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Usefulness of induction chemotherapy followed by definitive chemoradiotherapy for oropharyngeal cancer: implications for the selection of candidates for organ-preserving treatment based on the response to induction chemotherapy

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Summary. *Background and aim of the work:* This study aims to evaluate the usefulness of the response to induction chemotherapy (IC) in selecting candidates for definitive concurrent chemoradiotherapy in oropharyngeal cancer. *Methods:* Thirty-nine patients with oropharyngeal cancer received IC followed by definitive chemoradiotherapy or radiotherapy. The predominant IC regimens involved cisplatin and 5-fluorouracil with or without docetaxel. Patients who responded to IC received definitive organ-preserving treatment. Surgery was considered for patients who did not respond to IC. Only patients who underwent definitive radiotherapy were analyzed in this study. The associations between clinical parameters and local control (LC) or overall survival (OS) were also analyzed. *Results:* The follow-up periods of the surviving patients ranged from 9-170 months (median, 40). The 5-year LC and OS rates for all 39 patients were 81% and 60%, respectively. The 5-year LC and OS rates of the IC responders, complete response or partial response (CR, PR) were 89% and 65%, respectively, whereas those of the non-responders, stable disease or progressive disease (SD, PD) were 34% and 38%, respectively. Multivariate analysis demonstrated that the response to IC (p=0.00) and T-category (T1, 2 vs. T3, 4) (p=0.03) were correlated with LC, but only the response to IC was correlated with OS (p=0.04). None of the patients suffered severe late complications. *Conclusions:* Chemoselection appears to aid the selection of optimal treatments for patients with oropharyngeal cancer.

Key words: induction chemotherapy, oropharyngeal cancer, chemoselection

«Utilità della chemioterapia di induzione seguita da chemioradioterapia definitiva per tumore orofaringeo: conseguenze per la selezione di candidati al trattamento per il mantenimento degli organi basato sulla risposta alla chemioterapia di induzione»

Riassunto. *Ambito e scopo dello studio:* valutare l'utilità della risposta alla chemioterapia di induzione (CI) nella selezione di candidati alla chemio-radioterapia concomitante definitiva per tumore orofaringeo. *Metodi:* Trentanove pazienti con tumore orofaringeo hanno ricevuto CI seguita da chemio-radioterapia o radioterapia definitiva. I regimi predominanti CI comprendono cisplatino e 5-fluorouracile con o senza docetaxel. I pazienti rispondenti alla CI hanno ricevuto un trattamento definitivo di mantenimento degli organi mentre per quelli non rispondenti è stata preconizzata la chirurgia. Lo studio si è limitato ai soli pazienti sottoposti a radioterapia definitiva, analizzando inoltre le associazioni tra parametri clinici e controllo locale (CL) o sopravvivenza globale (SG). *Risultati:* I periodi di follow-up dei pazienti sopravvissuti erano di 9-170 mesi (mediamente 40). I tassi di sopravvivenza CL e SG a 5 anni per tutti i 39 pazienti erano rispettivamente dell'81% e 60%. I tassi CL e SG a 5 anni per i *responder* a CI (CR, PR) erano rispettivamente dell'89% e 65%,

mentre per i *non responder* (SD, PD) erano rispettivamente del 34% e 38%. Dall'analisi multivariata risulta che la risposta a CI (p=0,00) e alla categoria T (T1, 2 vs. T3, 4) (p=0,03) sono correlate con il CL, mentre solo la risposta a CI è correlata con SG (p=0,04). Nessun paziente ha riportato complicanze gravi tardive. *Conclusioni:* La chemoselettività sembra facilitare la selezione di trattamenti ottimali per pazienti con tumore orofaringeo.

Parole chiave: chemioterapia di induzione; cancro orofaringeo; chemoselettività

Introduction

The optimal treatment strategy for oropharyngeal cancer is disputed (1). Concurrent chemoradiation is considered to be the standard organ-preserving treatment, while the use of induction chemotherapy before definitive chemoradiotherapy or radiotherapy is one of the most promising treatment options for this type of cancer. However, some investigators have reported that induction chemotherapy did not produce any survival benefit (2-4). This might partly have been due to the fact that the response to induction chemotherapy was not taken into account when assessing the subsequent treatment options (5). Indeed we have previously reported promising results for definitive radiotherapy as a treatment for hypopharyngeal cancer, when the response to induction chemotherapy was used to select appropriate candidates for organ-preserving treatment (6). The strategy employed in the latter study was as follows: 1) patients who responded to induction chemotherapy received definitive organ-preserving treatment and 2) surgery was considered for patients who did not respond to induction chemotherapy. This strategy produced satisfactory results, especially in view of a high rate of larynx preservation among the surviving patients.

