T-status and an oral fluoropyrimidine, S-1, adjuvant chemotherapy are prognostic factors in reduced-RADPLAT for resectable hypopharyngeal cancer

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TITLE:

T-status and an oral fluoropyrimidine, S-1, adjuvant chemotherapy are prognostic factors in reduced-RADPLAT for resectable hypopharyngeal cancer

RUNNING HEAD:

Reduced RADPLAT for hypopharyngeal cancer

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None to declare.

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ABSTRACT

Conclusion: Reduced-RADPLAT for HPC achieved comparative survival and local control rates with lower toxicities compared with concurrent chemoradiotherapies including original RADPLAT. S-1 adjuvant chemotherapy showed a survival benefit.

Obejectives: To evaluate the efficacy and toxicities of targeted intra-arterial (IA) infusion of cisplatin with concurrent radiotherapy with a reduced dose (reduced-RADPLAT) for resectable hypopharyngeal cancer (HPC).

Methods: Between 1999 and 2012, 50 patients with stage II to IVA HPC primarily treated by reduced-RADPLAT were analyzed. They were treated by 2-5 courses of IA cisplatin infusion (100 mg per body) with simultaneous systemic infusion of sodium thiosulfate concurrent with conventional radiotherapy (66-70 Gy). After 2003, S-1, an oral fluoropyrimidine, adjuvant chemotherapy were administered to all eligible patients.

Results: During a median follow-up of 48.6 months, the estimated 3- and 5-year overall survival (OS), progression-free survival (PFS), local control, locoregional control, and laryngoesophageal dysfunction-free survival (LEDFS) rates were 76.0 and 62.0%, 58.0 and 50.0%, 72.0 and 70.0%, 66.0 and 62.0%, and 56.0% and 54.0%, respectably. Grade 3 toxicities were observed in 30.0%. No patient had grade 4 or severer toxicities. No patient required tube feeding or tracheotomy at 3 months after treatment. T4-lesions and S-1 administration were significant factors predicting poor

and good OS, PFS, and LEDFS, respectively.

KEY WORDS: concurrent chemoradiotherapy, hypopharyngeal cancer, intra-arterial chemotherapy, reduced-RADPLAT, S-1 adjuvant chemotherapy

INTRODUCTION

Hypopharyngeal cancer (HPC) carries one of the worst prognoses in squamous cell carcinoma of the head and neck (SCCHN), and is mostly diagnosed at an advanced stage requiring combined therapies.[1,2] For a long time, surgery followed by postoperative irradiation had been treatment of choice. A prospective randomized phase 3 study conducted by the European Organization for Research and Treatment of Cancer, the EORTC 24891 study, compared larynx-preserving (induction chemotherapy plus definitive radiation therapy in patients showing a complete response or surgery in those without a response) with conventional (total laryngectomy with partial pharyngectomy and postoperative radiotherapy) treatment in selected cases of advanced pyriform sinus carcinoma.[1] The results showed that the larynx-preserving treatment did not compromise either disease control or survival compared with conventional treatment. Individual patient data meta-analysis showed that the benefit of concurrent chemoradiotherapy was significantly greater than that of induction or adjuvant chemotherapy for non-metastatic head and neck cancer patients.[3,4] In sub-group analyses, the benefit of concurrent chemoradiotherapy for HPC was also confirmed.[3,4]

An alternative chemoradiation protocol involves 4 cycles of targeted intra-arterial (IA) infusion of high-dose (150 mg/m^2) cisplatin with concurrent radiotherapy (RADPLAT).[5] Simultaneous with each IA infusion, the neutralizing agent of cisplatin, sodium thiosulfate, is infused into the systemic circulation, allowing cisplatin administration at a level that is at least 6 times

higher than in the standard intravenous chemotherapy protocol, concurrent chemoradiotherapy (CCRT) protocol of the RTOG 91-11 study,[6] over a relatively short interval.

We previously evaluated the efficacy of a reduced-RADPLAT protocol in candidates for total laryngectomy.[7,8] The patients were treated with 2 or 3 cycles of a fixed dose of cisplatin IA infusion (100 mg per body) during 66-Gy irradiation. The protocol for resectable laryngeal carcinoma could achieve similar local control and survival to the standard CCRT protocol in the RTOG 91-11 study, but with lower toxicities.[7,8] Also, adjuvant chemotherapy with S-1, an oral fluoropyrimidine, following reduced-RADPLAT was an effective treatment option to control distant metastases for resectable laryngeal cancer.[7]

In the literature, there are only a few reports on the efficacy of IA chemotherapy (IAC) concomitant with radiotherapy for HPC.[9,10] Here, we retrospectively evaluated the efficacy and feasibility of our protocol, reduced-RADPLAT, for resectable HPC.

