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Treatment Outcomes and Prognostic Factors of Concurrent Chemoradiotherapy With Docetaxel, Cisplatin, and Fluorouracil in Advanced Head and Neck Cancer

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Treatment Outcomes and Prognostic Factors of Concurrent Chemoradiotherapy With Docetaxel, Cisplatin, and Fluorouracil in Advanced Head and Neck Cancer

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Abstract. *Background/Aim: Although the efficacy of docetaxel, cisplatin, and 5-Fluorouracil (TPF) as induction chemotherapy has been confirmed, the therapeutic outcome and prognostic factors of concurrent chemoradiotherapy (CCRT) should be investigated. Patients and Methods: Laboratory data of patients who underwent CCRT for advanced squamous cell carcinoma (SCC) of the head and neck were investigated to clarify the grade of side effects. Survival rates and prognostic scores were also calculated. Multivariate analysis was performed to examine the prognostic factors of the patients. Results: Although there were significantly more advanced cases in the TPF group (n=72) than those in the cisplatin group (n=50), there were no significant differences in patient survival rates. In the TPF group, the lymphocyte count, albumin level, and C-reactive protein level of the patients before treatment were significantly correlated with patient outcomes. Conclusion: CCRT using the TPF regimen had remarkable treatment effects in advanced head and neck cancer.*

Concurrent chemoradiotherapy (CCRT), a combination of chemotherapy and radiotherapy recommended as a curative treatment for squamous cell carcinoma (SCC) of the head and neck (HNSCC), is used mainly for advanced stage III and IV cancers and may also be used for stage II cancers depending on the site and advancement of the tumor. Cisplatin (cis-diamine-dichloro platinum, CDDP) is currently the standard chemotherapeutic agent recommended for CCRT in HNSCC, and a combination of CDDP and radiotherapy is often used as standard treatment (1). Docetaxel, cisplatin, and 5-FU (TPF) therapy have been used as induction chemotherapy (IC) or neoadjuvant chemotherapy (NAC) in HNSCC and have been shown to be effective (2-4); however, it has not been widely used in combination with radiotherapy due to the high toxicity of the three-drug combination (5). Therefore, feasibility studies have been conducted to reduce the dose of docetaxel and CDDP to allow their use in combination with radiotherapy (6), and their efficacy has been demonstrated at various sites (7-10). However, since it is used less frequently worldwide than the CDDP combination, its treatment results and related prognostic factors have not yet been analyzed. This study aimed to compare the survival rate of patients with HNSCC treated with CCRT using CDDP and TPF regimens in relation to laboratory data and side effects to obtain crucial information for future treatment selection. Furthermore, if the prognosis can be predicted even before the start of treatment, patients can receive a much wider range of options.

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Key Words: Concurrent chemoradiotherapy, squamous cell carcinoma, head and neck, prognostic factor, TPF.

Patients and Methods

Patients. We reviewed the charts of patients with advanced HNSCC who underwent CCRT as initial therapy at our hospital between 2014 and 2019, including age, sex, tumor site, stage, laboratory data, and side effects. Patients who did not receive CCRT as definitive therapy, such as postoperative chemoradiotherapy or recurrent cases, were excluded. Trends in laboratory data were accumulated and side effects were graded and classified. In this prognostic study, we investigated the events and observation period, including the presence of recurrence and subsequent additional treatment. If the patient was transferred to another hospital, moved

Table I. *Profiles of the patients*.

Subject		Total (n=122)	TPF (n=72)	CDDP (n=50)	*p*-Value
Sex	Female	23	9	14	0.031
	Male	99	63	36	
Age	>65	68	39	29	0.675
	≤65	54	33	21	
Site	Larynx	15	6	9	
	Nasopharynx	6	0	6	
	Oropharynx	34	19	15	
	Hypopharynx	35	23	12	
	Oral	14	12	2	
	Nasal	9	6	3	
	Ear canal	6	4	2	
	Unknown origin	3	3	0	
	Salivary glands	2	1	1	
p16 status	Positive	13	3	10	0.0026
T	T0	3	3	0	T1+2 *vs*. T3+4: 0.0001
	T1	4	2	2	
	T2	41	14	27	
	T3	26	13	13	
	T4	48	40	8	
N	N0	34	18	16	N0 *vs*. N1+2+3: 0.396
	N1	17	7	10	N0+1 *vs*. N2+3: 0.057
	N2	68	45	23	
	N3	3	2	1	
M	M1	7	6	1	0.139
Stage	I	3	1	2	I+II *vs*. III+IV: <0.0001
	II	22	4	18	
	III	18	7	11	
	IVA	63	45	18	
	IVB	10	10	0	
	IVC	6	5	1	
Radiotherapy	70 Gy	63	34	29	0.241
	≤66 Gy	59	38	21	

TPF: Docetaxel+CDDP+5-FU; CDDP: cis-diamine-dichloro platinum.

to a different location, or terminated, the observation period was up to the date of the last confirmation. Survival rates were calculated based on the results of prognostic studies and a multivariate analysis of associated factors was performed. Patients' information was recorded in a digital medical record system and updated whenever a clinical event occurred. Demographic, clinical, surgical, radiological, and pathological information were recorded in an Excel database. The database has been updated regularly.

Study design. This study was carried out according to the ethical standards of the responsible committee for human experimentation (institutional and national) and the Declaration of Helsinki of 1975, as revised in 2008 (11). This study was approved by the Institutional Review Board (MH2020-209). Written informed consent was obtained from all patients treated with CCRT. The study design was a retrospective review of the patient's medical records.

Statistical analyses. The Glasgow Prognostic Score (GPS) (12, 13), modified Glasgow Prognostic Score (mGPS) (14, 15), and Onodera Prognostic Nutritional Index (PNI) (16, 17) were calculated from

Table II. *Factors associated with prognosis in each group*.

