Induction Chemotherapy with Docetaxel, Cisplatin and Fluorouracil Followed by Surgery and Concurrent Chemoradiotherapy Improves Outcome of Recurrent Advanced Head and Neck Squamous Cell Carcinoma

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Abstract. *Background: Locally recurrent rate of advanced head and neck squamous cell carcinoma (HNSCC) still remains high and the treatment is controversial. Patients and Methods: We retrospectively analyzed ninety-three patients with recurrent advanced oral cancer from 2009 to 2013. Sixty-four patients are in the docetaxel with cisplatin and 5'-fluorouracil (TPF) group and the remaining twenty-nine patients are in the cisplatin and 5'-fluorouracil (PF) group. Results: The overall response rate was better in the TPF group (p=0.005) than the PF group. Patients who received induction chemotherapy, TPF, followed by surgery and concurrent chemoradiotherapy (CRT) had better overall survival (OS) (p=0.012) and progression-free survival (PFS) (p=0.038), while patients with prior intra-arterial-infusion-chemotherapy had an adverse impact on OS (p=0.039). Conclusion: We showed that induction chemotherapy with TPF, followed by surgery and consolidation CRT, is the ideal choice for recurrent advanced HNSCC with improving response rates and survival. However, prior intra-arterial-infusion-chemotherapy showed an adverse impact.*

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Key Words: TPF, head and neck cancer, IAIC.

Squamous cell carcinoma (SCC) of the head and neck is one of the most prevalent malignancies in the world. In Taiwan, the incidence is higher than in most other countries. The major reasons may be consumption of alcohol and use of betel quid (1). Other causes of head and neck SCC (HNSCC) are dental procedure and HPV infection (2). The disease is potentially curable at an early stage, but not in an advanced phase. Concurrent chemoradiotherapy (CRT) has largely replaced radiotherapy (RT) alone in the treatment of unresectable HNSCC (3). Taxanes work independently by both sensitizing cancer cells to radiotherapy and direct tumor cell killing (4). Taxanes-containing regimens have been used as induction chemotherapy since 2002. TAX 323 and TAX 324 study group revealed that the TPF (docetaxel, cisplatin and 5'fluorouracil) group showed better overall survival (OS) and progression-free survival (PFS) in a large number of patients with locally advanced HNSCC (5, 6).

Intra-arterial local chemotherapy (IAIC) is another option for treatment of HNSCC, which experienced a revival in the last decade. Mainly, it was used in concurrent combination with radiation or alone. Kovacs *et al*. reported long-term results of IAIC with high-dose cisplatin for oral and oropharyngeal cancer in 2004, showing good local response (69%) and 5 year OS and PFS of 77% and 59%, respectively (7).

Although there have been improvements in the treatment of HNSCC, local-regional recurrence is still problematic

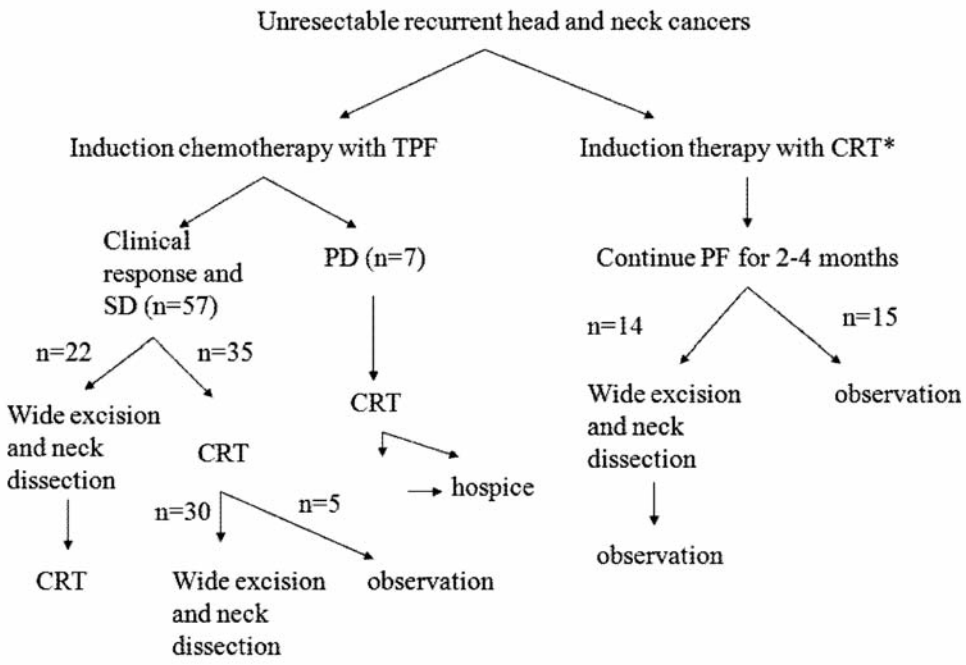

Figure 1. *Treatment Schema. *PF group.*

with an occurrence rate of 20% to 30% (5, 8, 9). For both scenarios, surgical intervention is the preferred treatment. However, not all patients are surgical candidates because of their advanced cancer status.