In this article, we report the outcomes obtained when the same strategy was used to treat oropharyngeal cancer. Lymph node metastases were treated according to the same strategy, but were assessed independently, because they can exhibit different responses to primary tumors. To evaluate the usefulness of this chemoselection strategy, patients who did not display a good response to induction chemotherapy but underwent definitive chemoradiation were also analyzed.

This article does not contain any experimental studies with human or animal subjects performed by any of the authors.

Methods

Patients

Between January 1999 and May 2012, 39 patients were treated with curative intent using induction chemotherapy followed by conventional radiotherapy or chemoradiotherapy at our hospital. The median age of the patients was 69 years (range, 39-82), 35 being males and 4 females. The patients' characteristics are summarized in Table 1. All patients gave their informed consent prior to treatment. All of the patients had histologically proven previously untreated oropharyngeal cancer. Little information about the patients' human papilloma virus (HPV) status was obtained in this study, so the effects of HPV status could not be analyzed.

Treatment strategy

The treatment strategy was basically the same as that reported for hypopharyngeal cancer (6). Two or three cycles of chemotherapy were administered in the induction setting. The TPF regimen (60 mg/m^2 docetaxel on day 1, 70 mg/m^2 cisplatin on day 1, and 600 mg/m^2 5-fluorouracil [5-FU] on days 1-5) or a regimen involving a platinum-based agent plus 5-FU or S-1 was employed. Among these last regimens, the most common was the CF regimen (70 mg/m^2 cisplatin on day 1 and 700 mg/m^2 5-FU on days 1-5).

Table 1. Patient characteristics.

		n	Responders	Non-responders	*P*-value
Age (years)					
	<70	21	17	4	0.26
	≥70	18	12	6	
Gender					
	Male	35	26	9	0.73
	Female	4	3	1	
TN (UICC* 7th)					
	T1	3	3	0	0.76
	T2	20	14	6	
	T3	6	4	3	
	T4a/4b	10	8	2	
	N0	5	5	0	0.67
	N1	7	5	2	
	N2a	1	1	0	
	N2b	13	9	4	
	N2c	9	7	2	
	N3	4	2	2	
Stage (UICC* 7th)					
	I	1	1	0	0.80
	II	2	2	0	
	III	6	4	2	
	IVa	25	19	6	
	IVb	5	3	2	
Subsite					
	Tonsils	29	22	7	0.15
	Base of the tongue	6	5	1	
	Soft palate	2	0	2	
	Posterior wall	2	2	0	
WHO performance status					
	2	5	1	4	0.01**
	1	28	23	5	
	0	6	5	1	

* International Union Against Cancer ** two-sided test

After induction chemotherapy, the patients were divided into candidates for radiotherapy or surgery. Patients whose primary tumors displayed a complete response (CR) or partial response (PR) or were classified as stable disease (SD) after induction chemotherapy received radiotherapy or chemoradiotherapy for their primary tumors. On the other hand, patients who exhibited progressive disease (PD) had the operability of their tumors reevaluated. When a primary tumor was considered resectable, surgery was recommended.

With respect to lymph node metastases, when they displayed a CR after induction chemotherapy, the affected nodes were also included in the irradiated field. When such lesions exhibited a PR or were classified as SD or PD, planned neck dissection was considered. When surgery for the primary tumor and/or neck lymph nodes was judged to be infeasible or was refused by the patient, organ-preserving therapy was performed. The patients that were treated according to the above strategy were included in the present study

and were compared with induction chemotherapy responders who underwent definitive radiotherapy with or without chemotherapy.

Radiotherapy/chemoradiotherapy

Our radiotherapy planning method was described in detail in a previous study (7). Three-dimensional treatment planning was performed. No patients were treated with intensity-modulated radiotherapy (IMRT). All patients were irradiated with 4 or 6 MV X-rays using once-daily fractionation. Depending on the treatment volume, the daily dose ranged from 1.8-2.0 Gy, and the planned total dose for the primary tumor ranged from 66-70 Gy. In the case of nodal irradiation, the whole neck region was subjected to prophylactic irradiation at a dose of 41.4-50 Gy, and neck lymph nodes that were positive before induction chemotherapy were boosted up to 66-70 Gy. Patients with normal renal function who recovered promptly from bone marrow suppression after induction chemotherapy underwent concurrent radiation and chemotherapy with carboplatin (area under the curve [AUC] = 1, weekly) or docetaxel (10 mg/m^2, weekly).