		TPF	CDDP	*p*-Value (*t*-test)
Albumin		3.67±0.41	3.82±0.39	0.05
CRP		0.97±2.04	0.23±0.50	0.015
Lymphocyte		1378±735	1374±641.7	0.97
PNI		43.6±5.85	45.1±4.51	0.12
GPS	0	49	40	0 *vs*. 1-2
	1	14	9	*p*=0.14
	2	9	1	
mGPS	0	58	47	0 *vs*. 1-2
	1	5	2	*p*=0.03
	2	9	1	

TPF: Docetaxel+CDDP+5-FU; CDDP: cis-diamine-dichloro platinum; CRP: C-reactive protein; PNI: prognostic nutritional index; GPS: Glasgow prognostic score; mGPS: modified Glasgow score prognostic score.

Table III. *Adverse events of patients who underwent concurrent chemoradiotherapy with cis-diamine-dichloro platinum (CDDP) and Docetaxel+CDDP+5-FU (TPF).*

	TPF (n=72)					CDDP (n=50)					
Grade	0	1	2	3	4	0	1	2	3	4	*p*-Value (χ^2 test)
Bilirubin	65	5	2	0	0	50	0	0	0	0	
Alkaline phosphatase	53	14	5	0	0	43	7	0	0	0	
γ-Glutamyl transpeptidase	42	18	6	6	0	19	16	10	5	0	G0-2 *vs*. G3-4 *p*=0.75
Aspartate transaminase	56	16	0	0	0	33	15	2	0	0	
Alanine transaminase	52	18	2	0	0	25	19	5	1	0	G0-2 *vs*. G3-4 *p*=0.23
Hypoalbuminemia	0	31	38	3	0	1	41	8	0	0	G0-2 *vs*. G3-4 *p*=0.14
Creatinine	53	18	1	0	0	41	9	0	0	0	
Hyponatremia	5	55	0	12	0	13	34	0	3	0	G0-2 *vs*. G3-4 *p*=0.078
Hyperkalemia	72	0	0	0	0	50	0	0	0	0	
Hypokalemia	45	22	0	4	1	29	17	0	3	1	G0-2 *vs*. G3-4 *p*=0.83
Leukocytes	3	0	5	24	40	7	2	25	14	2	G0-2 *vs*. G3-4 *p*≤0.0001
Neutrophils	3	3	8	8	50	9	12	13	14	2	G0-2 *vs*. G3-4 *p*≤0.0001
Lymphopenia	1	2	6	27	36	2	4	10	22	12	G0-2 *vs*. G3-4 *p*=0.0087
Hemoglobin	1	35	31	4	1	5	33	8	3	1	G0-2 *vs*. G3-4 p=0.83
Platelets	28	34	7	1	2	24	23	2	1	0	G0-2 *vs*. G3-4 p=0.51
Dermatitis	0	9	30	31	2	0	11	24	15	0	G0-2 *vs*. G3-4 p=0.078
Mucositis	2	3	16	44	7	2	9	19	19	1	G0-2 *vs*. G3-4 *p*=0.00068

pretreatment laboratory data. GPS, mGPS, and PNI are often considered risk factors for the long-term prognosis of other malignant diseases. GPS and mGPS were scored based on C-reactive protein (CRP) and albumin (Alb) levels. GPS was 0 if CRP ≤1.0, Alb ≥3.5; 1 if CRP >1.0 or Alb <3.5; and 2 if CRP >1.0 and Alb <3.5. The mGPS was 0 for CRP ≤1.0; 1 for CRP >1.0; and 2 for CRP >1.0 and further Alb <3.5. The PNI was calculated as 10×Alb (g/dl)+0.005×lymphocyte count (/μl).

The *t*-test and χ^2 test were used to compare each group of patients and evaluate statistical significance. Survival rates based on prognostic studies were calculated using the Kaplan-Meier method, and significant differences were assessed using the log-rank test. Fifty patients in the CDDP group (N=50) and 72 patients in the TPF group (N=72) were eligible for the analysis (Table I).

Multivariate analysis. First, we compared the treatment effects of CDDP and TPF on the risks of overall and disease-specific death using the Cox proportional hazards model. The multivariate analysis was adjusted for age, sex, stage classification, serum Alb level (≥3.7, <3.7), serum CRP level (<0.15, ≥0.15), and lymphocyte count (≤1,367, >1,367). In addition, we also examined models adjusted for PNI, GPS (1+2, 0), and mGPS (1+2, 0). Second, we used Cox proportional hazards models to examine whether the above factors were associated with the risk of overall and disease-specific death in each treatment group.

Results

Table I shows the profile of the patients included in this study: 50 in the CDDP group (patients who underwent CCRT with CDDP) and 72 in the TPF group (patients who underwent CCRT with TPF). There were significant differences in sex ratio, T classification, p16 status (*p*=0.0026), and stage. There were also significant differences in the levels of CRP and mGPS between the CDDP and TPF groups (Table II).

Table III shows the adverse events observed in this study. Subjects and grades of hepatic dysfunction, elevated serum creatinine, electrolyte abnormalities, blood counts, mucositis, and dermatitis are shown. The numbers of grade 0-2 and grade 3-4 were compared among patients who underwent CCRT in the CDDP and TPF groups. Higher grades of adverse events tended to appear in patients who underwent CCRT with the TPF regimen. The results showed significant differences in the following four subjects: leukocytes, neutrophils, lymphopenia, and mucositis.

We analyzed the outcomes of the patients using the Kaplan-Meier method. First, the overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) rates of all patients were calculated in each stage (Figure 1). The OS, DSS, and PFS rates of patients with stages I, II, III, IVA, IVB, and IVC tumors at 3 years were 100, 100, 67.7%; 95.5, 95.5, 89.8%; 100, 100, 84.4%; 67.0, 70.6, 67.5%; 55.6, 55.6, 55.6%; 25.0, 25.0, 16.7%, respectively. There were significant differences between the survival rates of patients with stages I, II, and III tumors and those with stage IV tumors (Figure 1). Second, the OS, DSS, and PFS rates of patients in the CDDP and TPF groups were calculated. The 5-year OS, DSS, and PFS rates were 70.3%, 87.9%, and 72.4%, respectively, for the CDDP group and 64.9%, 67.7%, and 60.2%, respectively, for the TPF group. There were no significant differences between the two groups (Figure 2).

