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ORIGINAL ARTICLE

Induction chemotherapy with dose-modified docetaxel, cisplatin, and 5-fluorouracil in Asian patients with borderline resectable or unresectable head and neck cancer

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Background: Significant ethnic differences in susceptibility to the effects of chemotherapy exist. Here, we retrospectively analyzed the safety and efficacy of induction chemotherapy (ICT) with dose-modified docetaxel, cisplatin, and 5-fluorouracil (TPF) in Asian patients with borderline resectable or unresectable head and neck squamous cell carcinoma (HNSCC).
Methods: Based on the incidence of adverse events that occurred during daily practice, TPF_{90} (90% of the original TPF dosage; docetaxel 67.5 mg/m^2 on Day 1, cisplatin 67.5 mg/m^2 on Day 1, and 5-fluorouracil 675 mg/m^2 on Days 1–5) was used for HNSCC patients who were scheduled to receive ICT TPF.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Results: Between March 2011 and May 2014, 52 consecutive patients with borderline resectable or unresectable HNSCC were treated with ICT TPF_{90} followed by concurrent chemoradiotherapy. Forty-four patients (84.6%) received at least three cycles of ICT TPF_{90}. The most commonly observed Grade 3–4 adverse events included neutropenia (35%), anemia (25%), stomatitis (35%), diarrhea (16%), and infections (13.5%). In an intention-to-treat analysis, the complete and partial response rates after ICT TPF_{90} were 13.5% and 59.6%, respectively. The complete and partial response rates following radiotherapy and salvage surgery were 42.3% and 25.0%, respectively. The estimated 3-year overall survival and progression-free survival rates were 41% [95% confidence interval (CI): 25–56%] and 23% (95% CI: 10–39%), respectively. The observed median overall survival and progression-free survival were 21.0 months (95% CI: 13.3–28.7 months) and 16.0 months (95% CI: 10.7–21.3 months), respectively.
Conclusion: TPF_{90} is a suitable option for Asian patients with borderline resectable or unresectable HNSCC who are scheduled for ICT.

Introduction

The combination of radiotherapy (RT) and chemotherapy (CT) may improve the clinical outcomes of patients with head and neck squamous cell carcinoma (HNSCC). In this regard, the meta-analysis of CT in head and neck cancer demonstrated that concomitant chemoradiotherapy (CCRT) confers an absolute benefit of 6.5% [hazard ratio, 0.81; 95% confidence interval (CI), 0.78–0.86; $p < 0.001$] at 5 years.[1] In contrast, induction CT (ICT) schedules do not generally show any positive impact on overall survival (OS), the only exception being the combination of cisplatin and 5-fluorouracil (PF).[1] Although Phase III ICT trials in HNSCC patients reported that a triple regimen comprising docetaxel, cisplatin, and 5-fluorouracil (TPF) is superior to PF in terms of clinical response and survival rates,[2–4] randomized trials do not provide strong support for the use of ICT.[5,6] In this scenario, the potential benefits of ICT in the clinical management of HNSCC patients remain a matter of debate. These observations notwithstanding, ICT continues to be commonly used for HNSCC patients.

In the era of organ-function preservation, the long-term results of the RTOG 91–11 and GORTEC 2000–01 studies demonstrated the clinical usefulness of ICT followed by RT in patients with advanced larynx or hypopharynx squamous cell carcinomas.[7,8] Other potential clinical advantages of ICT include the following: (1) reduction in symptoms and functional improvement before RT; (2) accelerated tumor shrinkage that can reduce the need for urgent maneuvers (e.g., tracheostomy for airway obstruction, tube feeding for swallowing problems); (3) acting as an effective bridge before definitive treatment when RT cannot be initiated immediately; (4) clearance of micrometastases; and (5) *in vivo* assessment of treatment response that may guide subsequent therapeutic interventions. Such potential advantages are paramount in the clinical management of patients with unresectable HNSCC, for whom ICT may confer a survival benefit.[9] In light of these findings, the Taiwanese National Health Insurance implemented (as of 2011) a reimbursement program for ICT TPF performed in patients with unresectable HNSCC.

