Table 6. Cox proportional hazard regression model analysis for overall survival

Variables	Hazard ratio (95% CI)	p
Age		
<62 vs. ≥62	0.708 (0.395–1.270)	0.247
Gender		
Male vs. female	0.941 (0.321–2.760)	0.912
T classification		
T1, 2 vs. T3, 4	0.298 (0.150–0.590)	0.001
N classification		
N0–2a vs. N2b–3	0.534 (0.277–1.029)	0.061
Subsite		
Lateral wall vs. anterior wall	0.566 (0.307–1.043)	0.068
Smoking status		
Never vs. ever	0.870 (0.335–2.261)	0.776
Alcohol consumption status		
Never vs. ever	0.973 (0.451–2.099)	0.945
Multiple primaries		
No vs. yes	0.726 (0.400–1.316)	0.291
Initial treatment		
CCRT vs. surgery	0.892 (0.514–1.548)	0.684

dependence immediately after initial treatment. For more accurate evaluation of swallowing function, detailed interviews with patients should be performed at several fixed times after treatment. On the other hand, Boscolo-Rizzo et al. [10] evaluated the long-term quality of life in patients with advanced OPC and compared the results of patients treated with surgery and postoperative RT with those undergoing CCRT. They reported that surgical patients showed a statistically higher incidence of problems with swallowing and social eating.

The matched-pair analysis method has been utilized for several reported retrospective cohort studies that included head and neck cancer research [22–24]. This method is based on retrospective analysis and the bias resulting from potential confounders can be limited using the matching procedure, especially in large-scale comparative studies. However, this method has some intrinsic limitations. Although the patients were matched for age, gender, subsite, and T and N status in this study, an imbalance was still present in variables that might become potential prognostic factors. Matched-pair analysis cannot replace prospective cohort studies and randomized clinical trials are required for proper comparisons between therapeutic strategies. However, it is unrealistically difficult to perform a randomized clinical trial comparing surgery versus CCRT. Furthermore, in a single institution analysis, even when matched-pair analysis is used, the selection of initial treatment can be biased by patient characteristics and clinician preferences. A large-scale multi-institutional joint research using the matched-pair analysis is thought to reduce such therapeutic bias and provide a feasible option to a randomized clinical trial comparing surgery with CCRT.

In conclusion, we compared the therapeutic outcomes for patients treated by surgery with those of patients receiving CCRT using a matched-pair analysis. Although overall survival, progression-free survival and local control rates for the CCRT group appeared similar to those for the surgery group, swallowing function based on the need for tube feedings immediately following treatment was significantly better in the CCRT group compared to patients treated with surgery ($p = 0.015$). A randomized prospective study comparing surgery with CCRT for the patients with advanced OPC is still required to confirm the reliability of the results of this study.

Disclosure Statement

The authors declare no conflicts of interest.

References

1 Gillison ML: Current topics in the epidemiology of oral cavity and oropharyngeal cancers. Head Neck 2007;29:779–792.

2 Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML: Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.

3 Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, Forastiere A,Gillison ML: Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100:261–269.

4 Forastiere A, Koch W, Trotti A, Sidransky D: Head and neck cancer. N Engl J Med 2001; 345:1890–1900.

5 Grant DG, Salassa JR, Hinni ML, Pearson BW, Perry WC: Carcinoma of the tongue base treated by transoral laser microsurgery, part one: untreated tumors, a prospective analysis of oncologic and functional outcomes. Laryngoscope 2006;116:2150–2155.

6 Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M: Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. Arch Otolaryngol Head Neck Surg 2003;129:36–43.

7 Leonhardt FD, Quon H, Abrahao M, O'Malley BW Jr, Weinstein GS: Transoral robotic surgery for oropharyngeal carcinoma and its impact on patient-reported quality of life and function. Head Neck 2012;34:146–154.
8 Weinstein GS, O'Malley BW Jr, Cohen MA, Quon H: Transoral robotic surgery for advanced oropharyngeal carcinoma. Arch Otolaryngol Head Neck Surg 2010;136:1079–1085.
9 Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, Schuller DE, Forastiere AA: 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 2003;21:92–98.
10 Boscolo-Rizzo P, Stellin M, Fuson R, Marchiori C, Gava A, Da Mosto MC: Long-term quality of life after treatment for locally advanced oropharyngeal carcinoma: surgery and postoperative radiotherapy versus concurrent chemoradiation. Oral Oncol 2009;45:953–957.
11 Pignon JP, le Maitre A, Maillard E, Bourhis J: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.
12 Chen AY, Schrag N, Hao Y, Stewart A, Ward E: Changes in treatment of advanced oropharyngeal cancer, 1985–2001. Laryngoscope 2007;117:16–21.
13 Cohan DM, Popat S, Kaplan SE, Rigual N, Loree T, Hicks WL Jr: Oropharyngeal cancer: current understanding and management. Curr Opin Otolaryngol Head Neck Surg 2009;17:88–94.
14 Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Calais G: Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69–76.
15 Olmi P, Crispino S, Fallai C, Torri V, Rossi F, Bolner A, Amichetti M, Signor M, Taino R, Squadrelli M, Colombo A, Ardizzoia A, Ponticelli P, Franchin G, Minatel E, Gobitti C, Atzeni G, Gava A, Flann M, Marsoni S: Locoregionally advanced carcinoma of the oropharynx: conventional radiotherapy vs. accelerated hyperfractionated radiotherapy vs. concomitant radiotherapy and chemotherapy – a multicenter randomized trial. Int J Radiat Oncol Biol Phys 2003;55:78–92.
16 Soo KC, Tan EH, Wee J, Lim D, Tai BC, Khoo ML, Goh C, Leong SS, Tan T, Fong KW, Lu P, See A, Machin D: Surgery and adjuvant radiotherapy vs. concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomised comparison. Br J Cancer 2005;93:279–286.
17 Rades D, Meyners T, Kazic N, Bajrovic A, Rudat V, Schild SE: Comparison of radiochemotherapy alone to surgery plus radio(chemo) therapy for non-metastatic stage III/IV squamous cell carcinoma of the head and neck: a matched-pair analysis. Strahlenther Onkol 2011;187:541–547.
18 Parsons JT, Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Villaret DB, Moore-Higgs GJ, Greene BD, Speer TW, Cassisi NJ, Million RR: Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. Cancer 2002;94:2967–2980.
19 Boscolo-Rizzo P, Gava A, Baggio V, Marchiori C, Stellin M, Fuson R, Lamon S, Da Mosto MC: Matched survival analysis in patients with locoregionally advanced resectable oropharyngeal carcinoma: platinum-based induction and concurrent chemoradiotherapy versus primary surgical resection. Int J Radiat Oncol Biol Phys 2011;80:154–160.
20 Fischer CA, Zlobec I, Green E, Probst S, Storck C, Lugli A, Tornillo L, Wolfensberger M, Terracciano LM: Is the improved prognosis of p16 positive oropharyngeal squamous cell carcinoma dependent of the treatment modality? Int J Cancer 2010;126:1256–1262.
21 Licitra L, Perrone F, Bossi P, Suardi S, Mariani L, Artusi R, Oggionni M, Rossini C, Cantu G, Squadrelli M, Quattrone P, Locati LD, Bergamini C, Olmi P, Pierotti MA, Pilotti S: High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. J Clin Oncol 2006;24:5630–5636.
22 Goldenberg D, Brooksby C, Hollenbeak CS: Age as a determinant of outcomes for patients with oral cancer. Oral Oncol 2009;45:e57–e61.
23 Roberts JC, Li G, Reitzel LR, Wei Q, Sturgis EM: No evidence of sex-related survival disparities among head and neck cancer patients receiving similar multidisciplinary care: a matched-pair analysis. Clin Cancer Res 2010;16:5019–5027.
24 Schrank TP, Han Y, Weiss H, Resto VA: Case-matching analysis of head and neck squamous cell carcinoma in racial and ethnic minorities in the United States – possible role for human papillomavirus in survival disparities. Head Neck 2011;33:45–53.

Int J Clin Oncol
DOI 10.1007/s10147-012-0449-x

ORIGINAL ARTICLE

Salvage surgery for recurrent oropharyngeal cancer after chemoradiotherapy

Satoshi Kano · Akihiro Homma · Ryuichi Hayashi · Kazuyoshi Kawabata · Kunitoshi Yoshino · Shigemichi Iwae · Yasuhisa Hasegawa · Kenichi Nibu · Takakuni Kato · Kiyoto Shiga · Kazuto Matsuura · Nobuya Monden · Masato Fujii

Received: 11 April 2012 / Accepted: 25 June 2012

Abstract
Background The current study aimed to assess the role of salvage surgery for failure cases of oropharyngeal cancer (OPC) undergoing initial chemoradiotherapy (CRT).
Methods The data for 523 patients with previously untreated OPC were gathered from 12 institutions belonging to the Head and Neck Cancer Study Group in Japan Clinical Oncology Group (JCOG).
Results Of the 170 patients who received CRT, 35 patients (21 %) had local recurrence or residual disease. Only 11 patients underwent further salvage surgery, and 24 patients received nonsurgical treatment. There were statistically significant differences between the two groups in terms of patient age and the presence of a simultaneous regional recurrence. The 5-year overall survival rates for the patients who underwent salvage surgery were 49.1 %, whereas those for the patients who received nonsurgical treatment were 16.3 %.
Conclusion The initial treatment method for OPC should be decided carefully and the limitations of salvage surgery should be fully considered.