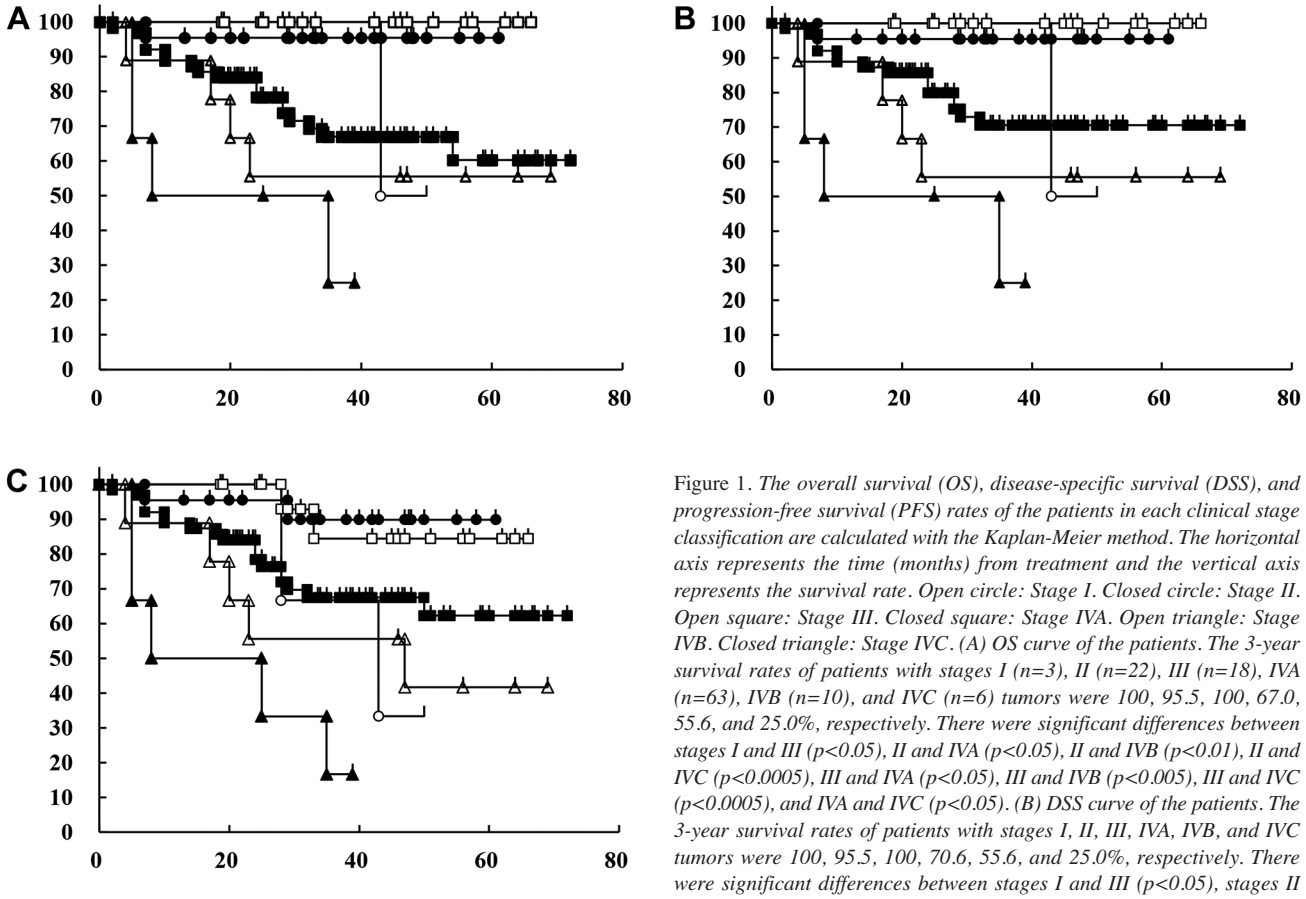

Figure 1. *The overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) rates of the patients in each clinical stage classification are calculated with the Kaplan-Meier method. The horizontal axis represents the time (months) from treatment and the vertical axis represents the survival rate. Open circle: Stage I. Closed circle: Stage II. Open square: Stage III. Closed square: Stage IVA. Open triangle: Stage IVB. Closed triangle: Stage IVC. (A) OS curve of the patients. The 3-year survival rates of patients with stages I (n=3), II (n=22), III (n=18), IVA (n=63), IVB (n=10), and IVC (n=6) tumors were 100, 95.5, 100, 67.0, 55.6, and 25.0%, respectively. There were significant differences between stages I and III ($p<0.05$), II and IVA ($p<0.05$), II and IVB ($p<0.01$), II and IVC ($p<0.0005$), III and IVA ($p<0.05$), III and IVB ($p<0.005$), III and IVC ($p<0.0005$), and IVA and IVC ($p<0.05$). (B) DSS curve of the patients. The 3-year survival rates of patients with stages I, II, III, IVA, IVB, and IVC tumors were 100, 95.5, 100, 70.6, 55.6, and 25.0%, respectively. There were significant differences between stages I and III ($p<0.05$), stages II and IVA ($p<0.05$), stages II and IVB ($p<0.01$), stages II and IVC ($p<0.0005$), III and IVA ($p<0.05$), stages III and IVB ($p<0.005$), stages III and IVC ($p<0.0005$), and stages IVA and IVC ($p<0.05$). (C) PFS curve of the patients. The 3-year survival rates of patients with stages I, II, III, IVA, IVB, and IVC tumors were 67.7, 89.8, 84.4, 67.5, 55.6, and 16.7%, respectively. There were significant differences between stages I and II ($p<0.05$), II and IVB ($p<0.05$), II and IVC ($p<0.0001$), III and IVB ($p<0.05$), III and IVC ($p<0.0005$), IVA, and IVC ($p<0.005$).*

In the CDDP group, patients with pretreatment CRP above the mean value (>0.23 mg/dl) had significantly worse prognosis regarding OS ($p<0.05$) and DSS ($p<0.01$) compared to patients below the mean value. Patients with a GPS of 1 or 2 had a significantly worse prognosis regarding OS ($p<0.01$) and DSS ($p<0.05$) than those with a GPS of 0. Patients with a PNI above the median value (45.15) had a significantly worse prognosis regarding OS and DSS than patients below the median value (Figure 3).