Follow-up

After treatment, the patients underwent follow-up evaluations of their disease status and toxicities at least every 3 months until disease progression or death. Toxicities of the skin and mucosa were graded according to the Radiation Therapy Oncology Group (RTOG) Toxicity Criteria for acute reactions and the RTOG/European Organization for Research and Treatment of Cancer Criteria for late reactions (8). Hematological adverse events were scored using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Prognostic factors

Inter-group differences in patient or tumor characteristics were examined using the chi-square test. Survival and local control rates were calculated from the date on which induction chemotherapy was started using the Kaplan-Meier method. In order to identify prognostic factors for overall survival and local control, we evaluated age, gender, performance status (PS), tumor location, T-category, N-category, overall disease stage, total dose, the induction chemotherapy regimen, the response to induction chemotherapy, and the presence/absence of concurrent chemotherapy. The log-rank test was used for univariate analyses, and the Cox proportional hazards model was used for multivariate analysis. All variables that produced p-values of ≤0.25 during univariate analysis were entered into multivariate analysis. All tests were two-sided, and p-values of <0.05 were considered statistically significant. All analyses were performed using the Statistics Package for Social Science (SPSS Inc., Chicago, IL) Version 13.0J and HALWIN (Gendaisuugakusha, Kyoto, Japan).

Results

Local control and overall survival

The median follow-up period for the surviving patients was 40 months (range, 9-170 months). The 5-year local control and overall survival rates for all 39 patients were 80% and 60%, respectively (Figure 1). Among the 39 patients, the primary tumor response to induction chemotherapy was CR in 13 patients, PR in 19, SD in 5, and PD in 2. The 5-year primary tumor local control rate of the induction chemotherapy responders (CR or PR; n=32) was 90%, whereas that of the non-responders (SD or PD; n=7) was 34% (Figure 2). The 5-year overall survival rate of the primary tumor responders was 66%, whereas that of the non-responders was 38% (Figure 3). Nineteen patients died. Eleven patients died of oropharyngeal cancer, and 8 died of other causes (secondary cancer in 6 patients, pneumonitis in 1, and a brain infarction in 1).

With respect to induction chemotherapy, the TPF regimen was used in 19 patients, and the CF regimen was used in 15. Although all patients were scheduled to receive the TPF or CF regimen, other regimens were used in 5 patients because of the physical condition of the patient (CDDP plus S-1 in 3 patients, CBDCA plus 5-FU in 1, and TS-1 alone in 1). The patient and tumor characteristics of the primary tumor responders and non-responders are shown in Table 1.

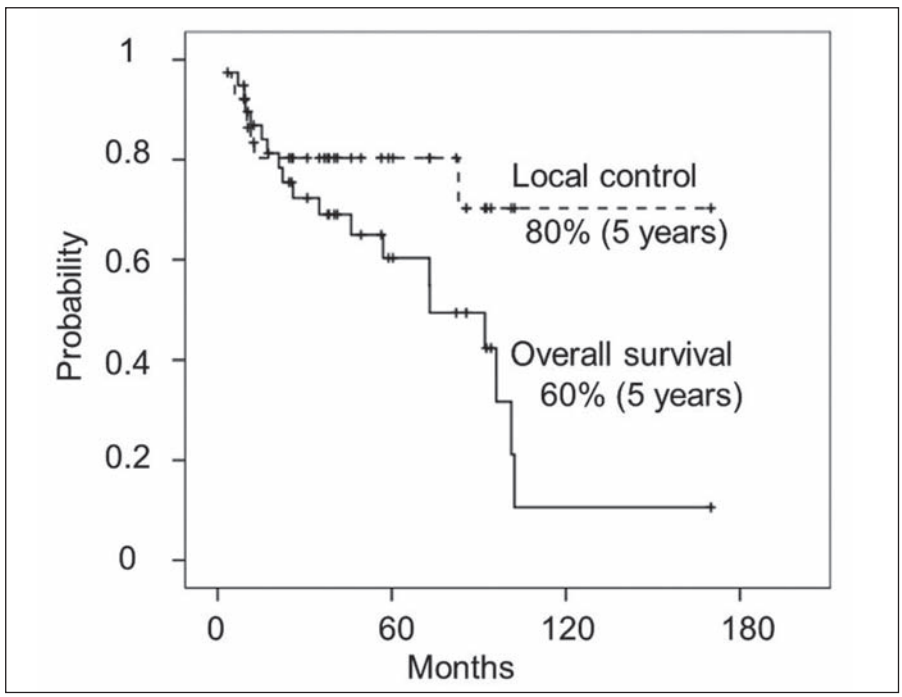

Figure 1. Local control and overall survival curves for all patients.