Although taxanes-containing regimens have improved the response of primary local advanced HNSCC, it is uncertain whether they respond well in recurrent HNSCC. We want to evaluate if taxane-containing regimen has better response in recurrent advanced HNSCC and whether prior treatment for primary cancer, including IAIC, surgery, RT and CRT has an impact on response and survival.

Patients and Methods

Patients' inclusion and treatment plans. This is a retrospective analysis of ninety-three patients with recurrence advanced HNSCC who received induction chemotherapy with TPF *versus* concurrent chemoradiotherapy (CRT) with PF (PF group) between May 2009 and January 2013. Patients had to be at least 18 years old of age with a World Health Organization (WHO) performance status of 0 or 1. From our patient records, the earliest primary oral cancer occurred in December 1988. This study is approved by the Institutional Review Board in Kaohsiung Medical University Hospital. Disease was staged according to the criteria of the American Joint Committee on Cancer, 7th edition (10). Tumor stage was based on computed tomography (CT) scan, Technetium-99m (Tc-99m) MDP bone scan, or/and whole body positron emission tomography (PET) scan.

For patients in the TPF group, we used 60-75 mg docetaxel per square meter of body surface area (mg/m^2), depending on age and performance status, administered over a 2-h intravenous infusion, followed by cisplatin (75 mg/m^2 adjusted by renal clearance rate) or carboplatin (area under the curve, AUC=4, if renal clearance rate less than 60 ml/min) infusion for 4 h on day 1 and a continuously 24 h infusion of 5- fluorouracil (5FU, 750 mg/m^2) for 4 days, every 3 to 5 weeks. The total cycle was 4 cycles of TPF, except one patient who stopped TPF after 3 cycles due to poor liver function. Twenty-two patients in the TPF group received surgery in 7 weeks after complete induction chemotherapy, and followed by CRT as a consolidation therapy after surgery. Thirty patients in the TPF groups who had clinical response (complete response and partial response) or had stable diseases received CRT in 2 months after finishing induction chemotherapy, followed by surgery. The other 5 patients in the TPF groups who had clinical response (complete response and partial response) or had stable diseases received CRT in 2 months after finishing induction chemotherapy, but not surgery because of poor local vessel condition for free flap reconstruction. The regimen of chemotherapy was cisplatin/ carboplatin with 5-FU for CRT.

Patients in the PF group received weekly PF (30 mg/m^2 cisplatin or carboplatin with AUC of 2, and 5- fluorouracil 1,500-2,000 mg/m^2) or monthly PFL (100 mg/m^2 cisplatin or carboplatin with AUC of 4-5, on day 1 and 5FU 1,000 mg/m^2 for 4 days with leucovorin). Total courses were 4 to 6 months. One patient, who died while waiting for RT, didn't receive CRT. Other patients in the PF group received CRT. RT was given with a dose of 45 GY to 72 GY in prior RT, prior CRT and concurrent with PF in the PF group. In order to define the response rate after chemotherapy, we performed the relevant measurements after 3 months of treatment.

We arranged image analysis 3-4 weeks after complete chemotherapy and every 3 months after the first follow-up image study. The response rate was based on the finding on CT scan and Tc-99m MDP bone scan, at diagnosis, at around 4 weeks after

chemotherapy and after complete treatments (TPF followed by concurrent CRT in the TPF group and around 6 months in the non-TPF group). The definition of response rate was based on Response Evaluation Criteris In Solid Tumors (RECIST) criteria (11) and patients who reached CR and PR were defined as "having clinical response". The treatment schema is shown in Figure 1.

The definition of betel nut abuse is the chewing more than 10 pieces for more than 5 years.The definition of alcohol abuse is more than 40 cc of alcohol consumption, at least 5 times a week, for more than 10 years. And the definition of cigarette abuse is smoking more than 1 pack everyday for more than 10 years.

Statistical analysis. We used the SPSS17.0 software for analysis (site or supplier). Pearson Chi-Square was used to compare the response rate between different treatment groups. Response rates was analyzed four weeks after complete chemotherapy. Intra-arterial infusion chemotherapy (IAIC), operation, CRT and RT performed before chemotherapy are used as co-factors to analyze treatment response.

Time-to-event analysis involved estimating the probability that an event will occur at different points in time. The follow-up time for survival was started at the date of diagnosis of recurrent cancers and was ended at the date of death or last observation up to May 6, 2013. The Kaplan-Meier estimates were computed for the risk among different categories and compared by Log-rank tests. We counted OS started from the date of recurrence HNSCC occurrence.

Two sets of hazard rate ratios (HRR) were computed for analysis factors by Cox-regression analyses. The univariate HRRs were estimated from separate Cox-regressions with one analysis factor at a time. The multivariable-adjusted HRRs were computed from Cox-regression with additional variables of treatment groups and prior treatment for primary HNSCC. The primary end point is OS and the secondary end points are PFS and response rate.