Patients with a GPS and mGPS of 2 in the TPF group had a significantly worse PFS than patients with 0 or 1 ($p<0.05$). Patients with pretreatment Alb below the mean value (<3.67 mg/dl) had a significantly worse PFS ($p<0.05$) and OS ($p<0.01$). Patients with a PNI below the mean value (<43.58) had significantly worse PFS ($p<0.005$) and OS ($p<0.005$) (Figure 3). Patients with pretreatment CRP above the median value (>0.2 mg/dl) had significantly worse PFS ($p<0.005$) and OS ($p<0.01$) (Figure 4). Patients with pretreatment lymphocyte counts below the mean (1,378/ml) had significantly worse PFS ($p<0.005$) and OS ($p<0.005$) (Figure 4).

Finally, we performed a multivariate analysis. The total number of person-months of observation was 4,272, and the mean duration of observation was 35.0 (standard deviation, 17.6) months. The number of overall deaths and the cumulative rate of overall deaths was 7 (14%) and 22 (30.6%) in the CDDP and TPF groups, respectively. For disease-specific deaths, the number and cumulative rates were 6 (12%) in the CDDP group and 20 (27.8%) in the TPF group. Table IV shows the results of the comparison between the therapeutic effects of CDDP and TPF. Compared to the CDDP group, the multivariate-adjusted hazard ratio (HR) [95% confidence interval (CI)] for overall death in the TPF group was 1.45 (0.58-3.59) ($p=0.427$), which was not statistically significant. Similar results were obtained after adjustment for PNI, GPS, and mGPS. There were also no significant differences in disease-specific death between the CDDP and TPF groups in multivariate analyses. In stratified analyses by treatment group, in the CDDP group, the factors associated with the risk of