S. Kano · A. Homma (✉)
Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan
e-mail: ak-homma@med.hokudai.ac.jp

R. Hayashi
Division of Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, Japan

K. Kawabata
Department of Head and Neck Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

K. Yoshino
Department of Otolaryngology, Head and Neck Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

S. Iwae
Department of Head and Neck Surgery, Hyogo Cancer Center, Akashi, Japan

Y. Hasegawa
Department of Head and Neck Surgery, Aichi Cancer Center, Nagoya, Japan

K. Nibu
Department of Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

T. Kato
Department of Oto-Rhino-Laryngology, Jikei University School of Medicine, Tokyo, Japan

K. Shiga
Department of Otolaryngology-Head and Neck Surgery, Tohoku University School of Medicine, Sendai, Japan

K. Matsuura
Division of Head and Neck Surgery, Miyagi Cancer Center, Sendai, Japan

N. Monden
Department of Otorhinolaryngology-Head and Neck Surgery, National Shikoku Cancer Center, Matsuyama, Japan

M. Fujii
Department of Otorhinolaryngology, National Tokyo Medical Center, Tokyo, Japan

Published online: 25 July 2012

Keywords Oropharyngeal cancer · Chemoradiotherapy · Local recurrence · Salvage surgery · Swallowing function

Introduction

In recent years, the initial treatment strategy for advanced head and neck cancer has shifted from surgery toward chemoradiotherapy (CRT) [1, 2]. This paradigm shift is particularly marked for oropharyngeal cancer (OPC), because OPC has high sensitivity to radiation and chemotherapy, and extended resection of the oropharynx leads directly to swallowing and speech disorders. The meta-analysis reported by Parsons et al. [3] revealed that organ preservation protocols have comparable survival rates, improved functional outcomes, and decreased severe complications compared to open surgery. Additionally, the relationship between human papilloma virus (HPV) and carcinogenesis of the oropharynx has been confirmed, and its treatment sensitivity has expedited a further paradigm shift [4, 5]. Although CRT is reported to show good results, patients with OPC are at risk of recurrence after initial therapy. Bachar et al. [6] reported that 239 of 640 patients (37 %) with tonsillar cancer recurred post radiotherapy.

Salvage surgery is the only curative treatment for patients with recurrence. However, the rate of successful surgical salvage has remained modest. Previously, we analyzed the effectiveness of salvage surgery for local recurrence after CRT or radiotherapy (RT) in hypopharyngeal cancer and reported that the successful salvage rate was only 17.1 % [7]. Goodwin [8] conducted a meta-analysis of 532 patients with recurrent pharyngeal cancer undergoing salvage surgery after definitive radiotherapy and reported a recurrence-free survival rate of only 25 % at 2 years and a 5-year overall survival rate of 26 %. Furthermore, although reconstructive surgery for oral and pharyngeal surgical defects, such as microvascular reconstructive techniques, has developed over the past several decades, Agra et al. [9] reported that postoperative complications after en bloc salvage surgery for head and neck cancer occurred in 53.2 % of patients, including 42.7 % of patients with minor complications, 18.5 % of patients with major complications, and 3.2 % of patients who died within the postoperative period.

Recently, a large-scale multi-institutional joint research for OPC was performed in Japan for the first time. Twelve institutions, mainly treating patients with cancer, participated in this research, and the data for 523 patients were obtained. In this study, we focused on the patients initially treated with CRT, and retrospectively analyzed the treatment failures, salvage surgeries, and survival rates of these patients.

Patients and methods

Patients

The data for 523 patients with previously untreated OPC from April 2005 to March 2007 were gathered from 12 institutions belonging to the Head and Neck Cancer Study Group in Japan Clinical Oncology Group (JCOG). Therapeutic strategy varied widely among the institutions, with the proportion of surgical interventions varying between 6 % and 59 % and that of RT with or without chemotherapy being 41–94 %. This study was a retrospective analysis, so the criteria of selection of therapeutic modality was decided by the institutional policies or patients' preference. In all, 37 patients who received palliative therapy were excluded from further analysis, and the data for the remaining 486 patients were analyzed retrospectively. Of the 486 patients with OPC treated with curative intent, 199 patients (41 %) were treated with surgery, 117 (24 %) with RT alone, and 170 (35 %) with CRT (Table 1). Between each therapeutic modality, there was no statistical difference in age, gender, subsite, or histology. However, the patients with advanced disease tended to undergo CRT compared to surgery or RT alone. The rate of T3 or T4 disease was 48 % in the group of CRT (37 % in surgery, 29 % in RT alone), that of neck lymph node metastasis was 77 % in the group of CRT (60 % in surgery, 64 % in RT alone), and that of clinical stage III or IV was 88 % in the

Table 1 Characteristics of patients treated initially with surgery, radiotherapy (RT), or chemoradiotherapy (CRT)

Variable	No. of patients (%)		
	Surgery (n = 199)	RT (n = 117)	CRT (n = 170)
Age (years)			
Median (range)	64 (36–84)	66 (38–96)	60 (37–80)
Gender			
Male/female	167/32 (84/16)	100/17 (85/15)	147/23 (86/14)
Subsite			
Lateral/anterior/ superior/posterior	106/52/34/7 (53/26/17/4)	78/21/11/7 (67/18/9/6)	105/45/8/12 (62/26/5/7)
T classification			
1, 2/3, 4	126/73 (63/37)	83/34 (71/29)	87/82 (51/48)
N classification			
0/1–3	80/119 (40/60)	42/75 (36/64)	39/131 (23/77)
Stage			
I, II/III, IV	64/135 (32/68)	35/82 (30/70)	21/149 (12/88)
Histology			
SCC/others	189/10 (95/5)	115/2 (98/2)	166/4 (98/2)

SCC squamous cell carcinoma

Table 2 T and N classification for patients treated with CRT

T classification	No. of patients by N classification						Total (%)
	0	1	2a	2b	2c	3	
1	4	0	2	5	2	5	18 (11)
2	17	9	9	22	8	4	69 (41)
3	9	7	1	10	8	3	38 (22)
4a	7	3	0	6	15	4	35 (21)
4b	2	0	0	1	2	4	9 (5)
X	0	0	0	0	1	0	1 (1)
Total (%)	39 (23)	19 (11)	12 (7)	44 (26)	36 (21)	20 (12)	170

group of CRT (68 % in surgery, 70 % in RT alone). The T and N classification for patients treated with CRT is shown in Table 2.

Time of assessment and evaluation method for tumors after CRT depend on the institution policies. It is difficult to differentiate between radiographic changes related to the treatment and scar tissue from persisting tumors. Over time, scar tissue remains stable, but persistent tumor tissue will progress, so a patient with radiologic changes that remained stable with no signs or symptoms of disease was considered to be progression free. Recurrence or persistent tumor was judged by apparent radiologic findings or proved by biopsy.

This multi-institutional joint research has been representatively approved by the appropriate ethical committees of National Hospital Organization Tokyo Medical Center, Tokyo, Japan, and written informed consent was obtained from all patients before entry into the study.

Statistical analysis

Associations between patient characteristics were tested using the unpaired Student's *t* test or the chi-square test, as appropriate. Overall survival curves were constructed using the Kaplan–Meier method and were analyzed using the log-rank test. A two-tailed P value < 0.05 was considered statistically significant. Statistical analyses were performed using XLSTAT 2011 (Addinsoft, NY, USA).

Results

Details of initial treatment

Table 3 shows details of initial treatment in the CRT group. The median irradiation dose was 70 Gy (range, 55–72 Gy). Most patients received conventional radiotherapy and 2 patients were treated with brachytherapy. Although the concomitant chemotherapy consisted of various regimens, about 76 % of patients treated with those regimens received cisplatin and 92 % received platinum-containing anti-cancer drugs. Intraarterial (IA) cisplatin infusion was performed for 16 patients with OPC, including 13 with anterior wall cancer. Forty-one patients (24 %) received induction chemotherapy and 5 patients (3 %) underwent neck dissection (ND) followed by CRT.

Table 3 Details of initial treatment

Irradiation dose	55–72 Gy (median 70 Gy) No. of patients (%)
Concomitant chemotherapy regimen	
Cisplatin, 5-FU	64 (38)
Cisplatin	39 (23)
Nedaplatin	14 (8)
Docetaxel	11 (7)
Cisplatin, 5-FU, docetaxel	9 (5)
Carboplatin, 5-FU	5 (3)
Nedaplatin, 5-FU	4 (2)
Carboplatin	3 (2)
S1	3 (2)
Cisplatin, etoposide	2 (1)
Cisplatin (IA)	16 (9)
Induction chemotherapy	41 (24)
ND followed by CRT	5 (3)

IA intraarterial, *ND* neck dissection

Survival by initial treatment

The median follow-up period was 4.4 years (range, 0.3–5.9 years). The 3-year overall survival rate for patients treated initially with surgery, RT, and CRT was 81.8, 75.4, and 75.8 %, respectively. The 5-year overall survival rate for patients treated initially with surgery, RT, and CRT was 74.8, 66.0, and 67.1 %, respectively (Fig. 1).

Local recurrence and salvage surgery

Of the 170 patients who received CRT, 35 patients (21 %) had local recurrence or residual disease regardless of neck

lymph node and distant metastasis. The median interval of local failure after CRT was 126 days (range, 0–715 days). Of the patients with local failure, 11 patients underwent salvage surgery. The most common surgical approach was open surgery, requiring microvascular free flap reconstruction (10 patients), whereas only 1 patient, who developed recurrence at the lateral wall, underwent transoral surgery. Following salvage surgery, 1 patient received postoperative reirradiation and 4 patients received adjuvant chemotherapy. Twenty-four patients received nonsurgical treatment, including reirradiation in 1, chemotherapy in 9, and best supportive care in 14 patients. Of 134 patients without local failure, 24 patients developed regional recurrences, 12 patients developed distant metastasis, and 7 patients developed both. Seventeen of the 134 patients were successfully salvaged. Additionally, there was 1 treatment-related death. The final outcome for each group is shown in Fig. 2.

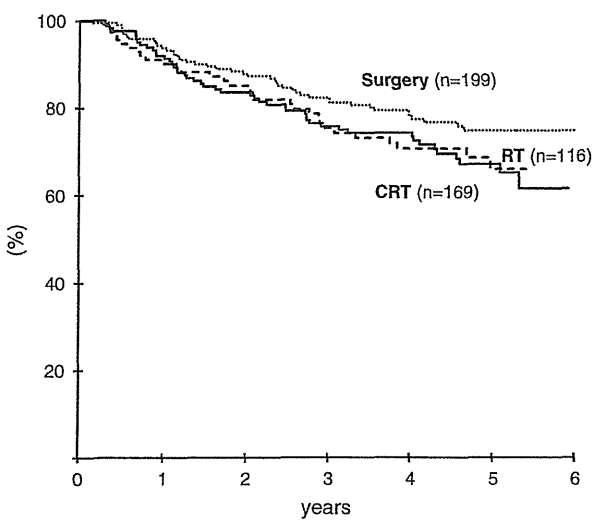

Fig. 1 Overall survival in 169 patients with oropharyngeal cancer treated with surgery, radiotherapy (*RT*), and chemoradiotherapy (*CRT*)

Characteristics of the patients undergoing salvage surgery or nonsurgical treatment for local recurrence or residual disease are summarized in Table 4. Statistically significant differences in patient age and the presence of a simultaneous regional recurrence were observed between the two groups. In addition, the patients who had more aggressive initial disease and developed distant metastasis tended to belong to the nonsurgical treatment group, although the difference was not significant.