Results

Demographics and baseline characteristics. The characteristics of the patients are presented in Table I. Sixty-four patients received TPF treatments and twenty-nine patients received PF treatments with radiotherapy (PF group). The stages of primary HNSCC ranged from stage II to IVC in those patients. Most cancers are in the oral cavity, with about 40% being buccal cancer. Only 5% of the SCCs are in the hypopharynx and oropharynx.

The median age was 54 years. Most of the patients were male with cigarette, betel nut or alcohol abuse, which are clear risk factors for HNSCC. There were no differences between age, sex, tumor site, TNM (tumor-node-metastasis) status, hepatitis B virus and hepatitis C status, habits (cigarette, betel nut and alcohol consumption), previous treatments (including surgery, radiotherapy, IAIC, and CRT), in both groups. However, patients in the TPF group were in a more advanced stage, with more than 95% being in stage IV.

Treatment response and survival. The median follow-up time from recurrence was 14.2 months, from 2 to 49 months. Patients who received TPF as induction chemotherapy showed better response rates with less progression disease

Table I. *Baseline characters of patients*.

	TPF (n=64)	PF (n=29)	Total (n=93)	*p*-Value
	n (%)	n (%)	n (%)	
Gender				0.369
Male	62 (96.88%)	27 (93.10%)	89 (95.70%)	
Female	2 (3.12%)	2 (6.90%)	4 (4.30%)	
Age[a]	54.5 (33~78)	51 (34~74)	54 (33~78)	0.980
Cancer site				0.346
Buccal	28 (43.75%)	11 (37.93%)	39 (41.94%)	
Gingival	5 (7.81%)	1 (3.45%)	6 (6.45%)	
Hypopharyngeal	2 (3.13%)	3 (10.34%)	5 (5.38%)	
Maxillary	2 (3.13%)	1 (3.45%)	3 (3.23%)	
Mouth floor	2 (3.13%)	1 (3.45%)	3 (3.23%)	
Palate	7 (10.94%)	2 (6.90%)	9 (9.68%)	
Tongue	15 (23.44%)	9 (3.10%)	24 (25.81%)	
Tonsil	0	1 (3.45%)	1 (1.08%)	
Double area	2 (3.13%)	0	2 (2.15%)	
Stage				0.016*
II	0	2 (6.90%)	2 (2.15%)	
III	3 (4.69%)	5 (17.24%)	8 (8.60%)	
IVA	40 (62.5%)	15 (51.72%)	55 (59.14%)	
IVB	17 (26.56%)	3 (10.34%)	20 (21.51%)	
IVC	4 (6.25%)	4 (13.79%)	8 (8.60%)	
Tumor status				0.169
T0	3 (4.69%)	1 (3.45%)	4 (4.30%)	
T1	5 (7.81%)	0	5 (5.38%)	
T2	9 (14.06%)	8 (27.59%)	17 (18.28%)	
T3	4 (6.25%)	5 (17.24%)	9 (9.68%)	
T4a	35 (54.69%)	13 (44.83%)	48 (51.61%)	
T4b	8 (12.5%)	2 (6.90%)	10 (10.75%)	
Node status				0.156
N0	11 (17.18%)	8 (27.59%)	19 (20.43%)	
N1	18 (28.13%)	11 (37.93%)	29 (31.18%)	
N2a	9 (14.06%)	0	9 (9.68%)	
N2b	14 (21.88%)	5 (17.24%)	19 (20.43%)	
N2c	5 (7.81%)	4 (13.79%)	9 (9.68%)	
N3	7 (10.94%)	1 (3.45%)	8 (8.60%)	
Metastasis				0.103
M0	60 (93.75%)	24 (82.76%)	84 (90.32%)	
M1	4 (6.25%)	5 (17.24%)	9 (9.68%)	
Virus status				
HBV carrier	10(15.63%)	1 (3.45%)	11 (11.83%)	0.093
HCV carrier	6 (9.38%)	3 (10.34%)	9 (9.68%)	0.553
Habits				
Smoking	57 (89.06%)	26 (89.66%)	83 (89.25%)	0.621
Betel nut	54 (84.38%)	23 (79.31%)	77 (82.80%)	0.373
Alcohol	54 (84.38%)	23 (79.31%)	77 (82.80%)	0.373
Treatment before C/T				
Surgery	24 (37.5%)	14 (48.28%)	38 (40.86%)	0.282
IAIC	30 (46.88%)	12 (41.38%)	42 (45.16%)	0.321
Radiotherapy	31 (48.44%)	13 (44.83%)	44 (47.31%)	0.353
Chemoradiotherapy	16 (25%)	8 (27.59%)	24 (25.81%)	0.542

C/T: Chemotherapy; IAIC: intra-arterial infusion chemotherapy; TPF: regimen with Taxotere+ cisplatin/carboplatin + 5FU. [a]Median age. *Statistical significance ($p<0.05$)

Table II. *Response rate after treatment*.