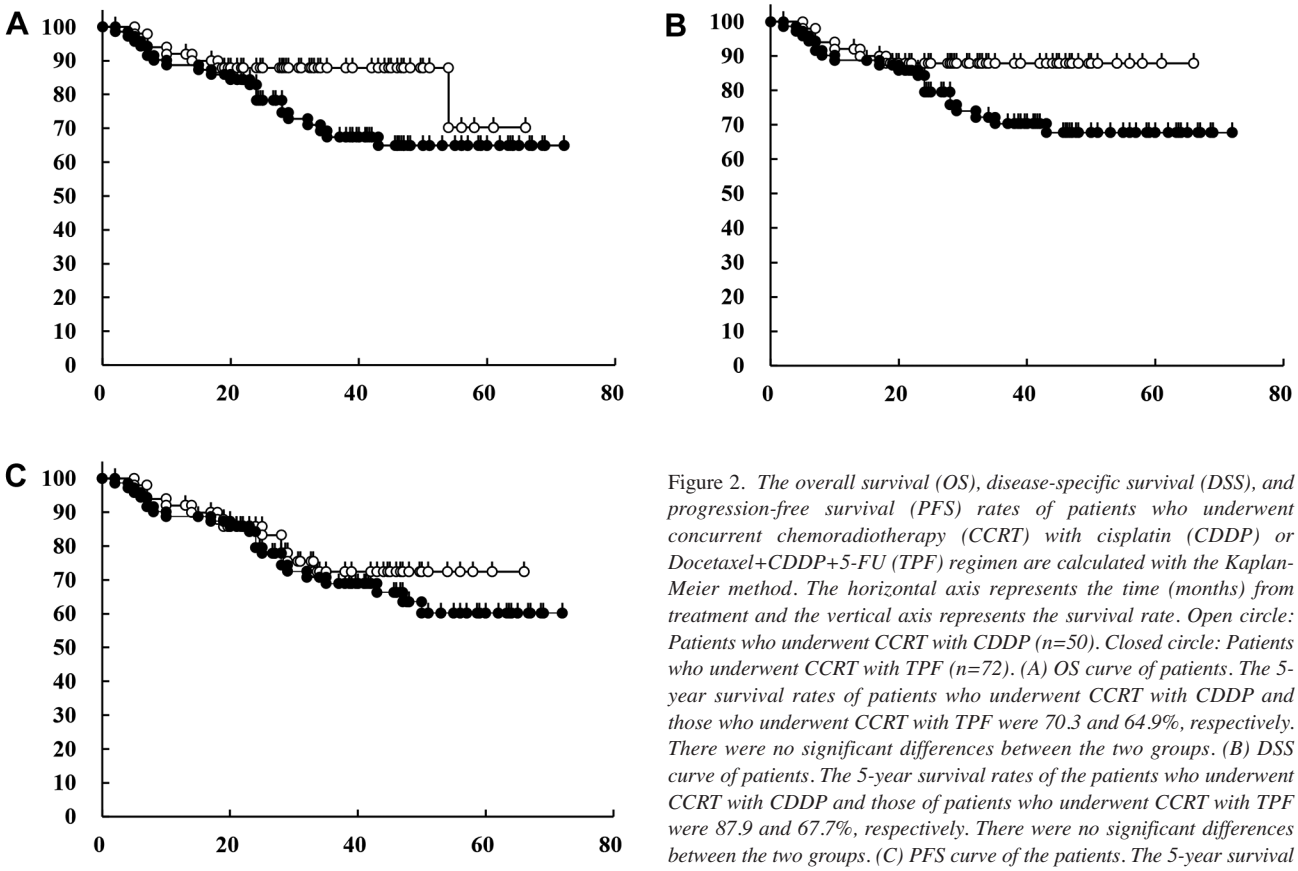

Figure 2. *The overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) rates of patients who underwent concurrent chemoradiotherapy (CCRT) with cisplatin (CDDP) or Docetaxel+CDDP+5-FU (TPF) regimen are calculated with the Kaplan-Meier method. The horizontal axis represents the time (months) from treatment and the vertical axis represents the survival rate. Open circle: Patients who underwent CCRT with CDDP (n=50). Closed circle: Patients who underwent CCRT with TPF (n=72). (A) OS curve of patients. The 5-year survival rates of patients who underwent CCRT with CDDP and those who underwent CCRT with TPF were 70.3 and 64.9%, respectively. There were no significant differences between the two groups. (B) DSS curve of patients. The 5-year survival rates of the patients who underwent CCRT with CDDP and those of patients who underwent CCRT with TPF were 87.9 and 67.7%, respectively. There were no significant differences between the two groups. (C) PFS curve of the patients. The 5-year survival rates of patients who underwent CCRT with CDDP and those who underwent CCRT with TPF were 72.4 and 60.2%, respectively. There were no significant differences between the two groups.*

overall death and disease-specific death were PNI and GPS (Table V). In the TPF group, CRP level, lymphocyte count, and PNI were associated with the risk of overall death and disease-specific death (Table VI).

Discussion

In this study, CDDP and modified TPF regimens were used in parallel as combination chemotherapy with CCRT for patients with advanced HNSCC. Although TPF has not been as widely used in CCRT as CDDP due to its toxicity to patients, its compliance has improved after dose reduction, that is, by using modified TPF. Adverse events, such as hepatic dysfunction, elevated serum creatinine, and electrolyte abnormalities, were observed in patients who underwent CCRT with a combination of CDDP and TPF (Table III). However, a higher grade of adverse events tended to occur in patients who underwent CCRT with the TPF regimen. In particular, significant differences were observed in lymphocyte count, neutrophil count, and mucositis. Adverse events were considered more obvious for the combination of the three chemotherapeutic agents in the TPF regimen, but were almost acceptable in our study.

The oncologic outcomes of patients who underwent CCRT with the TPF regimen were not significantly different from those who underwent CCRT with the CDDP regimen, although those who underwent CCRT with TPF had more advanced disease (Figure 2). The complete response rates were 92.0% for CCRT with CDDP and 94.4% for CCRT with TPF. The oncological outcomes of patients who underwent CCRT with TPF were not significantly different from those who underwent CCRT with CDDP, despite the significantly lower number of patients with p16-positive tumors (p=0.0026). Multivariate analysis also indicated that the therapeutic effects of CDDP and TPF were not significant under our patient conditions (Table IV). When compared under the same conditions, *i.e.*, a prospective study between patients with the same stage of disease, it is likely that those who underwent CCRT with TPF may show better outcomes. Since CCRT with TPF is often chosen for patients with more advanced cancers, comparison under the same conditions may be difficult. Future studies are needed to clarify the efficacy of CCRT with TPF in patients with HNSCC.