Of the 35 patients with local failure, only 11 patients (31 %) underwent further salvage surgery, of whom only 8 (23 %) were successfully salvaged for local failure. Tables 5 and 6 show the successful salvage rates by T classification and subsite, respectively.

There was no perioperative death among the patients who underwent salvage surgery. As to swallowing function, two patients depended on a feeding tube just after CRT, whereas five patients required tube-feeding support after salvage surgery. Furthermore, three patients required the removal of their larynxes (Table 7).

For the patients treated with CRT, the 3- and 5-year overall survival rates for those without local failure were 83.8 % and 75.5 %, respectively (Fig. 3). For the patients with local failure, the 3- and 5-year overall survival rates for those who underwent salvage surgery were 61.8 and 49.1 %, respectively; those for the patients who received nonsurgical treatment were 24.4 and 16.3 %, respectively. The overall survival rate for patients treated with salvage surgery was significantly higher than that for patients

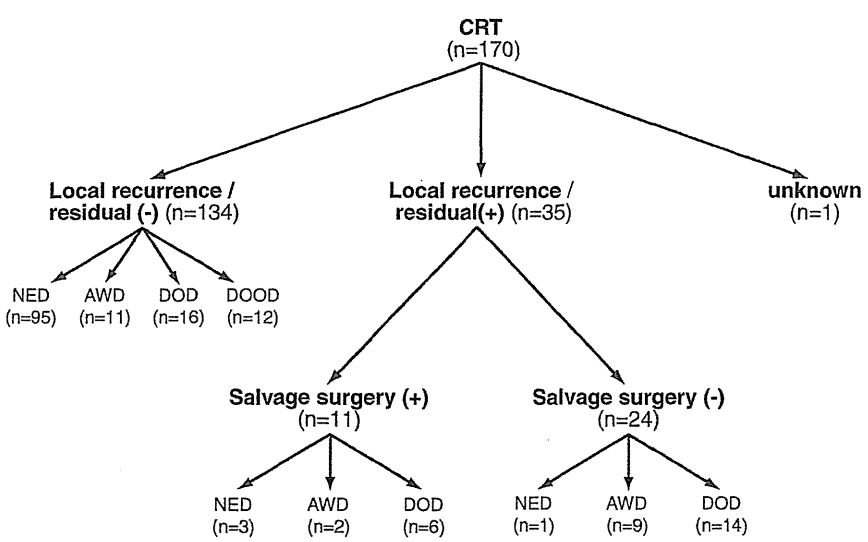

Fig. 2 Flowchart of 170 patients who received chemoradiotherapy for oropharyngeal cancer. *NED* no evidence of disease, *AWD* alive with disease, *DOD* dead of disease, *DOOD* dead of other disease

Table 4 Characteristics of patients who underwent salvage surgery or nonsurgical treatment for local recurrence or residual disease

Variable	No. of patients (%)		*P*
	Salvage surgery ($n = 11$)	Nonsurgical treatment ($n = 24$)	
Age (year)			
Median (range)	54 (42–75)	64.5 (46–78)	**0.04**
Gender			
Male/female	11/0 (100/0)	20/4 (83/17)	0.28
Comorbidity			
Diabetes	0 (0)	3 (13)	0.54
Hypertension	2 (18)	2 (8)	0.57
Cardiac disease	3 (27)	1 (4)	0.08
Pulmonary disease	0 (0)	2 (8)	1.00
Multiple primaries			
No/yes	5/6 (45/55)	16/8 (67/33)	0.41
Initial disease			
Subsite			
Lateral/anterior/ superior/posterior	5/3/1/2 (45/27/9/18)	16/5/1/2 (67/21/4/8)	0.95
T classification			
1, 2/3, 4	6/5 (55/45)	5/19 (21/79)	0.11
N classification			
0/1–3	6/5 (55/45)	6/18 (25/75)	0.18
Stage			
I, II/III, IV	3/8 (27/73)	2/22 (8/92)	0.30
Completion of CRT			
Yes/no	8/3 (73/27)	15/9 (63/37)	0.71
Nutrition after CRT			
Oral/oral + tube/tube	9/2/0 (82/18/0)	13/4/2[a] (54/17/8)	0.90
Recurrent/residual disease			
Disease status			
Recurrent/residual	8/3 (73/27)	14/10 (58/42)	0.48
Regional recurrence			
No/yes	10/1 (91/9)	11/13 (46/54)	**0.02**
Distant metastasis			
No/yes	11/0 (100/0)	18/6 (75/25)	0.15

P values < 0.05 were shown in bold

[a] Nutrition data were not available for 5 patients in the nonsurgical treatment group

treated without salvage surgery ($P = 0.04$), whereas it was significantly lower than that for patients without local failure ($P = 0.02$).

Discussion

In the current study, the local failure rate among patients treated with CRT was 21 %, the salvage surgery rate was 31 %, and the 5-year overall survival rate after salvage surgery was 49 %. Roosli et al. and Zafereo et al. [10, 11] also reported an analysis of salvage surgery for the local recurrence of OPC. Their local failure rates were 12 and 29 %, their salvage surgery rates were 21 and 22 %, and their 5-year overall survival rates after salvage surgery were 28 and 25 %, respectively. It should be noted that salvage surgery was performed in only 20 to 30 % of patients with local failure. There were significant differences in patient age and simultaneous regional recurrence between the patients who underwent salvage surgery and those receiving nonsurgical treatment for local failure in the current study. In addition, the opportunity for salvage surgery tended to be more limited in patients who initially had advanced primary disease. Although 10 patients experienced only local failure without neck disease or distant metastasis, they received nonsurgical treatment. According to the analysis of their characteristics, their ages ranged from 56 to 76 years (median, 63 years), the rate of T4a disease was 50, and 50 % of patients had such poor performance status that they experienced swallowing

Table 5 Successful salvage rate by T classification

T classification (no. of patients)	No. of patients (%)		
	Local recurrences/ residuals	Salvage surgeries	Successfully salvaged
T1 (18)	1	1 (100)	1 (100)
T2 (69)	10	5 (50)	3 (30)
T3 (38)	9	3 (33)	3 (33)
T4 (44)	15	2 (13)	1 (7)
Total (169)	35	11 (31)	8 (23)

Table 6 Successful salvage rate by subsite

Subsite (no. of patients)	No. of patients (%)		
	Local recurrences/ residuals	Salvage surgeries	Successfully salvaged
Lateral (105)	21	5 (24)	4 (19)
Anterior (45)	8	3 (38)	3 (38)
Superior (8)	2	1 (50)	0 (0)
Posterior (12)	4	2 (50)	1 (25)
Total (170)	35	11 (31)	8 (23)

Table 7 Swallowing function and larynx preservation in patients with local recurrence or residual disease after salvage surgery ($n = 11$)

Variable	No. of patients (%)	
	Preoperative	Postoperative
Nutrition		
Oral feeding	9 (82)	6 (55)
Oral and tube feeding	2 (18)	3 (27)
Tube feeding	0 (0)	2 (18)
Larynx preservation		
Yes	–	8 (73)
No	–	3 (27)

function disorders and required tube-feeding support after CRT. In contrast, in the patients undergoing salvage surgery, ages ranged from 42 to 75 years (median, 54 years), the rate of T4a disease was 18, and 18 % of patients required tube-feeding support after CRT. However, the presence of an advanced tumor is a high-risk factor for local failure and, moreover, the general condition after CRT in such cases is generally poor. Laryngeal cancer, by contrast, offers a greater opportunity for salvage surgery for local recurrence. One hundred and twenty-nine patients developed local recurrence in the RTOG 91-11 laryngeal cancer trial, and the disease was found to be resectable in all cases [12]. Consequently, there might be only a limited

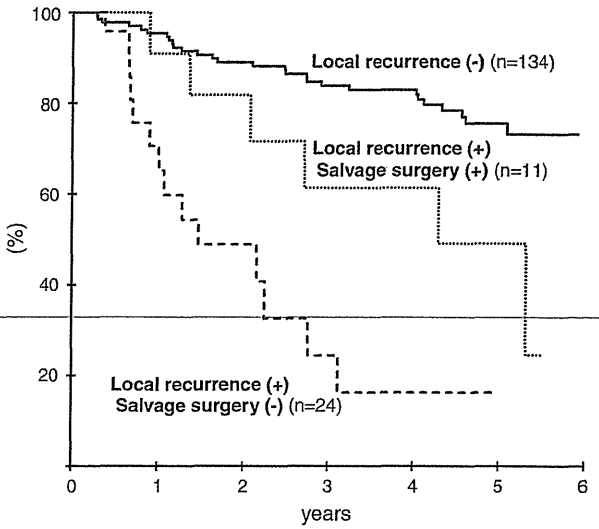

Fig. 3 Overall survival in 11 patients who underwent salvage surgery for local recurrence, 24 patients who did not undergo salvage surgery for local recurrence, and 134 patients who had no local recurrence

number of cases suitable for salvage surgery among patients who initially received CRT for advanced OPC and subsequently developed local recurrence.

Another point of controversy is that patients undergoing salvage surgery for local failure cannot always achieve long-term survival. In our study, 8 patients developed a second recurrence, including 3 cases of local recurrence, 3 of neck disease, and 5 of distant metastasis. Similarly, Zafereo et al. [11] reported that 26 of 39 patients (66.7 %) developed a second recurrence after salvage surgery. It has been regarded that patient age, disease-free interval, T and N classification of recurrent tumors, and surgical margin status influence survival and recurrence rate after salvage surgery for recurrent OPC [11, 13, 14]. However, at the moment, the fact remains that any salvage therapy is less effective than surgery. It is hoped that a novel adjuvant therapy after salvage surgery, such as molecular targeted drug therapy, will be developed in the future.