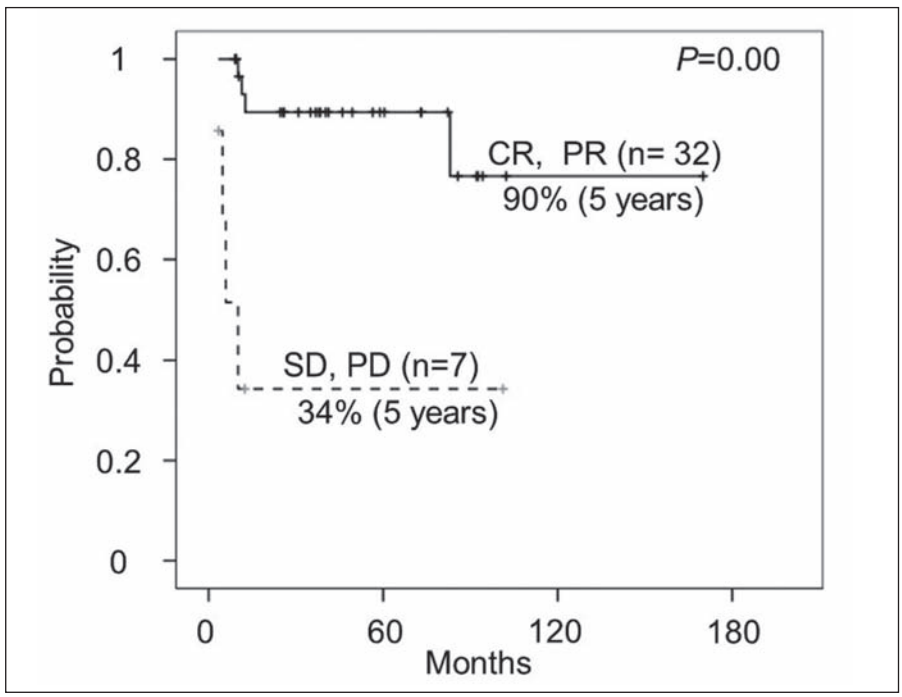

Figure 2. Local control curves for patients who achieved a CR or PR to induction chemotherapy and those who had SD or PD. The difference was significant (p=0.00). (CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease).

The non-responders tended to have worse PS than the responders (p=0.01).

Of the 34 patients who exhibited lymph node metastases at diagnosis, 4 achieved CR after induction chemotherapy. These 4 patients received definitive chemoradiotherapy without neck dissection. Only one of these patients suffered recurrent disease in their neck lymph nodes after radiotherapy, so 75% (3/4) of the patients who achieved CR had controlled neck nodes. As the patient who suffered recurrence was