	TPF (n=64) n (%)		PF (n=29) n (%)		*p*-Value
Overall					0.005*
CR	9 (14.06%)		8 (27.59%)		
PR	23 (35.94%)		4 (13.79%)		
SD	25 (39.06%)		7 (24.14%)		
PD	7 (10.94%)		10 (34.48%)		
Prior IAIC	Yes (32)	No (32)	Yes (12)	No (17)	0.005*
CR	4 (12.5%)	5 (15.63%)	2 (16.67%)	6 (35.29%)	
PR	10 (31.25%)	13 (40.63%)	2 (16.67%)	2 (11.76%)	
SD	15 (46.88%)	10 (31.25%)	1 (8.33%)	6 (35.29%)	
PD	3 (9.38%)	4 (12.5%)	7 (58.33%)	3 (17.65%)	
Prior Surgery	Yes (25)	No (39)	Yes (14)	No (15)	0.01*
CR	5 (20%)	4 (10.26%)	6 (42.86%)	2 (13.33%)	
PR	9 (36%)	14 (35.90%)	2 (14.29%)	2 (13.33%)	
SD	7 (28%)	18 (46.15%)	3 (21.43%)	4 (26.67%)	
PD	4 (16%)	3 (7.69%)	3 (21.43%)	7 (46.67%)	
Prior RT	Yes (33)	No (31)	Yes (16)	No (13)	0.032*
CR	6 (18.18%)	3 (9.68%)	2 (12.5%)	6 (46.15%)	
PR	11 (33.33%)	12 (38.71%)	2 (12.5%)	2 (15.38%)	
SD	14 (42.42%)	11 (35.48%)	3 (18.75%)	4 (26.67%)	
PD	2 (6.06%)	5 (16.13%)	6 (37.5%)	4 (26.67%)	
Prior CRT	Yes (16)	No (48)	Yes (8)	No (21)	<0.001*
CR	1 (6.25%)	8 (16.67%)	5 (62.5%)	3 (14.29%)	
PR	5 (31.25%)	18 (37.5%)	0	4 (19.05%)	
SD	7 (43.75%)	18 (37.5%)	3 (37.5%)	4 (19.05%)	
PD	3 (18.75%)	4 (8.33%)	0	10 (47.62%)	

RT: Radiotherapy; IAIC: intra-arterial infusion chemotherapy; CRT: chemoradiotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progression disease; Using RECIST criteria.

(PD) rate than patients in the PF group (Table II). Patients in the TPF group had a higher clinical response, compare with ones in PF group (50% *vs*. 41.38%). One patient in the TPF group had chemotherapy-induced mortality due to septic shock during a leucopenia status. There was no benefit of OS and PFS in TPF group, compared with the PF group (Figure 2A and 2B). We analyzed the subgroup of the TPF group by two treatment strategies, and noticed that the patients who received TPF as induction chemotherapy, followed by tumor wide excision and neck dissection and subsequently underwent CRT as consolidation therapy, exhibited the best OS (p=0.002; Figure 3A), and better PFS (p=0.144; Figure 3B). Patients received TPF as induction therapy, with clinical response or SD, followed by CRT directly, and then received surgery, showed worst OS and PFS (Figure 3A and 3B).

Subgroup analysis. There was no impact of virus carrier status, old age and life style, (including smoking, alcohol consumption, and betel nut abuse), TNM stage and cancer areas in the response rate after treatments (data not show). As far as the TPF group is concerned we observed a lower OS in patients with HNSCC over the buccal area, gingival area and mouth floor area than in palate and maxillary areas (p=0.025, median OS were 14.3, 8, 5.52 *versus* 28.4, 31.1 months separately). However, there was no difference in PFS between different sites of HNSCC. We also performed a subgroup analysis of OS and PFS according to baseline characteristics, to compare TPF and PF groups. There was neither a clear benefit nor an adverse effect of induction chemotherapy with TPF (Figure 4A and 4B).

The influence from prior treatments. (i) Prior IAIC had an adverse impact on the response of treatments and survival: in the TPF group, 43.75% of patients who received prior IAIC, achieved clinical response, while 56.25% of patients who never received IAIC achieved it only after TPF. In the non-TPF group, 47.06% of the patients were characterized as "having clinical response" if they did not previously have IAIC, whereas only 33.33% of the patients with prior IAIC could be successfully included in this category (Table II).