In this study, 10 patients (91 %) underwent microvascular free flap reconstruction for salvage surgery, with 5 patients (50 %) requiring tube-feeding support after surgery and the larynx preservation rate was 73 %. On the other hand, of the 40 patients who underwent reconstruction surgery with preoperative or postoperative irradiation as an initial treatment, 12 patients (31 %) required tube-feeding support after surgery and the larynx preservation rate was 78 %. Zafereo et al. [11] similarly reported that only 9 (22 %) patients required tube-feeding before salvage surgery, whereas 26 (64 %) required tube-feeding support after surgery. With regard to initial therapy for advanced OPC, it has been reported that patients treated with surgery show a statistically higher frequency of

swallowing disorders than those treated with CRT [15]. However, these results suggest that salvage surgery after CRT would worsen swallowing function in the patients in comparison with initial open surgery.

Chemoradiotherapy is more advantageous in organ and function preservation than definitive surgery; however, survival rates for patients treated with CRT are not always superior to those treated by surgery. Furthermore, it is difficult to salvage local failures, as already described. We have to make an effort to detect persistent tumor or recurrence as early as possible; this should lead to a higher salvage rate. In recent years, clinical trials of less-intensive therapy for patients with HPV-positive OPC have been undertaken by some groups. Considering the difficulty of salvage surgery, the initial treatment method for OPC should be decided carefully and the limitations of salvage surgery should be fully considered.

In conclusion, salvage surgery for OPC was indicated in a limited number of patients with local failure, and the survival rate of these patients was not so high as expected. In addition, swallowing function was worse in patients undergoing salvage surgery after CRT than in those undergoing initial open surgery. However, it is a fact that salvage surgery is the only curative treatment for the patients with recurrence after CRT in most cases. These results should be given adequate consideration when the initial treatment method for OPC is decided.

Conflict of interest No conflict of interest.

References

1. Chen AY, Schrag N, Hao Y et al (2007) Changes in treatment of advanced oropharyngeal cancer, 1985–2001. Laryngoscope 117:16–21
2. Cohan DM, Popat S, Kaplan SE et al (2009) Oropharyngeal cancer: current understanding and management. Curr Opin Otolaryngol Head Neck Surg 17:88–94
3. Parsons JT, Mendenhall WM, Stringer SP et al (2002) Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. Cancer (Phila) 94:2967–2980
4. Ang KK, Harris J, Wheeler R et al (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363:24–35
5. Fakhry C, Westra WH, Li S et al (2008) Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 100:261–269
6. Bachar GY, Goh C, Goldstein DP et al (2010) Long-term outcome analysis after surgical salvage for recurrent tonsil carcinoma following radical radiotherapy. Eur Arch Otorhinolaryngol 267:295–301
7. Taki S, Homma A, Oridate N et al (2010) Salvage surgery for local recurrence after chemoradiotherapy or radiotherapy in hypopharyngeal cancer patients. Eur Arch Otorhinolaryngol 267:1765–1769
8. Goodwin WJ Jr (2000) Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope 110:1–18
9. Agra IM, Carvalho AL, Pontes E et al (2003) Postoperative complications after en bloc salvage surgery for head and neck cancer. Arch Otolaryngol Head Neck Surg 129:1317–1321
10. Roosli C, Studer G, Stoeckli SJ (2010) Salvage treatment for recurrent oropharyngeal squamous cell carcinoma. Head Neck 32:989–996
11. Zafereo ME, Hanasono MM, Rosenthal DI et al (2009) The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. Cancer (Phila) 115:5723–5733
12. Weber RS, Berkey BA, Forastiere A et al (2003) Outcome of salvage total laryngectomy following organ preservation therapy: the Radiation Therapy Oncology Group trial 91–11. Arch Otolaryngol Head Neck Surg 129:44–49
13. Agra IM, Carvalho AL, Ulbrich FS et al (2006) Prognostic factors in salvage surgery for recurrent oral and oropharyngeal cancer. Head Neck 28:107–113
14. Nichols AC, Kneuertz PJ, Deschler DG et al (2011) Surgical salvage of the oropharynx after failure of organ-sparing therapy. Head Neck 33:516–524
15. Boscolo-Rizzo P, Stellin M, Fuson R et al (2009) Long-term quality of life after treatment for locally advanced oropharyngeal carcinoma: surgery and postoperative radiotherapy versus concurrent chemoradiation. Oral Oncol 45:953–957

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(10)927–933
doi:10.1093/jjco/hys128
Advance Access Publication 23 August 2012

Phase II Feasibility Trial of Adjuvant Chemoradiotherapy with 3-weekly Cisplatin for Japanese Patients with Post-operative High-risk Squamous Cell Carcinoma of the Head and Neck

Naomi Kiyota[1], Makoto Tahara[2,*], Susumu Okano[2], Mitsuhiko Kawashima[3], Kazuto Matsuura[4], Yuske Onozawa[5], Kenichi Nibu[6], Ryuichi Hayashi[7], Kenichi Yoshimura[8] and Atsushi Ohtsu[9]

[1]Department of Medical Oncology and Hematology, Kobe University Hospital, Kobe, [2]Division of Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, [3]Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, [4]Division of Head and Neck Surgery, Miyagi Cancer Center, Natori, [5]Division of Medical Oncology, Shizuoka Cancer Center, Shizuoka, [6]Department of Otolaryngology and Head and Neck Surgery, Kobe University Hospital, Kobe, [7]Division of Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, [8]Division of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital, Kyoto and [9]Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan

*For reprints and all correspondence: Makoto Tahara, Division of Head and Neck Medical Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan.
E-mail: matahara@east.ncc.go.jp

Received June 15, 2012; accepted July 15, 2012

Objective: The current standard of care for post-operative high-risk squamous cell carcinoma of the head and neck is concurrent chemoradiotherapy with a 3-weekly cycle of cisplatin (3W-CDDP/RT). In previous pivotal trials, the complete delivery rate of three cycles of cisplatin and radiation therapy was only ~60%. Here, we evaluated the feasibility and safety of 3W-CDDP/RT in a Japanese population.

Methods: The study enrolled post-operative high-risk squamous cell carcinoma of the head and neck patients. High-risk factors were a microscopically incomplete resection, extracapsular extension and two or more lymph node metastases. Subjects received three cycles of cisplatin at a dose of 100 mg/m^2 concomitant with radiation therapy (66 Gy/33 Fr).

Results: From August 2006 to May 2009, 25 eligible subjects were accrued, including 13 males, with a median age of 59 years, Eastern Cooperative Oncology Group performance status 0/1 (18/7), Stage III/IVA/IVB/recurrent (1/18/1/5) and oral cavity/oropharynx/hypopharynx/larynx (17/4/3/1). Protocol completion rate was 80%. The lower limit of the one-sided 90% confidence interval was 66%, which met the predefined statistical criteria. Grade 3/4 acute and late toxicities were almost identical to those in previous pivotal trials. No treatment-related deaths were observed. With a median follow-up of 39 months, 14 have had progression and 10 have died. Estimated 3-year locoregional control rate, relapse-free survival and overall survival were 74, 43 and 60%, respectively. On univariate analysis, oral cavity cancer and a cumulative cisplatin dose below 240 mg/m^2 appeared to be poor prognostic factors.

Conclusions: This is the first Phase II feasibility trial of adjuvant chemoradiotherapy with 3-weekly cisplatin for post-operative high-risk squamous cell carcinoma of the head and neck in a Japanese population. This treatment was feasible and the safety profile was identical to those in pivotal Phase III trials.

Key words: head and neck cancer – post-operative high risk patients – adjuvant chemoradiotherapy – cisplatin

INTRODUCTION

The current standard of care for post-operative high-risk squamous cell carcinoma of the head and neck (SCCHN) is concurrent chemoradiotherapy with a 3-weekly cycle of cisplatin at a dose of 100 mg/m^2 (3W-CDDP/RT). In two pivotal trials (RTOG 9501 and EORTC22931), post-operative 3W-CDDP/RT showed a significant improvement in locoregional control (LRC) and disease-free survival compared with radiation therapy alone, and EORTC 22931 also showed a significant improvement in overall survival (OS) (1,2). These significant benefits of post-operative 3W-CDDP/RT were further supported by a combined analysis of RTOG 9501 and EORTC 22931 (3). However, post-operative 3W-CDDP/RT is associated with greater toxicity than post-operative radiation therapy alone and the complete delivery rate of three cycles of cisplatin and RT in prior pivotal trials was only ~60% (1,2,4).

Few prospective data for post-operative 3W-CDDP/RT in Asian populations are available, and acceptance of adjuvant chemoradiotherapy in Japan is low. Here, we evaluated the feasibility and safety of post-operative 3W-CDDP/RT in a Japanese population.

PATIENTS AND METHODS

Patient Selection

All patients had pathologically confirmed locally advanced SCCHN arising in the oral cavity, oropharynx, hypopharynx or larynx without distant metastasis and had undergone surgical resection without gross residual disease. Patients with local recurrence who underwent surgical resection with curative intent were also enrolled in this feasibility trial.

At least one of the following high-risk pathologic features was required: (1) microscopically involved (5 mm or less) resection margins, (2) extracapsular spread in at least one lymph node and (3) two or more positive lymph nodes. Additional entry criteria included age 20–75 years; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and adequate hematologic and organ function, namely a white-cell count of at least 3500/m^3, platelet count of at least 100 000/m^3 and creatinine clearance of more than 70 ml/min. Patients with a history of previous chemotherapy or radiotherapy were excluded. The trial was conducted under a multi-institutional design in four institutions in Japan, the National Cancer Center Hospital East, Kobe University Hospital, Miyagi Cancer Center and Shizuoka Cancer Center. The study protocol was approved by the institutional review committee of each center, and all patients gave written informed consent before study entry in accordance with institutional guidelines.

Treatment Plan

All eligible patients underwent definitive surgery with curative intent. The extent of surgical resection of the primary tumor and/or neck dissection procedures followed accepted criteria for adequate excision, which depend on the volume and location of the tumor.