MATERIALS AND METHODS

Patients and Treatment Protocol

All patients had histologically proven HPC with clinical stage II to IVA disease using the staging system of the Union Internationale Contre le Cancer[11] without evidence of other malignancies and distant metastases at diagnosis, the surgical treatment of which requires total or partial laryngopharyngectomy with reconstructive surgery using a conventional free flap, such as from the forearm or jejunum.

Pretreatment staging, involving laryngoscopy and high-resolution computed tomography (CT) scanning of the primary tumor and neck, was performed before primary treatment. To rule out synchronous primary cancers, we performed CT of the chest, gastrointestinal fiberscopy, or positron emission tomography. Before starting therapy, all patients signed a letter of informed consent approved by our Institutional Review Boards (No. 5428).

All patients were treated primarily with reduced-RADPLAT, as described previously.[7] Briefly, all patients received irradiation by conventional once-a-day, 2 Gy-per-fraction regimen to a cumulative dose of 66-70 Gy. They were treated with 2 courses of IA cisplatin infusion (100 mg per body) during 40-Gy irradiation. An additional cisplatin dose (50 mg per body) was given by IA infusion to lymph nodes larger than 3 cm. Tumor responses were evaluated by endoscopy and CT. Patients who showed marked tumor reduction (more than 80%) received sequential irradiation

(26-30 Gy). Patients with clear residual disease (less than 80% reduction) received a third to fifth course of IA cisplatin during sequential irradiation (26-30 Gy).

Acute toxicity was assessed weekly, including a blood cell count, serum chemistry profile, and mucositis, during chemoradiotherapy. Toxicity assessments were based on Common Terminology Criteria for adverse Events version 3.0.

All patients were examined by endoscopic, CT, and/or magnetic resonance imaging 4 weeks after reduced-RADPLAT completion to evaluate their response.

Eligibility Criteria and Treatment Schedule of S-1 Adjuvant Chemotherapy

Before 2003, none of the patients received S-1 adjuvant chemotherapy. In the reduce-RADPLAT protocol, sodium thiosulfate is administered as a neutralizing agent for cisplatin to reduce toxicities; thus, the effect of cisplatin and irradiation to micro metastases at distant sites is not expected. Therefore, we administered S-1 to all eligible patients to receive the adjuvant chemotherapy within 3 months after reduced-RADPLAT after 2003. Only patients who achieved CR at the primary site were eligible for S-1 adjuvant chemotherapy. The S-1 dosage was selected as follows: for patients: with a body surface area (BSA) of less than 1.25 m^2, 60 mg per day; with a BSA of at least 1.25 m^2 but less than 1.5 m^2, 80 mg per day; with a BSA of at least 1.5, 100 mg per day. S-1 was administered for 2 weeks followed by 1 week rest for 1 year. Other detailed eligibility

criteria and the treatment protocol of S-1 adjuvant chemotherapy were described previously.[7,12]

Follow-Up

All patients were followed for relapse every month for 2 years, every 3 months for at least another 3 years, and every 6 months thereafter. Patients with evidence of pathological residual disease at the primary site were recommended to undergo salvage surgery. Neck dissection was performed in those with progressive disease or disease that persisted for longer than 6 months based on CT.

Statistical Analysis

Overall survival (OS), progression-free survival (PFS), local control (LC), locoregional control (LRC), and laryngoesophageal dysfunction-free survival (LEDFS) rates were analyzed with Kaplan-Meier methods. Survival and control periods were defined as the period between the start of the reduced-RADPLAT treatment and events. Events for LEDFS included death, local relapse, total or partial laryngectomy, tracheotomy at 2 years or later, or feeding tube use at 2 years or later.[13] Clinical characteristics were analyzed for their association with OS, PFS, LC, LRC, and LEDFS using the Cox-proportional hazards model. Predictive variables with *p*-values lower than 0.10 for the univariate Cox-proportional hazards model were included in a multivariate model and significance

of 0.05 was used to determine independent factors. The significance of differences in the cisplatin-dose between T1-3 and T4 tumors was assessed using the Mann-Whitney *U* test. All computations were carried out with IBM SPSS Statistics, version 19 (IBM, Armonk, USA).

RESULTS

Patient Characteristics

Between January 1999 and September 2012, 111 patients of squamous cell carcinoma of the hypopharynx were treated at the Division of Otolaryngology-Head and Neck Surgery, Kanazawa University Hospital. Among them, 51 patients were treated with reduced-RADPLAT protocol. One patient was excluded from the analyses because the primary tumor invaded the carotid artery, being classified as unresectable. Thus, we analyzed 48 patients in total, and their detailed characteristics and clinical courses are summarized in Table 1 and Fig. 1, respectively. All surviving patients had a minimum follow-up of 36 months (range, 0 to 154; median, 48.6).