Based on the Cox-regression analysis of risk factor for OS and PFS, prior IAIC was a risk factor for OS with a hazard ratio (HR) of 2.829 (95% CI=1.051-7.621, p=0.039, Table III) under multivariable analysis. However, there was no impact

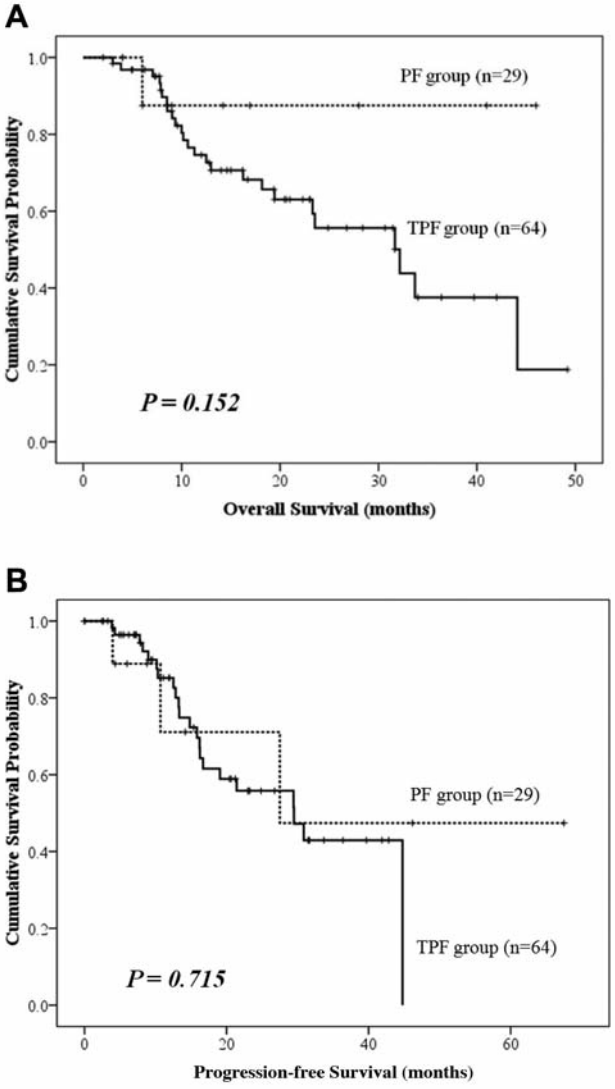

Figure 2. *There is no difference in (A) overall survival (OS), and (B) progression free survival (PFS) between TPF and PF groups. The OS and PFS were started from cancer recurrent date. The median OS of TPF group is 32.167 months (95% CI=18.304-46.030) versus the one of PF group is not reach. Median PFS of TPF group is 29.5 months (95% CI=16.911-42.089 months) versus the one of PF group is 27.5 months.*

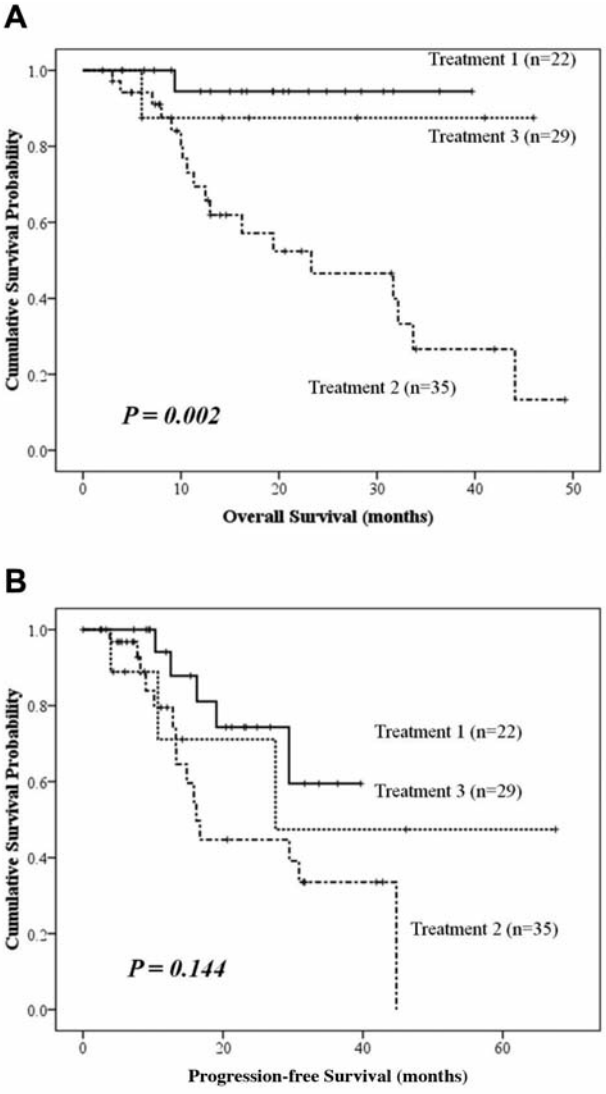

Figure 3. *(A) overall survival (OS) and (B) progression free survival (PFS) in patients received different treatments. Treatment 1: patients in the TPF group who achieved clinical response (CR+PR) and SD, received wide tumor excision and neck dissection after TPF induction chemotherapy, and followed by CCRT as consolidation treatment. Median OS: not reach under 40 months follow-up period. Treatment 2: Patients in the TPF group who achieved clinical response (CR + PR) and SD, received CCRT after 3-4 courses of TPF. Some patients received further wide excision and neck dissection if free flap can re-construction. Median OS: 23.3 months (95% CI=5.067-41.033 months). Treatment 3: patients received CCRT with PF. Median OS: not reach under more than 40 months follow-up period.*