All patients underwent radiation therapy within 8 weeks after definitive surgery consisting of conventionally fractionated doses of 2 Gy each in 5-weekly sessions. Target-volume doses and maximal dose to the spinal cord were recorded. Treatments were conducted on linear accelerators of 4–6 MV using egocentric techniques. A large volume encompassing the primary site and all draining lymph nodes at risk received a dose of more than 40 Gy in 20 fractions over a period of 4 weeks. Regions that were adjacent to the high-risk area received a dose of more than 46 Gy in 23 fractions over a period of 4.5 weeks. Regions that were at high risk for malignant dissemination or that had inadequate resection margins received a total of 66 Gy in 33 fractions over a period of 6.5 weeks. The dose to the spinal cord was limited to 46 Gy.

Concurrent chemotherapy consisted of three courses of cisplatin 100 mg/m^2 infused on Days 1, 22 and 43 of the course of radiotherapy. Patients received prophylactic hydration and antiemetic agents. Aprepitant was approved in Japan in October 2009, and was therefore not available during the study period. We therefore recommended the use of a 5-HT3 antagonist and dexamethasone 16–20 mg on Day 1 and dexamethasone 8–16 mg on Days 2–3. Cisplatin was postponed if the absolute neutrophil count fell below 1000/mm^3 or platelet count fell below 75 000/mm^3. Cisplatin dose was decreased to 80 mg/m^2 if creatinine clearance dropped to 50–60 ml/min, and to 60 mg/m^2 if it dropped to 40–50 ml/min. Dose was also decreased with Grade 4 hematological toxicity or febrile neutropenia from 100 to 80 mg/m^2 or from 80 to 60 mg/m^2; with neurotoxicity or hearing loss Grade 2 to 60 mg/m^2 and administration was discontinued in the case of neurotoxicity or hearing loss Grade 3 or more. We routinely recommend prophylactic insertion of a percutaneous endoscopic gastrostomy (PEG) for nutrition support before chemoradiotherapy.

Follow-up

Patients were evaluated every 3 months for the first 12 months and every 4 months for the next 24 months. Adverse effects, weight and performance status were assessed at baseline, weekly for the first 8 weeks, and at all follow-up assessments, which were conducted every 3 months.

Study Design

Patients were enrolled after surgery and assigned to receive adjuvant concurrent chemoradiotherapy with cisplatin. Principal eligibility criteria were checked at enrollment.

In accordance with the intention-to-treat principle, all patients were included in all statistical analyses. The primary endpoint was treatment completion rate. Treatment completion was defined as delivery of 66 Gy radiation and a

cumulative cisplatin dose of more than 240 mg/m^2. Secondary endpoints were OS, relapse-free survival (RFS), LRC and adverse events. OS was defined as the time from initiation of chemoradiotherapy to death from any cause, and RFS as the time from initiation of chemoradiotherapy to recurrence or death from any cause. The duration of LRC was defined as the time from initiation of chemoradiotherapy to the occurrence of locoregional recurrence. Survival curves were estimated using Kaplan–Meier methods (5) and comparisons between survival curves were performed using the log-rank test. Treatment-related adverse events were scored according to the Common Toxicity Criteria of the National Cancer Institute, version 3.0, and categorized as acute (occurring within 90 days after initiation of chemoradiotherapy) or late (continuing or occurring after 90 days). We also assessed the 1-year feeding tube rate, which was defined as the proportion of patients using tube feeding 1 year after the initiation of chemoradiotherapy without recurrence.

Based on the previous trials (1,2,4), we considered the results as positive when the estimated treatment completion rate was around 60%, with adequate precision. Twenty or more patients were required to ensure that the lower limit of the one-sided 90% confidence interval (CI) of the treatment completion rate would be >43%. We therefore planned to recruit 25 patients. An interim futility analysis was conducted after 10 patients were enrolled.

All analyses were conducted using the Windows version of SPSS Statistics version 18 (IBM Corporation, NY, USA).

RESULTS

Patient Characteristics

Twenty-five patients were enrolled between August 2006 and June 2009. Patient characteristics are summarized in Table 1. By age, the 13 females and 12 males ranged from 26 to 68 years, with a median of 59 years. Eighteen patients were ECOG PS 0 and seven were ECOG PS 1. Sixteen patients had primary sites in the oral tongue, four in the hypopharynx, three in the oropharynx and one each in the larynx and oral floor. Twenty patients had locally advanced disease and five had locoregional recurrent disease. All 25 patients underwent definitive surgery with curative intent. By pathological stage, 1 patient was classified as having Stage III disease, 18 as having Stage IVA and 1 as having Stage IVB. All five patients who experienced locoregional recurrence did so after partial glossectomy for T1N0 or T2N0 disease, and all five received definitive surgery for locoregional recurrent disease. Fifteen patients received reconstruction surgery using the following reconstruction methods: free rectus abdominis flap in five, free jejunal flap in four, free anterolateral thigh flap in three and free radial forearm flap in three. Regarding high-risk features, 6 patients had a microscopically involved margin (incomplete resection: ICR), 15 had extracapsular extension (ECE) and 22 had multiple lymph node metastases (two or more lymph nodes).

Table 1. Patient characteristics ($n = 25$)

	Number of patients
Age: median (range)	59 (26–68)
Gender: female/male	13/12
PS: 0/1	18/7
Primary site	
Oral cavity	17
Oropharynx	4
Hypopharynx	3
Larynx	1
Stage	
III	1
IVA	18
IVB	1
Locoregional recurrent disease	5
High-risk features	
ICR	6
ECE	15
Multiple lymph node metastases	22
Histology: squamous cell carcinoma	
Well differentiated	13
Moderately differentiated	6
Poorly differentiated	6

ICR, incomplete resection; ECE, extracapsular extension.

Twenty patients had at least ICR or ECE and five had only multiple lymph nodes. Three of these five patients received definitive surgery for locoregional recurrent disease, while the other two had three or more lymph node metastases. The median number of metastatic lymph nodes was 4, ranging from 0 to 28.

Compliance with and Delivery of Treatment

Median interval from surgery to the initiation of chemoradiotherapy was 47 days (range 28–56 days). Median duration of radiation was 49 days (range 45–58 days) and 24 of 25 patients completed radiation therapy of up to 66 Gy in 33 fractions, as specified in the protocol. One patient was considered to have not completed radiation therapy because of an unacceptable fraction size (66 Gy in 30 fractions).

A total of 23 patients received three cycles of cisplatin and 2 received two cycles. Dose reduction of cisplatin was conducted as specified in the protocol: reduction was necessary in 7 patients in the second cycle and in 12 in third cycle due to renal impairment in 13, hearing impairment in 2, infection in 1, and prolongation of anorexia 1, patient refusal and unacceptable deviation from the protocol in 1 each. In the case with unacceptable deviation from the

protocol, the patient received a third cycle of cisplatin divided into four doses of 20 mg/m^2 each. Median relative dose intensity (RDI) of cisplatin was 0.83 (range 0.51–1.00).

Treatment completion was defined as 66 Gy radiation delivery with a cumulative cisplatin dose of more than 240 mg/m^2. A total of 20 patients met these criteria, with radiation up to 66 Gy in 33 fractions. Treatment completion rate was thus 80% and the lower limit of the one-sided 90% CI was 66%, which met the statistical criteria specified in the protocol.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 and are listed in Tables 2 and 3. Grade 3/4 acute toxicity included mucositis (44%), dysphagia (28%), dermatitis (24%), nausea/vomiting (16%), neutropenia (32%) and anemia (36%). Grade 3/4 late toxicity included dysphagia (10%), xerostomia (5%) and osteonecrosis (5%). Twenty patients received prophylactic PEG insertion. During and within 30 days after adjuvant 3W-CDDP/RT, 17 of 20 patients used PEG for nutritional support, while 1 of 20 used total parenteral nutrition (TPN) instead of PEG and 2 of 20 did not use PEG at all. Two of five patients without PEG used a naso-gastric tube, one patient used TPN and one patient did not receive nutritional support. Finally, 84% (21/25) of patients received nutritional support during and within 30 days after adjuvant 3W-CDDP/RT. Among the disease-free patients, 3-, 6-month and 1-year feeding tube rates were 48% (10/21), 40% (6/15) and 20% (3/15), respectively. There were no major complications with the reconstruction flap and no treatment-related deaths within 30 days.

Table 2. Acute adverse events ($n = 25$)

Adverse event	Number of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3/4
Leucopenia	4	9	12	0	48
Neutropenia	5	11	8	0	32
Anemia	5	11	6	3	36
Thrombocytopenia	14	4	0	0	0
Nausea	4	17	4	0	16
Vomiting	13	6	0	0	0
Anorexia	1	11	10	0	40
Constipation	5	3	0	0	0
Dysphagia	4	13	7	0	28
Mucositis	2	12	11	0	44
Dermatitis	9	10	6	0	24
Hearing loss	1	2	0	0	0
Taste alteration	7	18	—	—	—
Xerostomia	7	18	0	0	0
Febrile neutropenia	—	0	0	0	0
Infection	0	1	5	0	20
Creatinin	8	7	1	0	4
Heart failure	0	0	1	0	4

Table 3. Late adverse events ($n = 21$)

Adverse event	Number of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3/4
Leucopenia	10	3	0	0	0
Neutropenia	7	2	0	0	0
Anemia	6	9	3	2	24
Thrombocytopenia	4	0	0	0	0
Dysphagia	8	7	2	0	10
Taste alteration	14	7	—	—	—
Xerostomia	8	12	1	0	5
Peripheral neuropathy	1	1	0	0	0
Hearing loss	0	2	0	0	0
Osteonecrosis	0	1	1	0	5
Creatinin	9	5	0	0	0
Infection	0	1	0	0	0
Hypothyroidism	1	0	0	0	0

Disease recurrence was observed in 14 patients, consisting of locoregional recurrence in 3, locoregional recurrence and distant metastasis in 2, and distant metastasis in 9. By site, nine cases of recurrence occurred in the lung, three in the cervical lymph nodes, one in the primary site and three in other sites.