Cycles and Infusion Arteries for reduced-RADPLAT

Four patients (8.0%) discontinued reduced-RADPLAT, to whom only 1 cycle of IAC was administered, for the following reasons: progressive anemia due to hereditary spherocytosis, advanced rectal cancer, allergic reaction to contrast medium, and patient refusal (Supplementary Table 1). Two patients underwent surgery after 2 courses of IAC plus 40-Gy irradiation. Patients were considered to have completed the course of treatment if administered at least 2 cycles of IAC and a 100% dose of radiation. A total of 47 patients (94.0%) completed radiation therapy, and 44 patients (88.0%) completed treatment. Details of the number of infusion arteries are summarized in

Supplementary Table 2. Twenty-one patients (42.0%) with a local tumor crossing the midline required bilateral infusions. In addition, 13 patients (26.0%) with N2b (n = 10), N2c (n =2), and N3 (n = 1) received IA infusions for neck lesions. The superior thyroid artery was the most frequently used for IA cisplatin infusion, and the occipital artery for neck lesions (Supplementary Table 3). Cisplatin doses in total and for primary tumors are listed in Supplementary Table 4. Total amounts of cisplatin were similar between T1-3 (297.8 ± 147.2) and T4 (355.0 ±179.1) diseases (p = 0.218), in contrast, the dose of cisplatin infused for a primary tumor was significantly higher in T4 (333.0 ± 159.9) than T1-3 (252.0 ± 92.2) primary lesions (p = 0.016).

Treatment Outcome

CR at both primary and regional sites was achieved in 44 patients (88.0%), a partial response (PR) in the neck with CR at the primary site in 1 patient (2.0%), and PR at both the primary site and neck in 5 patients (10.0%). The initial recurrent sites were the hypopharynx in 10, regional lymph nodes in 5, and distant sites in 5 (Fig. 1). Four patients were salvaged with surgery, however, other patients rejected salvage surgery or were not resectable because of invasions to carotid artery or prevertebral fascia.

Until July 2015, 27 patients (54.0%) were alive, and 25 of the 27 remained cancer-free. Six, 5, and 7 died of local recurrence, distant metastases, and unrelated causes, respectively. Among the 7

patients who died of unrelated causes, four had T4 disease: two cases of malignancy at other sites (bladder and esophagus), one of aspiration pneumonia, and of deep neck infection.

The OS and PFS curves are shown in Fig. 2. The estimated 3- and 5-year OS and PFS rates were 76.0 and 62.0%, and 58.0 and 50.0%, respectively. The LC, LRC, and LEDFS curves are shown in Fig. 3. The estimated 3- and 5-year LC, LRC, and LEDFS rates were 72.0 and 70.0%, 66.0 and 62.0%, and 56.0 and 54.0%, respectively.

Factors involved in OS, PFS, LC, LRC, and LEDFS

In multivariate analysis, both the T-status and S-1 administration remained as independent predictive factors for OS and PFS, respectively (Tables 2, 3). No clinical factor had a significant impact on LC and LRC (Supplementary Tables 5, 6). In multivariate analysis, the T-status and S-1 administration remained as independent factors to predict LEDFS (Table 4).

Toxicity

The occurrence and incidence of hematological and non-hematological toxicities of grade 3 or higher with reduced-RADPLAT are summarized in Table 5. No patient had catheter-related central nerovous system problems or peripheral neuropathy. There was a case of grade 3 thyrotoxicosis during the second cycle of cisplatin infusion into the superior thyroid artery. The patient completed

radiation therapy, but no additional cycle of IAC was administered. No patient required tube feeding at 3 months after reduced-RADPLAT completion, except for five patients rquiring feeding by gastrostomy tube after local recurrence. Seven patients required tracheotomy after reduced-RADPLAT for the following reasons: local recurrence (4 patients), temporary airway obstruction after neck dissection (1 patient), deep neck infection (1 patient), and recurrent laryngeal nerve palsy because of a second malignancy (esophageal cancer).

DISCUSSION

Although larynx-preserving approaches are assessed mainly in patients with laryngeal cancer, no single randomized phase 3 study has specifically addressed the role of concomitant chemoradiotherapy in HPC management. Therefore, a standard concomitant chemoradiotherapy protocol for HPC has not yet been established.

Caudell et al. reported that, in their study of advanced laryngeal and hypopharyngeal cancer, OS, PFS, LRC, and LEDFS at 3 years were 55.8, 64.6, 71.8, and 32.2%, respectively.[13] In the induction chemotherapy, with docetaxel, cisplatin, and 5-fluorouracil, followed by radiotherapy with or without additional chemotherapy, Pointreau et al. showed in resectable laryngeal and hypopharyngeal cancers, that OS, and disease-free survival at 3 years were 60 and 58%, respectively.[14] Samant et al. reported the efficacy and toxicities of RADPLAT in 25 pyriform sinus carcinoma patients.[10] The CR rate, and estimates of OS and LRC at 5 years were 92, 23, and 88%, respectively. The overall incidence of grade 3 or 4 toxicity was 40% in their series. One third of the patients alive with organ preservation were not able to swallow without depending on the feeding tube. In contrast, toxicities of grade 3 or more were observed only in 30% of patients in our study. Furthermore, no tracheotomy or gastrostomy was performed as late toxicities of reduced-RADPLAT in our study. Thus, our reduced-RADPLAT protocol achieved survival and LC rates comparable with the original RADPLAT protocol for pyriform sinus carcinomas, with lower toxicities.