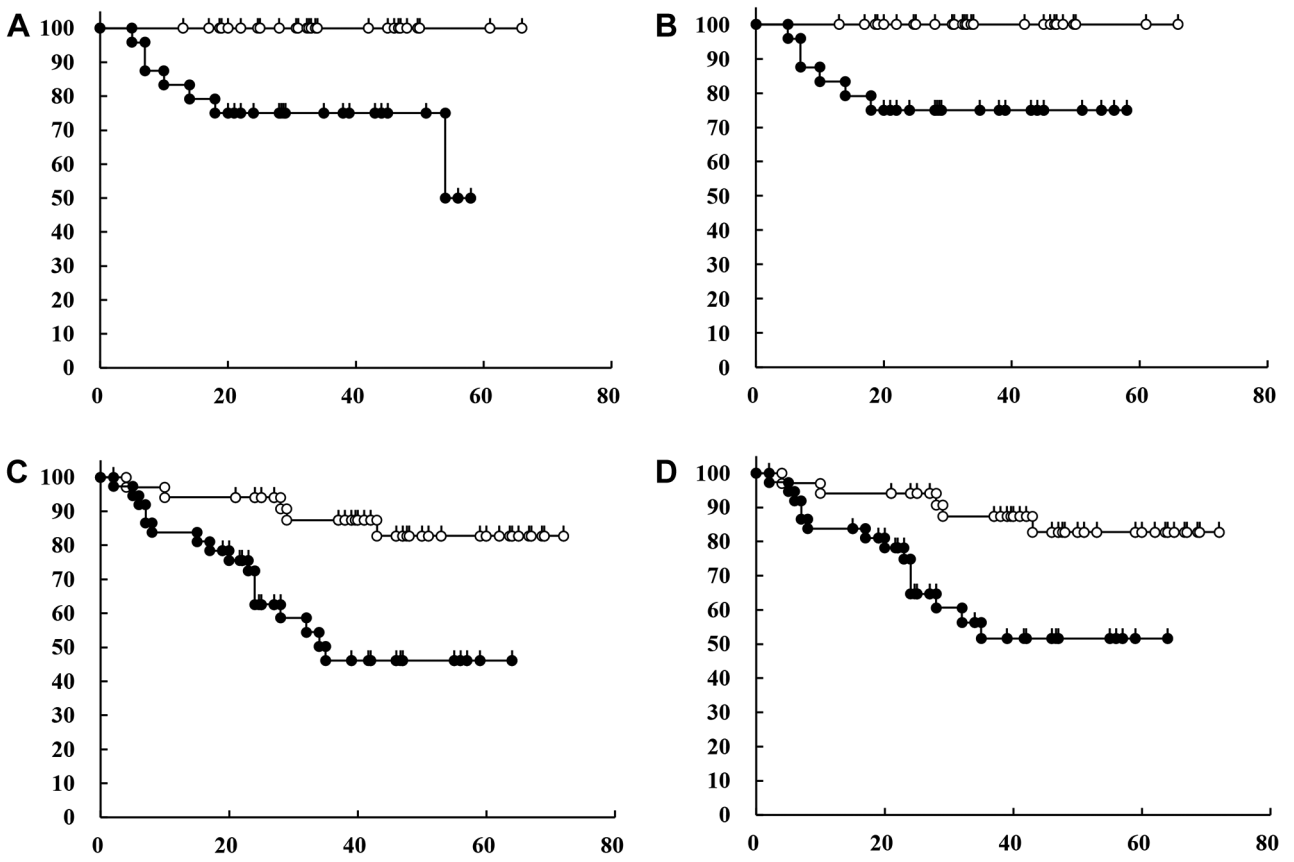

Figure 3. *The overall survival (OS) and disease-specific survival (DSS) rates of patients who underwent concurrent chemoradiotherapy (CCRT). The horizontal axis represents the time (months) from treatment and the vertical axis represents the survival rate. (A) OS and (B) DSS. Survival curves of patients who underwent CCRT with cisplatin (CDDP). Open circle: Patients whose pretreatment prognostic nutritional index (PNI) was above the median value (45.15) (n=26). Closed circle: Patients whose pretreatment PNI was below the median value (n=24). There were significant differences between the two groups in terms of OS and DSS (p<0.01). (C) OS and (D) DSS. Survival curves of patients who underwent CCRT with Docetaxel+CDDP+5-FU (TPF). Open circle: Patients whose pretreatment PNI was above the mean value (43.58) (n=34). Closed circle: Patients whose pretreatment PNI was below the mean value (n=38). There were significant differences between the two groups in terms of OS and DSS (p<0.005).*

Our study indicated that several factors could predict the patient's prognosis, even before treatment. Several studies have reported that malnutrition and poor immune status might increase the risk of postoperative complications, decrease the response to antitumor therapy, and be associated with poor survival (18, 19). The prognostic value of the systemic inflammatory response (SIR) has already been demonstrated in various solid tumors (20). Elevated CRP, an indicator of SIR, has been identified as a negative prognostic factor in many cancers, such as thymic epithelial tumors (21), lung cancer (22), and gastric cancer (23). In this study, patients who underwent CCRT with CDDP and CCRT with TPF showed significant differences in survival rates according to the pretreatment CRP level. Patients with higher CRP values had a worse prognosis than those with lower CRP values (both mean and median values). Multivariate analysis showed that the level of CRP was a significant prognostic factor for patients who underwent CCRT with TPF (Table VI).

Preoperative serum Alb level has been recognized as a valuable factor in prognosis prediction in patients with various types of cancer, such as epithelial ovarian cancer (24), bladder cancer (25), and colorectal cancer (26). Patients who underwent CCRT with TPF and had below average pretreatment Alb levels showed a significantly worse prognosis in terms of survival rate. Patients with pretreatment CRP levels above the median value had a significantly worse prognosis in terms of survival rate (Figure 4). GPS and mGPS were scored based on the CRP and Alb levels. Patients with a GPS of 1 or 2 in the CDDP group had significantly worse OS and DSS prognosis rates than those with a GPS of 0. Patients with GPS and mGPS of 2 in the TPF group showed a significantly worse PFS than patients with GPS and mGPS of 0 or 1. CRP and Alb levels