Survival outcomes were estimated by the Kaplan–Meier method. With a median follow-up period for survivors of 39 months (range 19–56 months), 3-year LRC, RFS and OS were 74, 43 and 60%, respectively (Figures 1–3).

Univariate Analysis

Univariate analyses for LRC, RFS and OS were performed using the following variables: gender, ECOG PS, site of the primary tumor, disease status (locoregional recurrence or not), tumor cell differentiation and cumulative cisplatin dose (Table 4). Allowing for the small sample size of this Phase II feasibility study, RFS was significantly poorer when the primary site was in the oral cavity ($P = 0.038$) and in patients who received a cumulative cisplatin dose below 240 mg/m^2 ($P = 0.005$). Moreover, OS was significantly poorer in patients who received a cumulative cisplatin dose below 240 mg/m^2 ($P = 0.033$).

DISCUSSION

The current standard of care for post-operative high-risk SCCHN is concurrent chemoradiotherapy with a 3-week

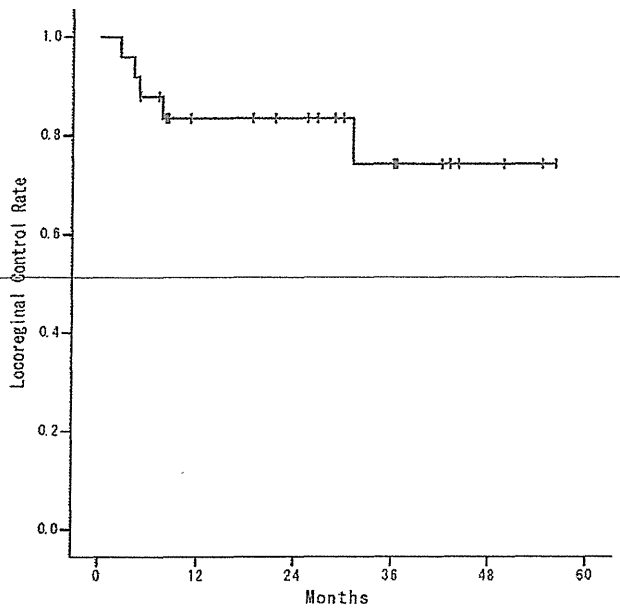

Figure 1. Kaplan–Meier estimates of locoregional control rate ($n = 25$).

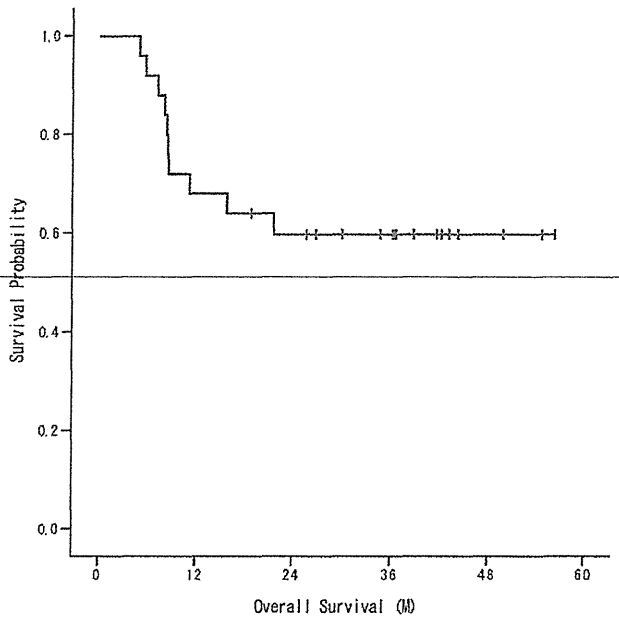

Figure 3. Kaplan–Meier estimates of overall survival ($n = 25$).

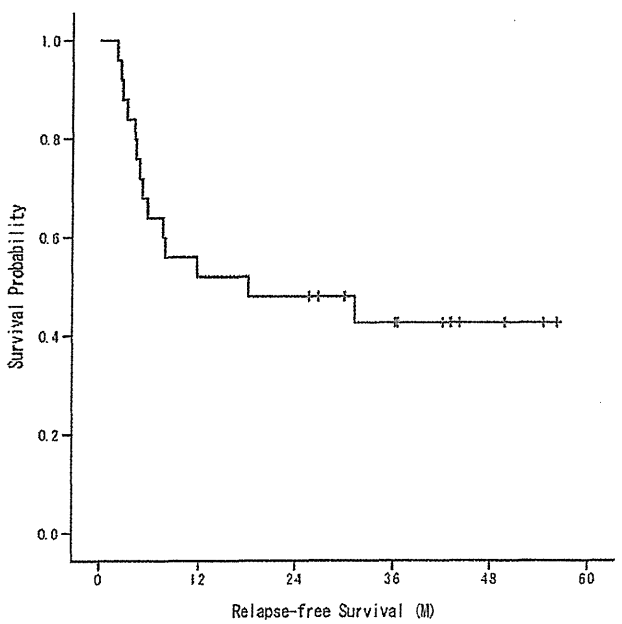

Figure 2. Kaplan–Meier estimates of relapse-free survival ($n = 25$).

cycle of cisplatin at a dose of 100 mg/m^2 (3W-CDDP/RT). In two pivotal trials (RTOG 9501 and EORTC22931), post-operative 3W-CDDP/RT showed a significant improvement in LRC and disease-free survival, and EORTC 22931 also showed a significant improvement in OS (1,2). These significant benefits of post-operative 3W-CDDP/RT were further supported by combined analysis of RTOG 9501 and EORTC 22931 (3). However, post-operative 3W-CDDP/RT is associated with greater toxicity than post-operative radiation therapy alone, and the complete delivery rate of three cycles of cisplatin and RT was only ~60% (1,2,4). This poor treatment compliance with 3W-CDDP/RT in the post-operative setting is of considerable concern. In their retrospective analysis of 3W-CDDP/RT at a reduced dose of 75 mg/m^2 in a post-operative setting, Franchin et al. (6) found that despite the reduced dose of cisplatin, only 48% (68/142) of patients were able to receive three cycles of cisplatin concurrent with radiation. Further, in their report of the safety and feasibility of 3W-CDDP/RT at a dose of 100 mg/m^2 in three nasopharyngeal cancer patients, Isobe et al. (7) concluded that 3W-CDDP/RT at 100 mg/m^2 was not tolerable for Japanese patients, while Nishimura et al. (8) recommended a dose reduction to 60–70 mg/m^2 owing to the poorer renal function of head and neck cancer patients in Japan than in western countries. In our Phase II feasibility trial, 20 patients (80%) received a total cisplatin dose of more than 240 mg/m^2 concurrent with RT and achieved an RDI of cisplatin of 0.83. Moreover, the incidence of adverse events was almost identical to that in previous pivotal trials (1,2,4) and no treatment-related deaths or severe complications with the reconstruction flap were seen. Considering that most patients (72%) were ECOG-PS 0 and the small sample size, these results indicted the tolerability and feasibility of adjuvant 3W-CDDP/RT for Japanese patients with post-operative high-risk SCCHN.

Against this, the relatively high incidence and severity of acute toxicities of 3W-CDDP/RT are also of concern. Among these, G3/4 hematological toxicities were seen in around 40% of patients who received with 3W-CDDP/RT (1,2,9). In our Phase II trial, 32% (8/25) of patients

Table 4. Univariate analysis for survival ($n = 25$)

	No. of patients	Three-year locoregional control rate (%)	*P* value	Three-year RFS (%)	*P* value	Three-year OS (%)	*P* value
Gender							
Female	13	79.1	0.399	59.3	0.09	69.2	0.281
Male	12	74.1		25.0		50.0	
ECOG PS							
0	18	70.7	0.721	42.9	0.663	66.2	0.307
1	7	85.7		42.9		42.9	
Site of primary tumor							
Oral cavity	17	58.8	0.987	23.5	0.038	46.3	0.055
Other	8	75.0		75.0		87.5	
Disease status							
Locally advanced disease	20	75.0	0.784	48.9	0.157	65.0	0.29
Locoregional recurrent disease	5	80.0		20.0		40.0	
Tumor differentiation							
Well or moderately differentiated	19	65.5	0.176	39.5	0.835	62.7	0.48
Poorly differentiated	6	100		50.0		50.0	
Cumulative cisplatin dose							
$\geq$240 mg/m^2	22	76.3	0.36	48.5	0.005	68.2	0.033
<240 mg/m^2	3	66.7		0		0	

LRCR, locoregional control rate; RFS, relapse-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status.

experienced G3/4 neutropenia. These may lead to infection at the surgical site after definitive surgery for advanced SCCHN. Moreover, 32% (8/25) of patients experienced Grade 2 or more serum creatinin elevation, and decreases in creatinin clearance led to a dose reduction of cisplatin in 52% (13/25) of patients. Given the suggested association between efficacy and total dose of cisplatin in concurrent chemoradiation for SCCHN (10–12), administration with a view to minimal renal impairment is important in maintaining the efficacy of concurrent chemoradiotherapy with cisplatin. Attempts to improve treatment compliance and safety in the adjuvant setting have also resulted in the investigation of weekly cisplatin concurrent with radiation (W-CDDP/RT) (13–16). In this regard, we are now planning a Phase III trial of adjuvant chemoradiotherapy comparing weekly with 3-weekly cisplatin in post-operative high-risk patients with SCCHN.

With regard to efficacy, 3-year RFS and OS after a median follow-up period for survivors of 39 months were 43 and 60%, respectively. In RTOG 95-01, 3-year event-free survival and OS were 47 and 56% (1), while 5-year event-free survival and OS in EORTC 22 931 were 47 and 53% (2), respectively. Considering that our present data included cases with local recurrence, survival in our study appears identical with the results of these previous pivotal Phase III trials (1,2).