The EORTC 24891 study showed a significant difference in the rate of distant metastases as the first failure between the immediate surgery (36%) and induction chemotherapy (25%) arms, and established the efficacy of chemotherapy for distant metastases in HPC.[1] However, in the RADPLAT protocol, sodium thiosulfate is administered as a neutralizing agent for cisplatin to reduce the toxicities; thus, the efficacy of cisplatin and irradiation to micro-metastases at distant sites is not expected. From some reports of RADPLAT for HPC, distant metastasis rates were from 14 to 40%.[9,10,15] In the current study, only 5 of 50 patients (10.0%) developed distant metastases, which is the lowest among reported studies. A phase 3 randomized study to evaluate S-1, the current generation of oral fuluoropyrimidine, compared with UFT, the previous generation of oral fluoropyrimidine, as a control in patients after curative therapy was conducted for advanced SCCHN.[16,17] In the study, S-1 significantly improved OS compared with UFT, one reason for which was the lower incidence of distant recurrence in the S-1 than UFT group, most likely contributing to better survival in the S-1 group. For advanced HPC with CR following reduced-RADPLAT, although statistical analysis was not performed because only 5 cases had distant metastases, S-1 adjuvant chemotherapy might have contributed to the low distant metastases rate, which resulted in better survivals, such as OS, PFS, and LEDFS rates as shown in our study.

Doweck et al. reported that the tumor volume was the most important factor predictive of the treatment outcome among advanced SCCHN patients in the RADPLAT study.[18] However, in the

current study, no difference in LC and LRC between patients presenting with T1-3 and T4 diseases was observed. We speculate that, for resectable HPC, the primary tumor volume is not a significant predictive factor to select patients for reduced-RADPLAT. Therefore, larger tumors, such as unresectable primary diseases, require an increased dose of cisplatin as in the RADPLAT regimen; however, reduced-dose cisplatin would be satisfactory to control moderately large tumors, such as resectable HPC, independent of the T-status.[7,8,19] In contrast, LEDFS was significantly poorer in T4 than in T1-3 diseases. The cause of the poorer LEDFS in T4 disease is at least in part because of death from other diseases. Total doses of cisplatin are similar between T1-3 and T4 lesions, but the amount of cisplatin infused into primary diseases is significantly greater in T4 than T1-3 lesions. The damage to local organs might be more severe in T4 cases, resulting in a higher mortality because of local dysfunction such as aspiration pneumonia and compromised resistance to infection. For the same reason, the other survival analyses, OS and PFS, also showed significantly poorer rates in T4 compared with T1-3 patients. The cause of higher mortality due to other diseases in T4 patients should be elucidated in future analyses.

In this study, tumor laterality (tumor does/does not extend across the midline) and number of infused arteries were not significant predictive factors of LC and LRC, respectively. Rasch et al., in the IAC arm of the comparative multi-institutional study between intravenous versus intra-arterial chemoradiotherapy, reported that better survival was associated with tumors not extending across the

midline: uni- or bilateral infusion was an important predictive factor.[20] In their study, patients were treated at five institutions with experience of at least five procedures before entering the trial, and neurological toxicities > grade 2 were observed in 6.7% patients. However, no catheter-related complication was observed in our single institutional setting. We speculate that the laterality and number of infused arteries are not significant predictive factors for LC and LRC if feeding arteries are correctly selected and resectable primary tumors are fully infused with cisplatin at an experienced institution.

In conclusion, reduced-RADPLAT for HPC achieved comparative survival and local control rates with lower toxicities compared with other chemoradiotherapy protocol including previous RADPLAT treatment. Although the study design was retrospective and the conclusion is limited, reduced-RADPLAT appears to be an effective and feasible option for advanced-stage resectable HPC. S-1 adjuvant chemotherapy also showed a survival benefit when combined with reduced-RADPLAT.

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LEGENDS FOR FIGURES

Fig. 1. Diagram of the clinical course of the 48 patients analyzed. CR, complete remission; PR, partial remission. CR/PR means that the primary site was CR and the regional site was PR.

Fig. 2. Kaplan-Meier plots of overall survival (OS) (A) and progression-free survival (PFS) (B) for all patients. The estimated 3- and 5-year OS and PFS rates were 76.0 and 62.0%, and 58.0 and 50.0%, respectively.

