chemotherapy with concurrent radiotherapy (n=30)

Figure 1.

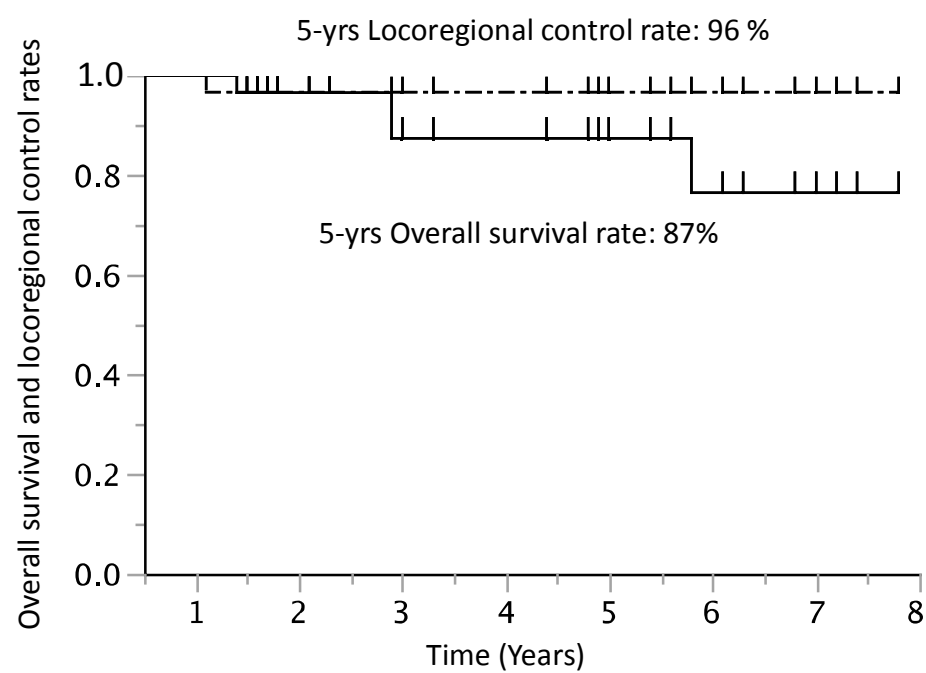


Figure 2.

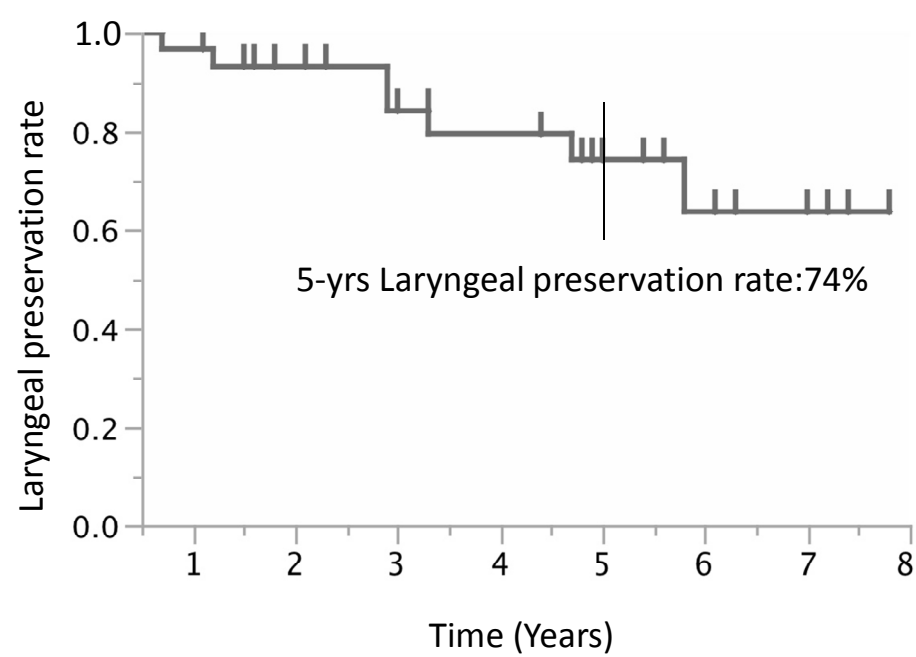


Table 1. Patient Demographics

Characteristic	No. of patients (%)
Total	30
Gender	
Male	30 (100%)
Female	0 (0%)
Age, years	
Median	62
Range	47-76 (Ave. 62)
T classification	
1	1 (3%)
2	21 (70%)
3	6 (20%)
4a	2 (7%)
N classification	
0	12 (40%)
1	5 (17%)
2a	1 (3%)
2b	11 (37%)
2c	0 (0%)
3	1 (3%)

Table 2. A summary of the five patients who did not completed weekly cisplatin chemoradiotherapy

Age	Sex	Classification		Radiation dose (Gy)	Chemotherapy (times)	Total dose of cisplatin (mg/m ²)	Reason for suspending radiotherapy	Reason for suspending chemotherapy	Outcome
		T	N						
57	M	2	0	64	5	200	Pneumonia (Grade 3)	-	No evidence of disease
57	M	2	0	70	4	160	-	Dermatitis (Grade 3)	No evidence of disease
74	M	2	2b	70	4	160	-	Hypokalemia (Grade 3)	Dead of lung metastasis
67	M	3	1	70	3	120	-	Mucositis (Grade 3)	No evidence of disease
76	M	4a	0	70	2	80	-	Renal Failure (Grade 1)	No evidence of disease

Table 3. Acute toxicity of weekly cisplatin chemotherapy with concurrent radiotherapy
(n=30)

Toxicity	Grade			
	1	2	3	4
Leukopenia	6	11	11	
Neutropenia	6	11	8	
Anemia	12	12	6	
Thrombocytopenia	7	3	2	
Febrile neutropenia			3	
Nausea/vomiting	7	1	3	
Mucositis	1	16	13	
Dermatitis	6	14	10	
Renal dysfunction	8			
Liver dysfunction	9	2		
Infection		1	3	
Dysphagia		1		1
Hyponatremia	23		5	