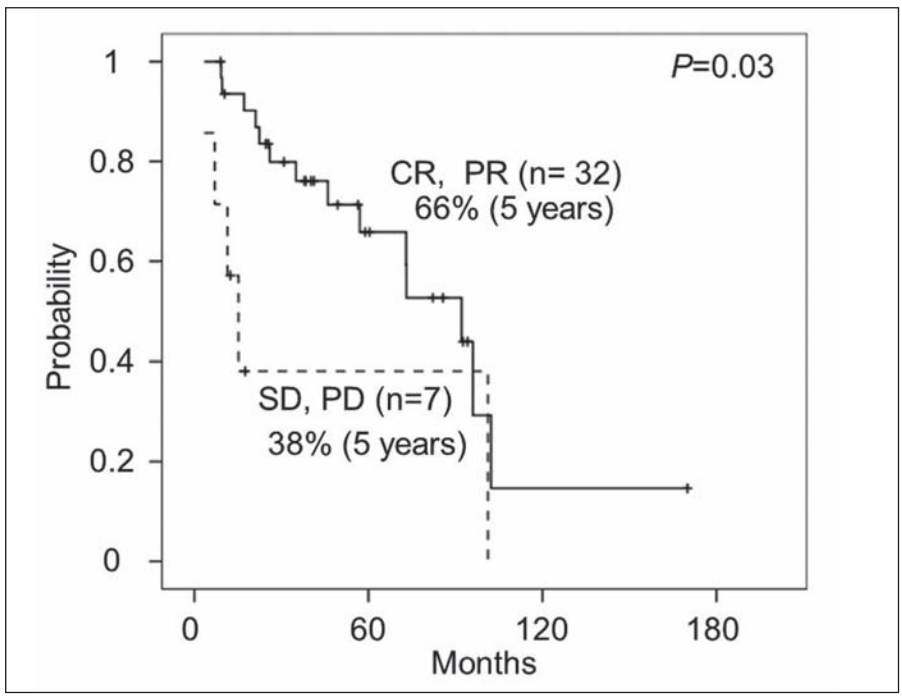

Figure 3. Overall survival curves for patients who achieved a CR or PR to induction chemotherapy and those who had SD or PD. The difference was significant (p=0.03). (CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease).

rescued with salvage surgery, the overall control rate of the lymph node metastases that demonstrated CR after induction chemotherapy was 100%. Among the remaining 30 patients who displayed a PR, SD, or PD after the induction chemotherapy, 19 patients received surgery, and 11 received organ-preserving therapy because they refused surgery. There were no significant differences in the nodal control rates of these two groups.

Among the patients who suffered recurrence, the initial recurrence occurred in the primary region (T) in 7 patients, the nodal region (N) in 6 patients, and a distant organ (M) in 1 patient. Eight patients suffered local recurrence, and 2 of these patients received salvage surgery.

Prognostic factors

In univariate analysis, the response to induction chemotherapy (CR or PR vs. SD or PD) was found to significantly influence both local control (p=0.00) and overall survival (p=0.03) (Table 2). Neither survival nor local control was affected by whether the administered chemotherapy regimen included docetaxel.

Table 2. Univariate analysis of potential predictors of local control and overall survival.

	P-value (Log rank test)	
	Local control	Overall survival
Age (<70 vs. ≥70 years)	0.28	0.43
Gender	0.42	0.90
PS (0 or 1 vs. 2)	0.14	0.14
Location*	0.57	0.32
T-category (1 or 2 vs. 3 or 4)	0.12	0.17
N-category (0 or 1 vs. 2 or 3)	0.05	0.28
Stage (I-III vs. IV)	0.10	0.24
Total dose (<70 vs. ≥70 Gy)	0.71	0.96
IC regimen (DOCE + vs. -)	0.22	0.37
Response to IC	0.00**	0.03**
Concurrent chemotherapy	0.10	0.14

Location (tonsils vs. base of the tongue vs. soft palate vs. posterior wall); IC: induction chemotherapy;
** significant (p<0.05)
DOCE: docetaxel

Multivariate analysis demonstrated that the response to induction chemotherapy (p=0.00) and T-category (T1, 2 vs. T3, 4) (p=0.03) were associated with local control, and the response to induction chemotherapy was correlated with overall survival (p=0.04) (Table 3).

Table 3. Multivariate analysis of potential predictors of local control and overall survival.

	Regression coefficient	Hazard ratio	CI	*P*-value
Local control				
Response to IC	3.0	20.2	3.3-124.0	0.00*
T-category (1 or 2 vs. 3 or 4)	2.0	7.1	1.2-42.8	0.03*
Overall survival				
Response to IC	1.1	3.1	1.1-9.2	0.04*

CI: 95% confidence interval; IC: induction chemotherapy
* significant ($p<0.05$)

Toxicities

Three patients developed grade 3 acute skin reactions, but none developed worse late skin reactions. Ten and 14 patients developed grade 3 and 2 acute mucosal reactions, respectively. A percutaneous endoscopic gastrostomy tube was inserted in one patient as he developed late phase mucosal edema. The hematological grade 3-4 adverse events that occurred during induction and concurrent chemotherapy are shown in Table 4. No treatment-related deaths occurred in this study.

Discussion

We here report on response to induction chemotherapy as a way to select oropharyngeal cancer patients who would benefit from definitive conservative treatment. Our finding is that taking the response to induction chemotherapy into consideration when deciding the subsequent treatment strategy is generally important for obtaining the maximum benefit from induction chemotherapy. These suggestions are based on the hypothesis that chemosensitive tumors are also radiosensitive (9). The fact that the 5-year local control rates of the induction chemotherapy responders (CR or PR) and non-responders (SD or PD) were 90% and 34%, respectively, and that their 5-year overall survival rates were 66% and 38%, respectively, appear to support this concept.

Table 4. Hematological grade 3-4 adverse events encountered during induction and concurrent chemotherapy.