on PFS. (ii) Prior surgical intervention had good effect in the PF group: Patients with previous surgical intervention for their primary HNSCC showed higher clinical response rates in both TPF and PF groups (Table II). However, the PD rate was also high if patients had prior operation in TPF group (16% *versus* 7.69%; Table II). Survival analysis showed that there was no impact on OS and PFS (Table III), using the multivariate analysis approach. (iii) Prior chemoradiotherapy (CRT) showed an adverse effect in the response after TPF, but good impact in PF group: Patients who previously had CRT for primary HNSCC showed less response for TPF, with a CR rate of 6.25% *versus* 16.67% in the PF group, and a more than PR rate of 31.25% *versus* 37.5% (with prior CRT *versus* without prior CRT, p=0.5). The clinical response rate was also better in patients with prior CRT in the PF group (p=0.012, Table

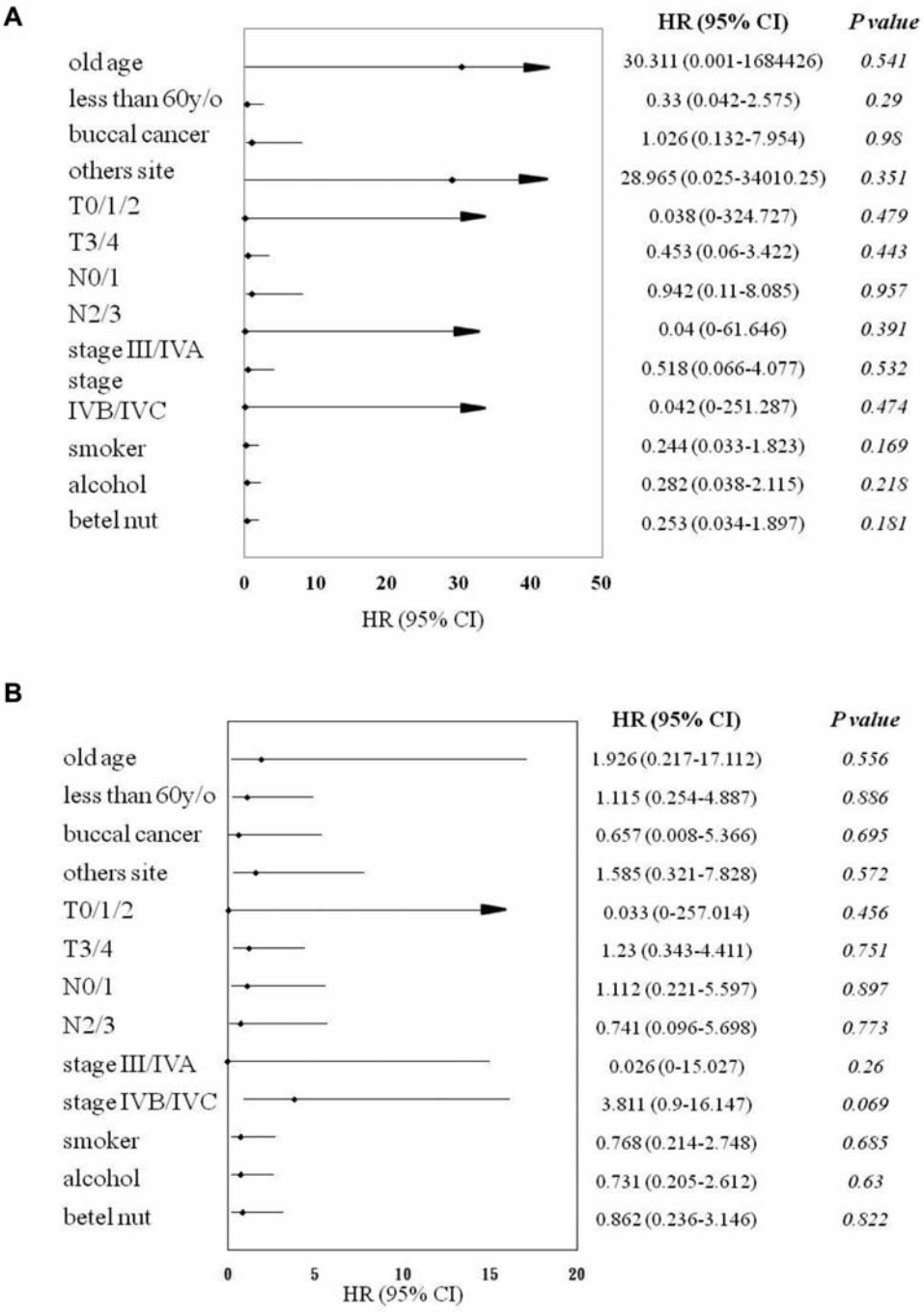

Figure 4. *Subgroup analysis of (A) overall survival and (B) progression free survival in TPF and PF groups. HR, hazard ratio.*