Fig. 3. Kaplan-Meier plots of local control (LC) (A), locoregional control (LRC) (B), and laryngoesophageal dysfunction-free survival (LEDFS) (C) for all patients. Events for LEDFS include death, local relapse, total or partial laryngectomy, tracheotomy at 2 years or later, or feeding tube use at 2 years or later. The estimated 3- and 5-year LC, LRC, and LEDFS rates were 72.0 and 70.0%, 66.0 and 62.0%, and 56.0 and 54.0%, respectively.

Table 1. Baseline characteristics of patients

Characteristics	No. of patients (%)
PS	
0	34 (68.0)
1	12 (24.0)
2	4 (8.0)
Sex	
Male	39 (78.0)
Female	11 (22.0)
Age	
Range	45-83
Median	65
Subsite	
Pyriform sinus	35 (70.0)
Postcricoid	4 (8.0)
Posterior wall	11 (22.0)
TNM classification	
Tumor	
1	1 (2.0)
2	10 (20.0)
3	19 (38.0)
4	20 (40.0)
Node	
0	14 (28.0)
1	10 (20.0)
2a	1 (2.1)
2b	18 (36.0)
2c	5 (10.0)
3	2 (4.0)
Stage	
II	5 (10.0)
III	11 (22.0)
IV	34 (68.0)

PS, performance status.

Table 2. Results of uni- and multivariate analyses of factors affecting overall survival

		Univariate analysis			Multivariate analysis		
Factor	Level (n)	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	≦65 (26)	1	0.428-2.602	0.907			
	≧66 (24)	1.055					
Sex	Male (39)	1	0.602-1.670	0.991			
	Female (11)	1.003					
T-status	T1-3 (30)	1	1.054-2.560	0.028	1	1.057-2.611	0.023
	T4 (20)	1.645			1.675		
N-status	N0-1 (24)	1	0.794-1.946	0.343			
	N2-3 (26)	1.242					
Stage	II or III (16)	1	0.791-2.181	0.291			
	IV (34)	1.314					
PS	0 (34)	1	0.575-2.128	0.204			
	1 or 2 (16)	1.346					
Cisplatin dose (mg)	<300 (16)	1	0.576-1.461	0.717			
	≧300 (34)	0.918					
Number of infused arteries	≦2 (25)	1	0.488-1.181	0.222			
	≧3 (25)	0.759					
Laterality	Unilateral (29)	1	0.624-3.617	0.363			
	Bilateral (21)	1.503					
S-1 administration	S-1 (+) (14)	1	1.002-4.331	0.049	1	1.024-4.431	0.043
	S-1 (-) (36)	2.084			2.13		

CI, confidence interval; HR, hazard ratio; PS, performance status; S-1 (+), patients with S-1 adjuvant chemotherapy; S-1 (-), patients without S-1 adjuvant chemotherapy.

Table 3. Results of uni- and multivariate analyses of factors affecting progression-free survival

		Univariate analysis			Multivariate analysis		
Factor	Level (n)	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	≦65 (26)	1	0.559-1.261	0.400			
	≧66 (24)	0.840					
Sex	Male (39)	1	0.595-1.596	0.917			
	Female (11)	0.974					
T-status	T1-3 (30)	1	1.063-2.398	0.024	1	1.046-2.364	0.030
	T4 (20)	1.597			1.572		
N-status	N0-1 (24)	1	0.867-1.961	0.203			
	N2-3 (26)	1.304					
Stage	II or III (16)	1	0.861-2.176	0.184			
	IV (34)	1.369					
PS	0 (34)	1	0.767-1.754	0.483			
	1 or 2 (16)	1.160					
Cisplatin dose (mg)	<300 (16)	1	0.763-1.852	0.444			
	≧300 (34)	1.189					
Number of infused arteries	≦2 (25)	1	0.857-1.938	0.223			
	≧3 (25)	1.289					
Laterality	Unilateral (29)	1	0.589-2.941	0.503			
	Bilateral (21)	1.316					
S-1 administration	S-1 (+) (14)	1	1.032-0.039	0.039	1	1.016-3.426	0.044
	S-1 (-) (36)	1.894			1.865		

CI, confidence interval; HR, hazard ratio; PS, performance status; S-1 (+), patients with S-1 adjuvant chemotherapy; S-1 (-), patients without S-1 adjuvant chemotherapy.