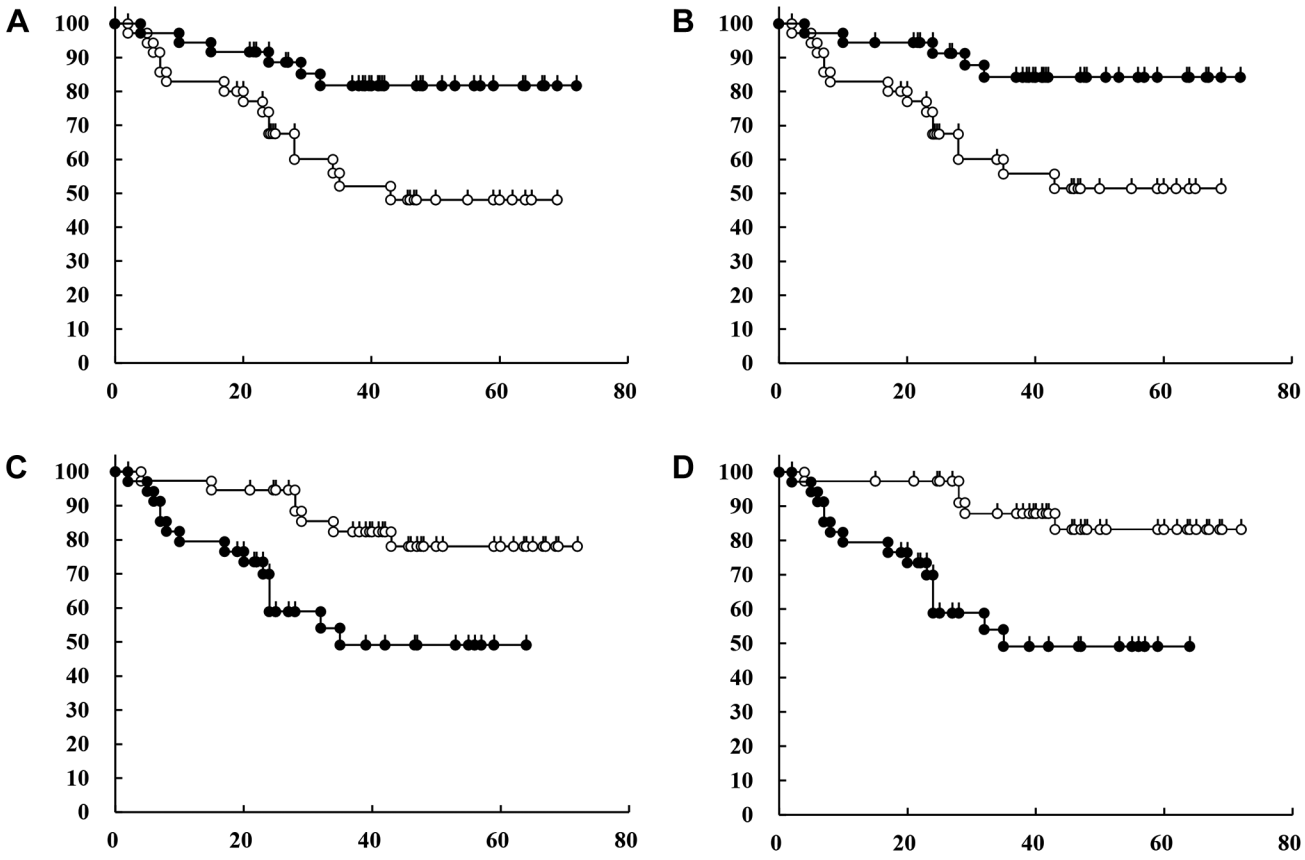

Figure 4. *The overall survival (OS) and disease-specific survival (DSS) rates of patients who underwent concurrent chemoradiotherapy (CCRT) with Docetaxel+CDDP+5-FU (TPF). The horizontal axis represents the time (months) from treatment and the vertical axis represents the survival rate. (A) OS and (B) DSS. Survival curves of patients who underwent CCRT with TPF. Open circle: patients whose pretreatment CRP level was above the median value (0.2 mg/dl) (n=36). Closed circle: Patients whose pretreatment PNI was below the median value (n=36). There were significant differences between the two groups in terms of OS and DSS (p<0.01). (C) OS and (D) DSS. Survival curves of patients who underwent CCRT with TPF. Open circle: Patients whose pretreatment lymphocyte count was above the mean value (1,378/μl) (n=37). Closed circle: Patients whose pretreatment lymphocytes were below the mean value (n=35). There were significant differences in OS and DSS between the two groups (p<0.005 and p<0.001, respectively).*

were prognostic factors that showed significant differences in the prognoses of the patients in this study. Because GPS and mGPS combine these two factors, they could be very useful in predicting the prognosis of patients.

Lymphocyte and serum Alb levels are significantly associated with the prognosis of cancer patients (27). PNI, which is calculated by lymphocyte count and serum Alb level of patients, has been reported to be related to therapeutic effects and predict the survival of patients with various solid tumors (28-30). In this study, pretreatment Alb, CRP, lymphocyte count, GPS, mGPS, and PNI of patients who underwent CCRT with TPF were correlated with the patient's prognosis. Patients who underwent CCRT with TPF and had below average pretreatment lymphocyte counts showed a significantly worse prognosis in terms of survival rate (Figure 4; Table VI). Multivariate analysis also revealed that PNI showed a significant difference in CCRT with CDDP and CCRT with TPF in terms of patient survival rates, suggesting that it is useful as a prognostic factor for patients with HNSCC (Figure 3; Table V, Table VI).

There are several limitations to this study. First, it was a retrospective study conducted at a single institution. More patients and multicenter studies are needed for a prospective design. Second, although we included consecutive patients and minimized bias, selection bias could not be eliminated. Further validation in large prospective studies is needed to evaluate the efficacy of CCRT with TPF in patients with HNSCC and prognostic factors in the future.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Table IV. *Multivariate analysis of all patients.*

	Overall death		Disease-specific death	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
TPF *vs*. CDDP	1.45 (0.58-3.59)	0.427	1.67 (0.62-4.49)	0.312
Males *vs*. females	0.44 (0.15-1.28)	0.13	0.43 (0.15-1.26)	0.125
Age	0.99 (0.96-1.03)	0.789	1.00 (0.96-1.04)	0.948
Stage III+IV *vs*. Stage I+II	3.29 (0.74-14.65)	0.118	2.76 (0.60-12.59)	0.19
Albumin ≤3.7	2.34 (1.00-5.49)	0.05	1.98 (0.83-4.73)	0.124
CRP ≥0.15	3.74 (1.39-10.01)	0.009	3.26 (1.18-8.97)	0.022
Lymphocyte ≤1367	1.85 (0.83-4.14)	0.135	2.20 (0.92-5.26)	0.076
TPF *vs*. CDDP	1.49 (0.60-3.68)	0.391	1.69 (0.63-4.50)	0.294
Males *vs*. females	0.75 (0.28-2.03)	0.574	0.67 (0.25-1.84)	0.442
Age	0.99 (0.95-1.03)	0.51	0.99 (0.95-1.03)	0.659
Stage III+IV *vs*. Stage I+II	2.52 (0.55-11.57)	0.235	2.21 (0.47-10.37)	0.316
PNI	0.84 (0.78-0.91)	<0.001	0.85 (0.79-0.92)	<0.001
TPF *vs*. CDDP	1.40 (0.57-3.46)	0.462	1.66 (0.63-4.40)	0.306
Males *vs*. females	0.68 (0.25-1.87)	0.459	0.64 (0.23-1.77)	0.39
Age	0.98 (0.94-1.02)	0.351	0.99 (0.95-1.03)	0.576
Stage III+IV *vs*. Stage I+II	3.30 (0.73-14.99)	0.122	2.81 (0.61-13.02)	0.186
GPS=1+2 *vs*. GPS=0	2.90 (1.36-6.23)	0.006	2.20 (0.98-4.94)	0.057
TPF *vs*. CDDP	1.54 (0.62-3.82)	0.348	1.78 (0.67-4.72)	0.246
Males *vs*. females	0.81 (0.30-2.19)	0.678	0.72 (0.26-1.97)	0.521
Age	0.99 (0.95-1.03)	0.537	0.99 (0.95-1.04)	0.723
Stage III+IV *vs*. Stage I+II	3.22 (0.71-14.67)	0.13	2.80 (0.61-12.94)	0.187
mGPS=1+2 *vs*. mGPS=0	1.43 (0.56-3.61)	0.454	1.27 (0.47-3.47)	0.639

TPF: Docetaxel +CDDP+5-FU; CDDP: cis-diamine-dichloro platinum; HR: hazard ratio; CRP: C-reactive protein; PNI: prognostic nutritional index; GPS: Glasgow prognostic score; mGPS: modified Glasgow prognostic score.