In univariate analysis, prognosis appeared to be poorer in patients with oral cavity cancer and those who received a cumulative cisplatin dose of <240 mg/m^2. Three-year RFS and OS for patients with oral cavity cancer were 23.5 and 46.3%, respectively. The poor prognostic significance attached to oral cavity cancer is well known (17–20), and our present results appeared consistent with these previous reports. In contrast, the relationship between cumulative cisplatin dose and the efficacy of chemoradiotherapy has been a matter of debate. From their analysis of previous trials (10–12), Ang et al. noted that a cumulative cisplatin dose of ~200 mg/m^2 might be sufficient to yield a beneficial antitumor effect, independently of schedule. These authors also reported that LRC was significantly worse in patients receiving two cycles of cisplatin than in those receiving three [hazard ratio (HR): 1.7, 95% CI: 1.20–2.54] and that OS with only a single cycle was significantly worse than that with three cycles (HR: 2.1, 95% CI: 1.35–3.32) (21). Our data also suggested that survival outcome deteriorated with a cumulative cisplatin dose below 240 mg/m^2, which may suggest the superiority of continuing cisplatin cycling for as long as possible.

In conclusion, this is the first Phase II feasibility trial of adjuvant chemoradiothrapy with 3-weekly cisplatin for post-operative high-risk patients with SCCHN in a Japanese population. This treatment was feasible and had an identical safety profile to those in pivotal Phase III trials. Oral cavity

cancer and a cumulative cisplatin dose below 240 mg/m^2 appeared to be associated with a poor survival outcome.

Funding

This study was supported in part by the National Cancer Research and Development Fund (23-A-21).

Conflict of interest statement

None declared.

References

1. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *New Engl J Med* 2004;350:1937–44.
2. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *New Engl J Med* 2004;350:1945–52.
3. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* 2005;27:843–50.
4. Al-Sarraf M, Pajak TF, Byhardt RW, Beitler JJ, Salter MM, Cooper JS. Postoperative radiotherapy with concurrent cisplatin appears to improve locoregional control of advanced, resectable head and neck cancers: RTOG 88–24. *Int J Radiat Oncol Biol Phys* 1997;37:777–82.
5. Kaplan E, Meter P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
6. Franchin G, Minatel E, Politi D, et al. Postoperative reduced dose of cisplatin concomitant with radiation therapy in high-risk head and neck squamous cell carcinoma. *Cancer* 2009;115:2464–71.
7. Isobe K, Kawakami H, Uno T, et al. Concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: is intergroup study 0099 feasible in Japanese patients? *Jpn J Clin Oncol* 2003;33:497–500.
8. Nishimura G, Tsukuda M, Horiuchi C, et al. Decrease of creatinine clearance rate with aging in patients with head and neck cancer in Japan. *Int J Clin Oncol/Jpn Soc Clin Oncol* 2007;12:120–4.
9. Zenda S, Onozawa Y, Tahara M, et al. Feasibility study of single agent Cisplatin and concurrent radiotherapy in Japanese patients with squamous cell carcinoma of the head and neck: preliminary results. *Jpn J Clin Oncol* 2007;37:725–9.
10. Ang KK. Concurrent radiation chemotherapy for locally advanced head and neck carcinoma: are we addressing burning subjects? *J Clin Oncol* 2004;22:4657–9.
11. Huguenin P, Beer KT, Allal A, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. *J Clin Oncol* 2004;22:4665–73.
12. Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. *J Clin Oncol* 2000;18:1458–64.
13. Rampino M, Ricardi U, Munoz F, et al. Concomitant adjuvant chemoradiotherapy with weekly low-dose cisplatin for high-risk squamous cell carcinoma of the head and neck: a phase II prospective trial. *Clin Oncol (R Coll Radiol)* 2011;23:134–40.
14. Otty Z, Skinner MB, Dass J, et al. Efficacy and tolerability of weekly low-dose cisplatin concurrent with radiotherapy in head and neck cancer patients. *Asia Pac J Clin Oncol* 2011;7:287–92.
15. Porceddu SV, Campbell B, Rischin D, et al. Postoperative chemoradiotherapy for high-risk head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2004;60:365–73.
16. Bachaud J, Cohen-Jonathan E, Alzieu C. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys* 1996;36:999–1004.
17. Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. *Int J Radiat Oncol Biol Phys* 1997;39:137–48.
18. Dinshaw KA, Agarwal JP, Laskar SG, Gupta T, Shrivastava SK, Cruz AD. Head and neck squamous cell carcinoma: the role of post-operative adjuvant radiotherapy. *J Surg Oncol* 2005;91:48–55.
19. Peters L, Helmuth G, Ang K. Evaluation of the dose for postoperative radiation therapy of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1993;26:3–11.
20. Argiris A, Li Y, Forastiere A. Prognostic factors and long-term survivorship in patients with recurrent or metastatic carcinoma of the head and neck. *Cancer* 2004;101:2222–9.
21. Ang K, Zhang Q, Wheeler RH, et al. A phase III trial (RTOG 0129) of two radiation-cisplatin regimens for head and neck carcinomas (HNC): impact of radiation and cisplatin intensity on outcome. *J Clin Oncol* 2010;28:15s, abstr.5507.

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(8)691–696
doi:10.1093/jjco/hys096
Advance Access Publication 3 July 2012

Induction Chemotherapy with Docetaxel, Cisplatin and S-1 Followed by Proton Beam Therapy Concurrent with Cisplatin in Patients with T4b Nasal and Sinonasal Malignancies

Susumu Okano[1,4], Makoto Tahara[1,*], Sadamoto Zenda[2], Nozomu Fuse[1], Takayuki Yoshino[1], Toshihiko Doi[1], Mitsuhiko Kawashima[2], Takashi Ogino[2], Ryuichi Hayashi[3] and Atsushi Ohtsu[1]

[1]Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, [2]Division of Radiation Oncology, National Cancer Center Hospital East, [3]Division of Head and Neck Surgery, National Cancer Center Hospital East, Chiba, and [4]Department of Oto-Rhino-Laryngology, Jikei University School of Medicine, Tokyo, Japan

*For reprints and all correspondence: Makoto Tahara, Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa-shi, Chiba 277-8577, Japan. E-mail: matahara@east.ncc.go.jp

Received February 11, 2012; accepted May 29, 2012

Objective: For the treatment of patients with T4b nasal and sinonasal malignancies, definitive chemoradiotherapy was contraindicated due to the risk of brain damage and blindness. However, combination chemotherapy with docetaxel, cisplatin and S-1 is well tolerated and effective. We conducted a retrospective analysis to evaluate the efficacy and feasibility of induction chemotherapy using docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin.

Methods: Thirteen patients treated with docetaxel, cisplatin and S-1 were analyzed. Docetaxel, cisplatin and S-1 consisted of 60–70 mg/m^2/day docetaxel on day 1, 70 mg/m^2/day cisplatin on day 1 and 60–80 mg/m^2/day S-1 on days 1–14. Treatment was repeated every 3–4 weeks with a maximum number of three treatment cycles. According to the response to docetaxel, cisplatin and S-1, patients received either proton beam therapy concurrent with 20 mg/m^2/day cisplatin on days 1–4 every 3 weeks or proton beam therapy alone.

Results: Neutropenia represented the most common Grade 3/4 hematological toxicity (76.9%), while the most frequently observed non-hematological toxicity was nausea (23.0%). After the completion of docetaxel, cisplatin and S-1, the overall response rate was 38.4% (5 of 13), with 1 patient achieving complete response and 4 patients achieving partial response. Subsequently, 10 patients received proton beam therapy concurrent with cisplatin, 2 received proton beam therapy alone and 1 received palliative radiation. No severe toxicity was observed during proton beam therapy. After the completion of proton beam therapy, 11 patients (84.6%) achieved complete response and no brain damage or blindness occurred.

Conclusions: Induction chemotherapy with docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin is well tolerated and displays promising antitumor activity that warrants further investigation.

Key words: nasal – sinonasal – induction chemotherapy – proton – head and neck

INTRODUCTION

Nasal and sinonasal malignancies are rare, representing only 3–5% of all head and neck cancers (HNC) (1,2). Although a variety of malignancies arise in this region, squamous cell carcinoma is most frequent, followed by adenocarcinoma and adenoid cystic carcinoma (3). As the nasal and sinonasal regions have limited anatomical access and permit the asymptomatic growth of malignancies, most patients first realize symptoms when tumors reach a large size or invade the surrounding normal critical organs, and are often initially diagnosed with unresectable disease (4). These patients are not candidates for gross total resection and are typically treated with either definitive radiotherapy or concurrent chemoradiotherapy. However, due to the proximity of critical organs to malignancies in the nasal and sinonasal sinuses, 15–30% of the patients develop radiation-induced serious complications, including brain necrosis, hearing loss, meningitis, unilateral or bilateral blindness, optic neuritis, cataracts, osteoradionecrosis and central nervous system damage (5–7). Despite the use of radiotherapy with or without chemotherapy, outcomes are often poor in these patients due to the high occurrence of local relapse, as reflected in the reported 5-year overall survival (OS) rate of only 15% (8).

To reduce radiation-induced toxicity and improve treatment outcomes for locally advanced nasal and sinonasal malignancies, we previously evaluated two treatment strategies involving induction chemotherapy (IC) and proton beam therapy (PBT) (9). In the first approach, we demonstrated that IC led to reduced tumor sizes and avoided brain damage and ocular/visual toxicity that often results from radiotherapy (9). We also examined IC with irinotecan plus docetaxel (ID) for olfactory neuroblastoma, but the relatively poor treatment outcomes suggested that ID was not a suitable approach (9). We subsequently performed a Phase I clinical study of IC with docetaxel, cisplatin and S-1 (TPS) and found that this treatment was well tolerated, feasible and showed a good antitumor activity with locally advanced HNC, which included several nasal and sinonasal malignancies (10). As the response rate to TPS was 70%, IC combined with TPS appears to be a superior approach than IC with ID.

In addition to IC, we have also evaluated the use of PBT for the treatment of nasal and sinonasal malignancies (11,12). PBT was anticipated to improve tumor local control probability and decrease acute and late toxicities of the surrounding normal tissue (13–15). A previous retrospective analysis of 14 patients with olfactory neuroblastoma from our institute who were treated with PBT displayed excellent local control and survival outcomes without serious adverse effects, suggesting that PBT allows the delivery of tumoricidal doses with minimal complications (11).

Here, we conducted a retrospective analysis to evaluate the efficacy and feasibility of IC with TPS followed by PBT concurrent with cisplatin for the treatment of T4b nasal and sinonasal malignancies.