Table 4. Results of uni- and multivariate analyses of factors affecting laryngo-esophageal dysfunction-free survival

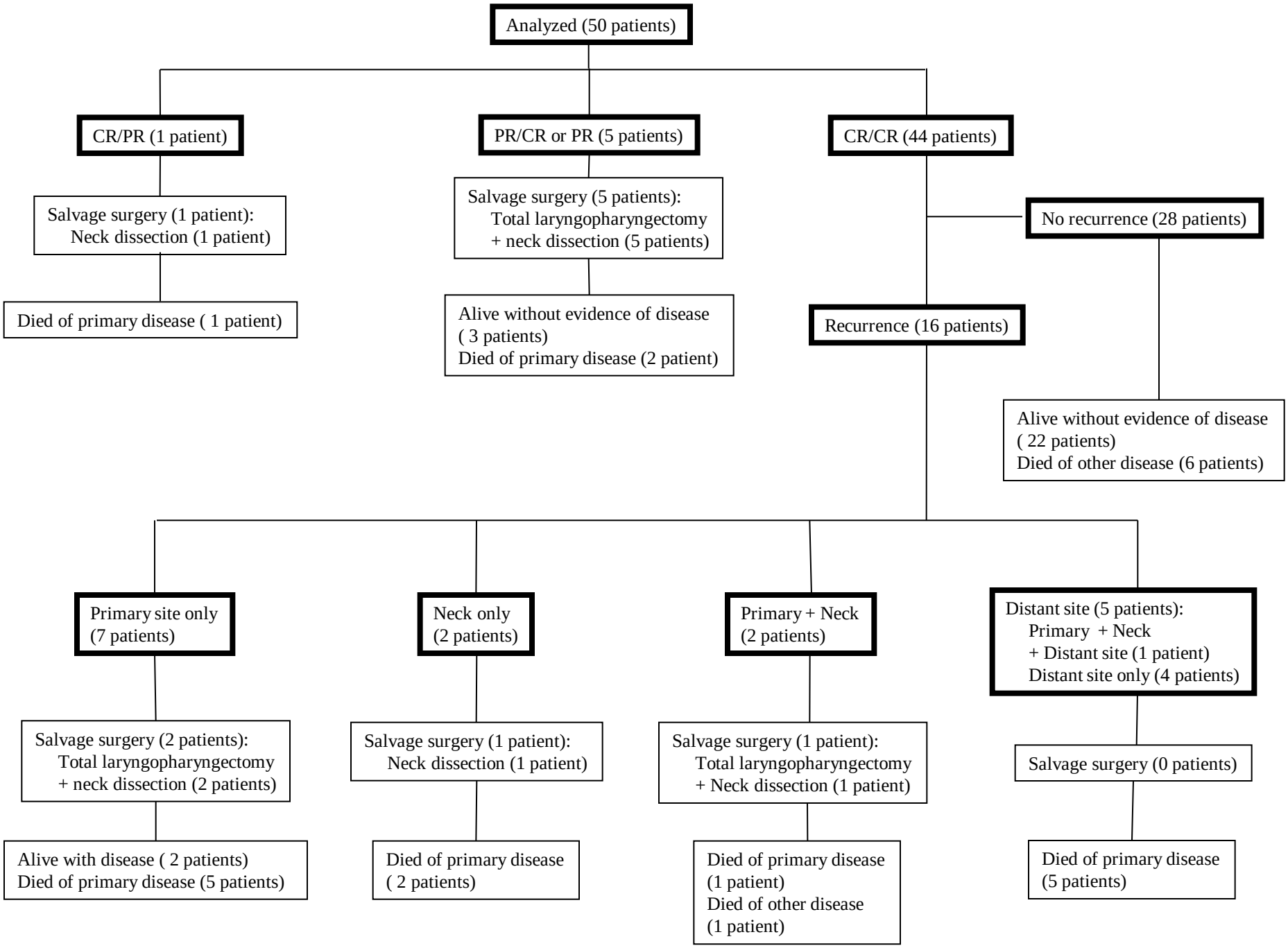
		Univariate analysis			Multivariate analysis		
Factor	Level (n)	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	≦65 (26)	1	0.523-1.656	0.226			
	≧66 (24)	0.781					
Sex	Male (39)	1	0.563-1.504	0.740			
	Female (11)	0.920					
T-status	T1-3 (30)	1	1.203-2.688	0.004	1	0.825-1.287	0.002
	T4 (20)	1.796			1.934		
N-status	N0-1 (24)	1	0.811-1.789	0.356			
	N2-3 (26)	1.205					
Stage	II or III (16)	1	0.902-2.265	0.129			
	IV (34)	1.429					
PS	0 (34)	1	0.717-1.626	0.714			
	1 or 2 (16)	1.080					
Cisplatin dose (mg)	<300 (16)	1	0.694-1.613	0.792			
	≧300 (34)	1.058					
Number of infused arteries	≦2 (25)	1	0.808-1.808	0.354			
	≧3 (25)	1.209					
Laterality	Unilateral (29)	1	0.772-3.729	0.188			
	Bilateral (21)	1.697					
S-1 administration	S-1 (+) (14)	1	1.126-3.773	0.019	1	1.212-4.100	0.010
	S-1 (-) (36)	2.061			2.23		