II). However, there was no impact on OS and PFS under multivariable risk factors analysis (Table III). (iv) Prior radiotherapy (RT) showed adverse effect in response, but good impact in OS in the TPF group: Patients with previous RT-alone for primary HNSCC showed better response rate with less PD in the TPF group (6.06% *versus* 16.13%, with prior RT *versus* without prior RT), but opposite incident in the PF groups (37.5% *versus* 26.67%, with prior RT *versus* without prior RT; Table II).

Under the OS and PFS analysis, there was no impact of prior RT on all patients (Table III). However, in the TPF group, prior RT showed a good impact on OS, but not PFS

Table III. *Cox proportional hazard regression of survival*.

Variable	Overall survival				Progression free survival			
	Univariable analysis Hazard ratio (95%CI)	*p*-Value	Multivariable analysis Hazard ratio (95% CI)	*p*-Value	Univariable analysis Hazard ratio (95%CI)	*p*-Value	Multivariable analysis Hazard ratio (95% CI)	*p*-Value
Chemotherapy[a]	3.907 (0.525-29.094)	0.183	5.961 (0.643-55.233)	0.116	0.889 (0.471-1.677)	0.716	2.160 (0.700-6.664)	0.180
TPF followed by surgery[b]	0.219 (0.071-0.681)	0.009*	0.074 (0.01-0.569)	0.012*	0.617 (0.323-1.178)	0.143	0.331 (0.117-0.938)	0.038*
Prior surgery	0.805 (0.355-1.826)	0.604	0.935 (0.348-2.516)	0.895	1.479 (0.674-3.248)	0.329	2.181 (0.936-5.084)	0.071
Prior RT	0.595 (0.271-1.308)	0.196	0.481 (0.18-1.281)	0.143	1.093 (0.487-2.455)	0.829	1.056 (0.396-2.819)	0.913
Prior IAIC	2.184 (0.968-4.93)	0.06	2.829 (1.051-7.612)	0.039*	0.885 (0.396-1.979)	0.767	0.742 (0.294-1.874)	0.527
Prior CRT	1.049 (0.456-2.417)	0.910	0.754 (0.261-2.18)	0.602	1.237 (0.534-2.870)	0.620	0.935 (0.332-2.636)	0.9

RT: Radiotherapy; IAIC: intra-arterial infusion chemotherapy; CRT: chemoradiotherapy. [a]TPF *vs*. PF; [b]TPF followed by surgery and CCRT *vs*. TPF followed by CCRT and with/without surgery. *$p<0.05$.

(OS: HR=0.38; 95% CI=0.153-0.942; $p=0.037$; PFS: HR=0.593; 95% CI=0.232-1.517; $p=0.276$).

Adverse effects. Adverse effects from chemotherapy are shown in Table IV. Concerning the hematological toxicity, patients who received TPF had higher rates of leucopenia ($p=0.007$). However, the occurrence rate of thrombocytopenia was higher in the PF group ($p=0.025$). The occurrence rate of anemia was statistically similar for patients in the two treatment groups. Considering other side-effects, like, infection rate, fatigue due to treatment, cachexia rate, gastro-intestine (GI) toxicity with nausea/vomiting, diarrhea, and constipation, the occurrence rates were similar in both the TPF induction chemotherapy group and the PF group (Table IV).

Table IV. *Adverse effect*.

	TPF (n=64)	PF (n=29)	*p*-Value
	n (%)	n (%)	
Leukocytopenia	49 (76.56%)	15 (51.72%)	0.007*
Grade 3/4	21 (32.81%)	4 (13.79%)	
Anemia	47 (73.44%)	20 (68.97%)	0.336
Need PRBC transplantation	27 (42.19%)	12 (41.38%)	
Thrombocytopenia	28 (43.75%)	18 (62.07%)	0.025*
GI side-effect	16 (25%)	10 (34.48%)	0.242
Fatigue	49 (76.56%)	22 (75.86%)	0.568
Cachexia[a]	28 (43.75%)	13 (44.83%)	0.550
Infection during Chemotherapy	34 (53.13%)	17 (58.62%)	0.395

[a]Defined as lose 10% body weight during chemotherapy treatment (in 6 months). *Statistical significance ($p<0.05$).