PATIENTS AND METHODS

Patients

We reviewed the case records of 13 patients who were treated for T4b nasal and sinonasal malignancies at the 'Search' between January 2006 and March 2012. Tumor staging in the present study was evaluated based on sections of the nasal cavity and sinonasal sinuses using the TNM classification of the UICC 6th edition, regardless of the histology type.

Treatment Plan

Induction Chemotherapy

Patients received three cycles of TPS chemotherapy followed by PBT concurrent with cisplatin. The chemotherapy regimen consisted of a 1 h infusion of docetaxel at 60–70 mg/m^2/day on day 1, a 2 h infusion of cisplatin at 70 mg/m^2/day on day 1 and S-1 twice daily on days 1–14 at 60–80 mg/m^2/day. The treatment was repeated every 3–4 weeks with a maximum number of three treatment cycles. Ciprofloxacin was administered as a prophylactic on days 5–15.

Chemotherapy Concurrent with PBT

After the completion of TPS, patients received PBT concurrent with cisplatin, which was administered at 20 mg/m^2 daily for 4 days. The treatment was repeated every 3 weeks with a maximum of three treatment cycles. The total dose of PBT was 65 cobalt Gray equivalents (GyE) for 4–5 fractions per week in 2.5 GyE once-daily fractions.

PBT planning was performed using a three-dimensional computed tomography (CT) planning system. In this system, the proton beam was generated using a Cyclotron C235 with an energy of 235 MeV at the exit. Relative biologic effectiveness was defined as 1.1, based on our preclinical experiments (16). Dose distribution was optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Gross tumor volume (GTV) was determined by examination using CT, magnetic resonance imaging (MRI) and/or positron emission tomography-CT. Clinical target volume (CTV) was defined as the GTV plus a 5 mm margin and the sinuses adjacent to the GTV. In cases of tumor invasion into the brain, the area of T2 prolongation on MRI was also included in the CTV. Planning target volume (PTV) was basically defined as the CTV plus a 3 mm margin, but was finely adjusted where necessary in consideration of organs at risk. Beam energies and spread-out Bragg peaks were fine-tuned such that the PTV was minimally covered by a 90% isodose volume of the prescribed dosage. The irradiated dose was minimized by the delivery of the proton beam with two or three beam arrangements.

Elected nodal irradiation was not planned because of the low incidence of lymph node metastases in these diseases.

Evaluations

Pretreatment evaluation consisted of complete history and physical examinations, complete blood counts, liver function tests, chest X-rays and ECGs. All patients were imaged with CT and MRI scans of the head and neck. Bone scans and CT scans of the abdomen or chest were performed when clinically indicated. Treatment responses were assessed radiographically according to RECIST 1.0 criteria after the third cycle of chemotherapy and on the completion of chemoradiotherapy. The National Cancer Institute Common Toxicity Criteria (version 3.0) was used to describe chemotherapy- and chemoradiation-related toxicities.

Statistical Methods

The follow-up time for each patient was calculated as the time from the start of treatment to 31 March 2012. A survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat population, defined as all patients enrolled in the study who received at least one dose of chemotherapy. Progression-free survival (PFS) was calculated from the date of the first administration of chemotherapy to the first documentation of disease progression, subsequent therapy or death. OS was determined from the date of the first administration of chemotherapy to the date of death or the last confirmation of survival. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc. Chicago, IL, USA).

RESULTS

Patient Characteristics

The clinical and disease characteristics of the 13 patients with histologically proven tumors examined in this retrospective analysis are summarized in Table 1. The median patient age was 47 years (range, 28–60 years). The primary tumor sites involved the nasal cavity (9 of 13) and ethmoid sinus (4 of 13). The leading histology was olfactory neuroblastoma. No patients had clinical or pathologic evidence of neck disease at the time of initial treatment.

Nine patients (69%) completed the three cycles of planned IC. Three patients who were refractory to IC did not receive the third cycle of IC, while one patient received only one cycle due to disease progression. Ten patients received PBT concurrent with cisplatin and two patients received PBT alone, while the patient who experienced disease progression during IC received palliative radiotherapy.

Table 1. Patient characteristics

Characteristic	No. of patients ($n = 13$)
Age (years)	
Median	47
Range	28–60
Sex	
Male	9
Female	4
ECOG performance score	
0	13
Site of primary tumor	
Nasal cavity	9
Ethmoid sinus	4
Histology	
Olfactory neuroblastoma	7
Squamous cell carcinoma	3
Adenocarcinoma	1
Undifferentiated carcinoma	1
Small cell carcinoma	1

Table 2. Toxicities experienced during induction chemotherapy

Toxicity	No. of patients ($n = 13$)				Percent Grade 3–4
	Grade				
	1	2	3	4	
Hematological toxicity					
Leukopenia	1	7	5	0	38.4
Neutropenia	0	2	4	6	76.9
Febrile neutropenia	0	0	0	0	0
Anemia	8	5	0	0	0
Thrombocytopenia	5	2	0	0	0
Non-hematological toxicity					
Nausea	6	2	3	0	23.0
Vomiting	2	4	0	0	0
Anorexia	7	6	0	0	0
Mucositis	2	0	0	0	0
Diarrhea	2	0	0	0	0

Adverse Events

The acute toxicities experienced during the TPS treatment are listed in Table 2. Although 10 patients (76.9%) experienced Grade 3 or 4 neutropenia and 3 patients (23.0%) experienced Grade 3 nausea, toxicity was as expected and manageable.

Acute toxicity scores of chemoradiotherapy are summarized in Table 3. Two patients (16.6%) experienced Grade 3 mucositis, which developed on the hard palate and to a lesser degree on the cheek and pharynx. Interference with

Table 3. Toxicities experienced during proton beam therapy

Toxicity	No. of patients ($n = 12$)				Percent Grade 3–4
	Grade				
	1	2	3	4	
Hematological toxicity					
Leukopenia	9	3	0	0	0
Neutropenia	0	1	0	0	0
Febrile neutropenia	0	0	0	0	0
Anemia	8	4	0	0	0
Thrombocytopenia	5	0	0	0	0
Non-hematological toxicity					
Mucositis	0	1	2	0	16.6
Anorexia	4	5	0	0	0
Nausea	4	3	0	0	0
Vomiting	2	0	0	0	0
Infection	0	0	0	0	0

nutrition was minor, and no patients required a feeding tube. No brain damage or blindness was recorded. In addition, late toxicities were not observed at the time of March 2012.

Treatment Outcomes

Efficacy data for the TPS therapy are listed in Table 4. All patients enrolled in the present study were assessable for a response to TPS. Objective response rate (ORR) was documented in five patients (38.4%), including one patient with complete response (CR) and four with partial responses (PRs) after the IC of TPS (Figs 1 and 2). After the completion of chemoradiotherapy, ORR was documented in 12 patients (92.3%), including 11 with CR and 1 with PR. Each ORR to TPS according to the histology was 14.2% for patients with olfactory neuroblastoma, 33.3% for patients with squamous cell carcinoma and 100% for patients with others.

The median follow-up time was 56.5 months (range, 0.6–63.5months), and the 5-year PFS and OS were 33.8 and 75.5%, respectively. Eight of the 13 patients were alive at the time of this report with no evidence of disease, while 2 patients were alive with disease. Two patients died due to local disease progression and one died as a result of distant metastasis.

Local relapse developed in three patients. The median time to local relapse was 14.4 months (range, 0.3–25.1 months). Relapses occurred within the irradiated region in two patients and on the margin of the irradiated region in one patient. Of the three patients with local relapses, two subsequently died of their disease, while one patient is presently alive with disease and continue to receive chemotherapy. Regional relapse developed in four patients; two of

Table 4. Treatment outcomes

CR	PR	SD	PD	RR (%)	95% CI
Induction chemotherapy ($n = 13$)					
1	4	7	1	38.4	17.7–64.4
IC → PBT with cisplatin[a] or palliative RT					
11	1	0	1	92.3	66.6–98.6

CR, complete response; PR, partial response; PD, progression disease; RR, response rate; SD, stable disease.
[a]Two patients did not receive cisplatin due to refractory disease following TPS.

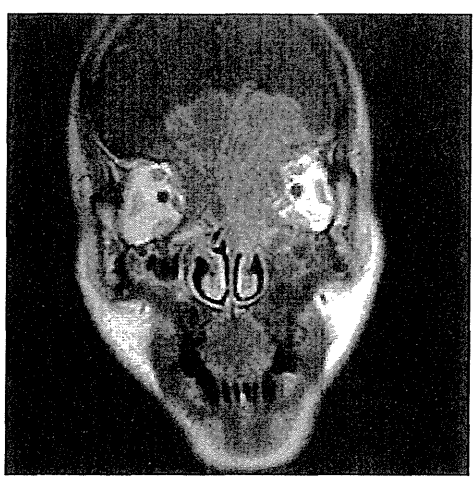

Figure 1. Coronal magnetic resonance imaging (MRI) of a patient with a T4b squamous cell carcinoma in the nasal cavity, with invasion of the orbit and intracranial extension.

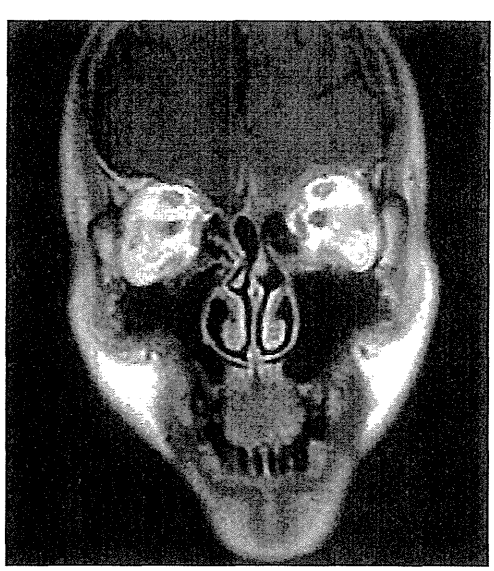

Figure 2. The MRI was repeated after three cycles of docetaxel, cisplatin and S-1, demonstrating a complete response.