	Induction chemotherapy		Concurrent chemotherapy	
CTCAE grade	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	2	0	1	0
Leukopenia	11	2	2	1
Thrombocytopenia	0	0	0	0
Febrile neutropenia	5	0	0	0

CTCAE: Common Terminology Criteria for Adverse Events

Concurrent chemoradiotherapy is regarded as the most effective form of conservative treatment for advanced head and neck carcinoma (2). However, some studies have found that patients who underwent concurrent chemoradiotherapy suffered adverse effects during long-term follow-up (10, 11). For example, an unexplained increase in deaths that were not attributable to cancer was detected among patients who received concurrent chemoradiotherapy (12). This might have been due to the treatment being too intense for some patients. In the present study, severe toxicities were uncommon. This was considered to be because chemoselection based on the response to induction chemotherapy made it possible to select patients who would benefit from conservative treatment.

The results obtained in some studies of induction chemotherapy seemed to fall short of expectations (3). However, the results obtained for the good responders in our present analysis were comparable with those described in historical data (13, 14). For example, the GORTEC 94-01 study, in which conventionally fractionated radiotherapy was combined with concurrent chemoradiotherapy, reported a 5-year local control rate of 48% and an overall survival rate of 22% in patients with stage III or IV oropharyngeal cancer (15). Furthermore, in a study of patients with stage III or IV oropharyngeal cancer who were treated with IMRT (16), implementation of IMRT in the setting of concurrent chemotherapy resulted in a 3-year local progression-free survival rate of 95% and an overall survival rate of 91%. In the present study, the local control and overall survival rates of our stage III/IV patients were 88% and 73%, respectively, at 3 years, and 88% and 63%, respectively, at 5 years. Thus, the outcomes obtained in the present study, in which IMRT was not employed, fell between those of conventional radiotherapy and IMRT. By taking the response to induc-

tion chemotherapy into consideration, patients who are not suitable for intensive chemoradiation-based organ-preserving treatment are not subjected to unnecessary risks, which hopefully leads to better outcomes. In order to achieve even better results**,** we have started to combine our chemoselection strategy with escalation of the total IMRT dose using the simultaneous integrated boost method.

In terms of the treatment of lymph node metastases, the ultimate control rate of the regional nodes that exhibited CR after induction chemotherapy was 100% (4/4). On the other hand, among the patients who displayed PR, SD, or PD, there was no difference in the neck disease control rate between patients who received organ-preserving therapy and those who underwent neck dissection (p=0.86). We consider that these results validate our policy regarding lymph node metastases.

Some clinicians might be concerned that the use of induction chemotherapy increases the total treatment time, which might reduce treatment efficacy. To avoid this, fiberscopic or computed tomography examinations should be performed at least once a week during induction chemotherapy, and irradiation should be started within one or two weeks of completing induction chemotherapy. We also found that cancer boards help multidisciplinary teams including clinical oncologists, head and neck surgeons, and radiation oncologists to prepare for radiotherapy/chemoradiotherapy or surgery after induction chemotherapy. Furthermore, we reduced the TPF dose to 60-80% of the standard dose in order to avoid the treatment period being prolonged due to toxicity. In the upshot, only 3 patients were treated for more than 60 days (data not shown). We consider that this played an important role in the good results achieved in this study. In addition, Cohen *et al.* (4) reported that induction chemotherapy significantly decreased the cumulative incidence of distant failure. If this is an advantage of induction chemotherapy, the fact that only one patient developed distant metastasis in the present study seems to validate our dose reduction strategy.

There are a number of limitations in this study. First, various regimens were used in the induction or concurrent settings; in addition to the TPF or CF regimen, other regimens (CDDP plus S-1, CBDCA plus 5-FU, and TS-1 alone) were also used owing to the physical conditions of the patients. Second, the total number of the patients was small. This must have affected the heterogeneity of the outcomes especially in terms of multivariate analysis. Third, although it is known that oropharyngeal cancer patients with positive HPV titers have a good prognosis (17, 18), little attention was paid to this at the time of this study. Thus, we have insufficient data about our patients' HPV titers, and we cannot discuss this issue in the present study.

Conclusion

In oropharyngeal cancer, chemoselection after induction chemotherapy appears to be useful for selecting candidates for organ-preserving treatment, and this is true for both primary tumors and neck metastases. In order to further improve cure rates, we have started combining our chemoselection strategy with IMRT dose escalation using the simultaneous integrated boost method.

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