Discussion

HNSCC has a higher prevalence in Taiwan than in other countries. For advanced stage disease, it is difficult to receive curative treatment. Management after recurrence has relied on the use of systemic therapy. Platinum-based chemotherapy has been the standard choice of treatment. Although higher response rates are observed with combination treatments, no survival advantage has been demonstrated for any regimen over cisplatin monotherapy, unless combined with the epidermal growth factor receptor antagonist, cetuximab (12, 13). The median progression-free survival (PFS) for patients with recurrent or metastatic disease and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 is reported to be 2 months (13) while the 5-year OS is 36% (14). TAX323 and TAX324 have provided useful information for induction chemotherapy with TPF which can reach a better response rate and survival (5, 6). The patients in TAX323 and TAX324 trials had advanced HNSCC without previous chemotherapy or radiotherapy, and no cancer diagnosis within the previous 5 years, and no previous definitive surgery for HNSCC. The overall response rate was 72%, with a CR rate of 17%, in the TPF group (5). In the group of recurrent advanced HNSCC patients we studied, TPF did increase response rate, compared to that of the PF group ($p=0.05$). However, our study showed CR rates of 14.06% and more than PR rate of 35.94% in the TPF group, which were lower than the rates of the TAX323 and 324 trials. This discrepancy could be related to resistance to chemotherapy in recurrent HNSCC, while most of the patients received cisplatin and 5-FU as primary chemotherapy for previous HNSCC. Based on our analysis, patients with HNSCC over the buccal area, gingival and mouth floor area showed worse survival. The major population of our patients comprises buccal cancer patients (43.75% in the TPF and 37.93% in the PF group), which may account for less response to chemotherapy.

Zhong *et al*. reported a randomized phase III trial of induction chemotherapy with TPF for 2 cycles, followed by surgery, compared with up-front surgery in locally-advanced resectable oral squamous cell carcinoma. They

showed that there was no benefit of induction chemotherapy with TPF in survival (15). We also noticed that TPF did not improve OS and PFS, but we observed a trend of worsening survival. When we separated TPF to two groups *i.e.* induction TPF, followed by surgery, then CRT (treatment 1) and induction TPF, followed by CRT, with or without surgery (treatment 2), there was benefit on OS and PFS in treatment 1 (Table III, Figure 3A and 3B). This may be explained by the difficulty to cure recurrent HNSCC by non-surgical intervention, even with CR under image study. High and rapid re-recurrence would take place without surgery with wide excision and neck dissection. This may be due to the fact that local resection could remove residual cancer, including cancer stem cells. Chiou *et al.* reported that oral cancer patients with Nanog/Oct-4/CD133 triple positive oral cancer stem-like cells had the worst survival prognosis (16). For patients without surgical intervention, it is possible that they may retain cancer cells or cancer stem-like cells, that may not be detected influencing thus overall survival.

Previous treatment choices for primary head and neck cancer influenced the response of chemotherapy in recurrent cancers, and had an impact on survival. In this work, prior IAIC showed adverse impact on the response rate of chemotherapy and OS. This is possibly because of the local infusion high-dose chemotherapy that may induce local arterial and capillary injury, which can then decrease local perfusion. On the other hand, the chemotherapy agents used in IAIC were the same as those used in systemic chemotherapy, *i.e.* cisplatin, methotrexate, and 5FU, which could induce drug resistance of cancer cells. We also analyzed if prior IAIC duration was one of the factors influencing the treatment response to recurrent or second primary HNSCCbut no impact was found (data not shown).

In the TPF group, prior RT showed good impact, while prior CRT showed adverse impact on response rate. Prior RT also showed independent good prognostic factor for OS, but not PFS. This may also be related to cancer cell resistant to previous chemotherapy, but not radiotherapy.

In the PF group, prior surgery and previous CRT had good impact, when prior RT showed adverse impact on response rate. However, there was no impact on survival analysis. Patients in our PF group received CRT again. Prior RT may induce local skin fibrosis and vessel damage, which may reduce the effect from 2nd CRT. Radiation also would increase hypoxia inducible factor -1 (HIF-1) (17), which is related to chemotherapy and further radiotherapy resistance (18). Due to the fact that patients rested from prior RT for more than 2 years, they still had good impact on the PFS and OS in the TPF group, even without good response rate in patients with prior radiotherapy, but not in the PF group. However, prior surgery may clean most of the cancer cells, including cancer stem cells, that may cause less resistant rate from further CRT with PF. In patients who received prior CRT, the stage of cancer was less advanced ranging from stage II to IVa, compared to patients who did not receive previous CRT (majority with stage IVa and IVb) (data not shown).

This and similar studies are limited by the patient number, especially in the PF group. The present work is a retrospective study, which was not randomized. However, we continue to clinically follow-up these patients and enroll more patients in both groups.

We showed a benefit on treatment response rate of induction chemotherapy with TPF, compared to CRT with PF, in recurrent advanced HNSCC. We also reported a survival benefit on OS and PFS in patients received induction chemotherapy with TPF, followed by wide excision and neck dissection, and CRT. Oral squamous cell carcinoma over the buccal area, gingival area and mouth floor showed poor prognosis under TPF treatments. Finally, prior IAIC showed adverse impact on treatment response and survival.

Conflicts of Interest

The Authors declare no financial and/or personal relationship with other organizations.

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