Table V. *Multivariate analysis of patients who underwent concurrent chemoradiotherapy with cis-diamine-dichloro platinum (CDDP).*

CDDP				
	Overall death		Disease-specific death	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Males *vs*. females	0.44 (0.04-4.60)	0.494	0.38 (0.04-4.04)	0.422
Age	0.99 (0.92-1.06)	0.733	0.99 (0.92-1.06)	0.778
Stage III+IV *vs*. stage I+II	4.58 (0.41-51.67)	0.218	4.11 (0.39-43.83)	0.242
Albumin ≤3.7	5.07 (0.48-53.86)	0.178	4.51 (0.44-46.37)	0.206
CRP ≥0.15	2.98 (0.40-21.99)	0.284	2.67 (0.37-19.01)	0.327
Lymphocyte ≤1367	0.47 (0.08-2.77)	0.407	0.44 (0.07-2.72)	0.38
Males *vs*. females	0.89 (0.12-6.77)	0.908	0.77 (0.10-5.91)	0.804
Age	0.96 (0.88-1.03)	0.252	0.96 (0.89-1.04)	0.328
Stage III+IV *vs*. stage I+II	2.77 (0.28-27.65)	0.385	2.67 (0.27-25.87)	0.398
PNI	0.80 (0.67-0.95)	0.011	0.81 (0.68-0.97)	0.023
Males *vs*. females	0.19 (0.01-2.38)	0.196	0.19 (0.02-2.39)	0.199
Age	0.95 (0.88-1.02)	0.148	0.95 (0.88-1.03)	0.182
Stage III+IV *vs*. stage I+II	5.39 (0.59-49.20)	0.136	5.04 (0.55-45.92)	0.152
GPS=1+2 *vs*. GPS=0	20.06 (1.95-206.73)	0.012	17.08 (1.52-191.36)	0.021
Males *vs*. females	0.64 (0.10-4.12)	0.637	0.57 (0.09-3.67)	0.554
Age	0.97 (0.91-1.04)	0.456	0.98 (0.91-1.05)	0.549
Stage III+IV *vs*. stage I+II	4.72 (0.46-48. 80)	0.193	3.99 (0.40-39.53)	0.237
mGPS=1+2 *vs*. mGPS=0	NA		NA	

TPF: Docetaxel+CDDP+5-FU; HR: hazard ratio; CRP: C-reactive protein; PNI: Prognostic Nutritional Index; GPS: Glasgow Prognostic Score; mGPS: modified Glasgow Prognostic Score.

Table VI. *Multivariate analysis of patients who underwent concurrent chemoradiotherapy (CCRT) with Docetaxel+CDDP+5-FU (TPF).*

	Overall death		Disease-specific death	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Males *vs*. females	0.45 (0.12-1.70)	0.239	0.46 (0.12-1.73)	0.248
Age	1.00 (0.96-1.05)	0.872	1.01 (0.96-1.06)	0.645
Stage III+IV *vs*. stage I+II	2.26 (0.30-17.29)	0.431	1.81 (0.23-14.10)	0.57
Albumin ≤3.7	1.98 (0.77-5.08)	0.155	1.63 (0.62-4.28)	0.32
CRP ≥0.15	3.24 (1.02-10.31)	0.046	2.80 (0.87-9.02)	0.084
Lymphocyte ≤1367	2.71 (1.06-6.90)	0.037	4.00 (1.4-11.42)	0.01
Males *vs*. females	0.73 (0.21-2.52)	0.617	0.65 (0.19-2.27)	0.501
Age	1.00 (0.96-1.05)	0.968	1.01 (0.96-1.06)	0.798
Stage III+IV *vs*. stage I+II	1.53 (0.20-11.81)	0.686	1.36 (0.17-10.63)	0.768
PNI	0.84 (0.77-0.92)	<0.001	0.85 (0.78-0.93)	<0.001
Males *vs*. females	0.80 (0.23-2.82)	0.734	0.73 (0.21 2.58)	0.622
Age	0.99 (0.94-1.05)	0.826	1.00 (0.95 -1.06)	0.924
Stage III+IV *vs*. stage I+II	2.03 (0.27-15.36)	0.493	1.80 (0.24-13.72)	0.57
GPS=1+2 *vs*. GPS=0	2.14 (0.91-5.03)	0.081	1.70 (0.68-4.25)	0.252
Males *vs*. females	0.86 (0.25-3.03)	0.818	0.76 (0.21-2.68)	0.666
Age	1.00 (0.94-1.05)	0.861	1.00 (0.95-1.06)	0.897
Stage III+IV *vs*. stage I+II	1.95 (0.25-14.93)	0.522	1.75 (0.23-13.53)	0.592
mGPS=1+2 *vs*. mGPS=0	1.62 (0.62-4.24)	0.329	1.43 (0.50-4.04)	0.503

CDDP: Cis-diamine-dichloro platinum; HR: hazard ratio; CRP: C-reactive protein; PNI: Prognostic Nutritional Index; GPS: Glasgow Prognostic Score; mGPS: modified Glasgow Prognostic Score.

Authors' Contributions

Conceptualization, K.S; methodology, K.S. and K.T.; investigation, T.K.; resources, T.K., K.S., K.K., D.S., S.O., A.I., K.T., J.M., Y.O., and H.A.; writing—original draft preparation, T.K., and K.S.; funding acquisition, K.S., K.K., and D.S. All Authors have read and agreed to the published version of the article.

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