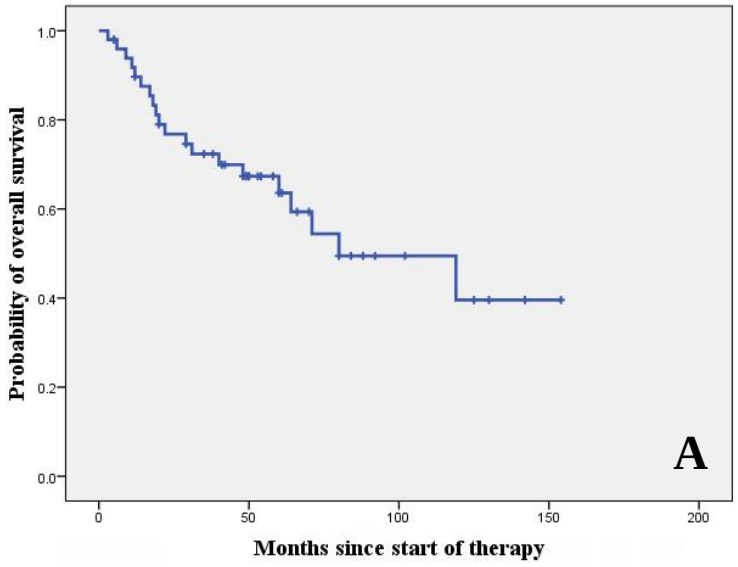
CI, confidence interval; HR, hazard ratio; PS, performance status; S-1 (+), patients with S-1 adjuvant chemotherapy; S-1 (-), patients without S-1 adjuvant chemotherapy.

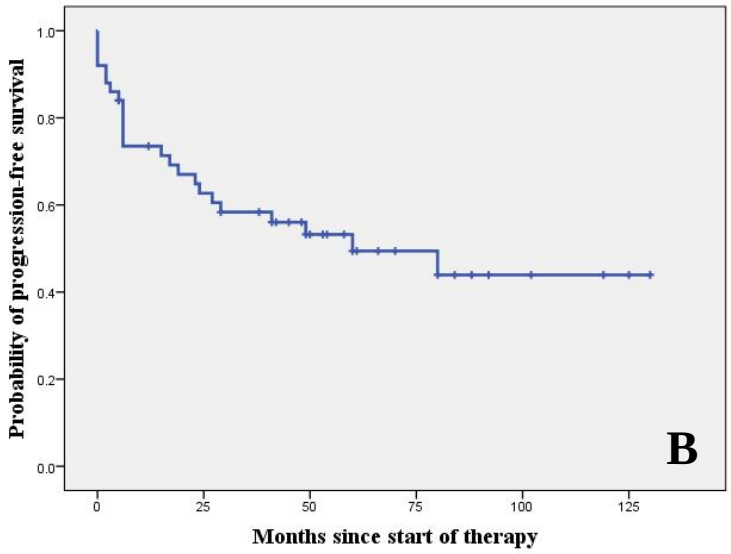
Table 5. Adverse events

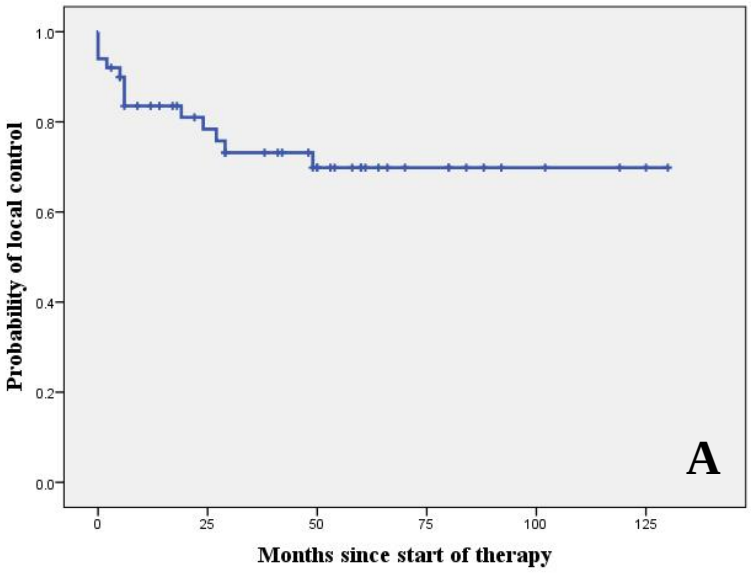
Events	Number of Grade 3 events (%)
Hemoglobin	3 (6.0)
Leukocytes	13 (26.0)
Mucositis	8 (16.0)
Renal	0 (0)
Thyrotoxicities	1 (2.0)
Overall worst grade of toxicity per patient	15 (30.0)

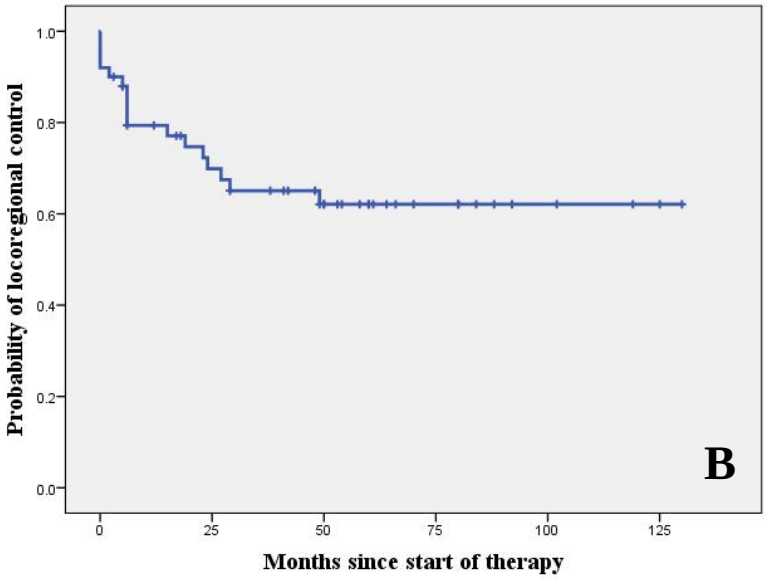
No patient had Grade 4 or more severe toxicity.

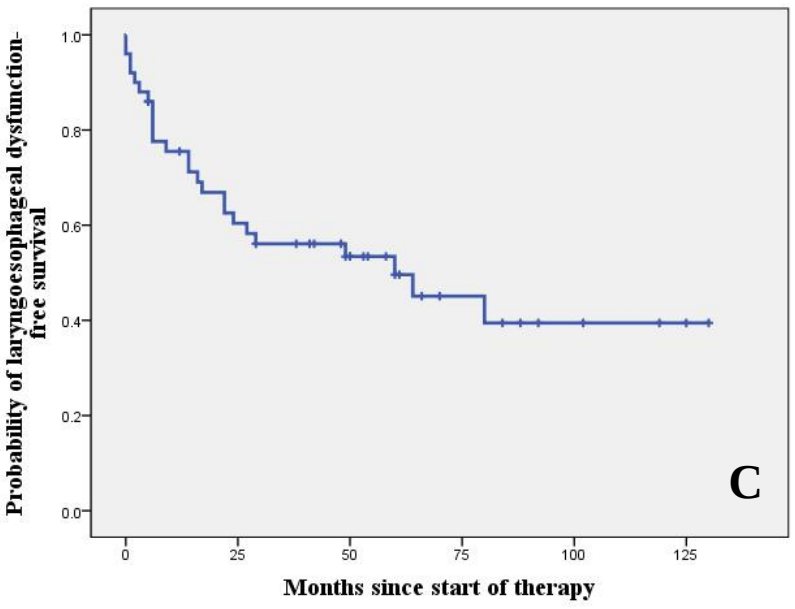

Analyzed (50 patients)
CR/PR (1 patient)
PR/CR or PR (5 patients)
CR/CR (44 patients)
Salvage surgery (1 patient):
Neck dissection (1 patient)
Salvage surgery (5 patients):
Total laryngopharyngectomy
+ neck dissection (5 patients)
No recurrence (28 patients)
Died of primary disease (1 patient)
Alive without evidence of disease
(3 patients)
Died of primary disease (2 patient)
Recurrence (16 patients)
Alive without evidence of disease
(22 patients)
Died of other disease (6 patients)
Primary site only
(7 patients)
Neck only
(2 patients)
Primary + Neck
(2 patients)
Distant site (5 patients):
Primary + Neck
+ Distant site (1 patient)
Distant site only (4 patients)
Salvage surgery (2 patients):
Total laryngopharyngectomy
+ neck dissection (2 patients)
Salvage surgery (1 patient):
Neck dissection (1 patient)
Salvage surgery (1 patient):
Total laryngopharyngectomy
+ Neck dissection (1 patient)
Salvage surgery (0 patients)
Alive with disease (2 patients)
Died of primary disease (5 patients)
Died of primary disease
(2 patients)
Died of primary disease
(1 patient)
Died of other disease
(1 patient)
Died of primary disease
(5 patients)


Probability of overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
Months since start of therapy
A


Probability of progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
25
50
75
100
125
Months since start of therapy
B


Probability of local control
1.0
0.8
0.6
0.4
0.2
0.0
0
25
50
75
100
125
Months since start of therapy
A


Probability of locoregional control
1.0
0.8
0.6
0.4
0.2
0.0
0
25
50
75
100
125
Months since start of therapy
B


Probability of laryngoesophageal dysfunction-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
25
50
75
100
125
Months since start of therapy
C