Unfortunately, ICT TPF can be associated with serious side effects, including subsequent inability to undergo definitive therapy and deaths, in a substantial proportion of patients with advanced HNSCC (especially in those with a low socioeconomic status and poor general conditions).[10] Significant ethnic differences in susceptibility to the effects of docetaxel exist, with Asian patients having a 19-fold increased risk of docetaxel-induced severe neutropenia compared with non-Asian individuals.[11] Consequently, docetaxel dose reduction has been proposed in Asian HNSCC patients.[12,13] Another point that merits consideration is the high prevalence of betel quid chewing in the Taiwanese population, with > 80% of HNSCC patients being betel quid chewers. Notably, the incidence of severe (≥ Grade 3) mucositis in Taiwanese patients treated with ICT PF is significantly higher (approx. 40%) than that observed in Western populations (8–11%),[14] possibly because of betel quid chewing-related mucosa damage.[14,15] In this scenario, a dosage adjustment optimization that can protect against toxicity without reducing the efficacy of treatment would be of paramount importance. We therefore presented the safety and efficacy of dose-modified ICT TPF in Asian patients with borderline resectable or unresectable HNSCC.

Materials and methods

Patients

TPF was reimbursed for unresectable HNSCC by the Taiwan National Health Insurance since January 2011. Since then, patients with biopsy-proven HNSCC judged to be borderline resectable or unresectable by a multidisciplinary tumor board were enrolled if their consent to ICT TPF was obtained. All patients were staged according to the American Joint Committee on Cancer 2010 staging criteria.[16] Patients had to meet the following criteria to receive ICT TPF: (1) age ≤ 70 years; (2) Eastern Cooperative Oncology Group performance status between 0 and 2; (3) adequate bone marrow function (leukocyte count ≥ 4000/L; platelet count ≥ 100,000/L); and (4) acceptable renal (serum creatinine < 2.0 mg/dL) and liver (total bilirubin ≤ 1.5 × the upper limit of normal; serum glutamic

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oxaloacetic transaminase and serum glutamic pyruvic transaminase $\leq 2.5 \times$ the upper limit of normal) function. Exclusion criteria were as follows: (1) presence of distant metastases; (2) previous history of malignancies, CT, or RT; (3) serious concomitant illness (e.g., liver cirrhosis, angina, or myocardial disease); and (4) active uncontrolled infections. Written informed consent was obtained from all the patients before therapy. This retrospective analysis was approved by the local Institutional Review Board.

Dose-modified TPF regimen

The standard TPF regimen,[2] consisting of docetaxel (Sanofi-Aventis, Paris, France, or TTY BioPharm Co. Ltd., Taipei, Taiwan) at a dose of 75 mg/m^2 given as a 1-hour infusion on Day 1, followed by cisplatin at a dose of 75 mg/m^2 administered as a 2-hour infusion on Day 1, and 5-fluorouracil at a dose of 750 mg/m^2/d given by continuous infusion on Days 1–5, was used for reimbursed daily practice. However, two patients experienced neutropenic fever and one patient had Grade 3 diarrhea in our first six patients who received the standard TPF dosage. The dosage of TPF was then de-escalated to 90% of the original TPF dosage (TPF_{90}) (consisting of docetaxel 67.5 mg/m^2 on Day 1, cisplatin 67.5 mg/m^2 on Day 1, and 5-fluorouracil at a dose of 675 mg/m^2/d on Days 1–5) for the following six patients. One patient experienced two episodes of upper gastrointestinal bleeding of unknown cause during the two ICT TPF_{90} cycles. No other severe adverse event was observed in other patients of this cohort. In accordance with the above observation, TPF_{90} was recommended for the following patients who were scheduled to receive ICT TPF.

Treatment design

ICT TPF_{90} was administered every 3 weeks (defined as 1 cycle) for up to three to four cycles. However, the treatment was stopped in the presence of the following conditions: (1) progressive disease; (2) unacceptable adverse events occurring during the first or the second cycle; and (3) withdrawal from the study. Ciprofloxacin prophylaxis (500 mg orally twice a day) was performed from Day 8 to Day 14 of each cycle for their possible effect on the decrement of infection.[2,17] Granulocyte colony-stimulating factor was permitted only in patients with febrile neutropenia or infections. Patients who experienced $\geq$ Grade 3 neutropenia in previous treatment would receive reduced-dosage TPF rather than prophylactic granulocyte colony-stimulating factor.

Patients who received ICT TPF at the recommended dosage were allowed to delay the next cycle until the severity of adverse events resolved to $\leq$ Grade 1. However, delays of 2 weeks or longer were considered as treatment discontinuations. Dose modifications in subsequent cycles were required in presence of Grade 3 toxicity (the only exceptions being the onset of alopecia, fatigue, malaise, and nail changes). We planned a 10% parallel dose de-escalation of each agent at each step of dose modification. However, we did not perform docetaxel dose reductions when adverse events were obviously caused by cisplatin (e.g., nephrotoxicity) or 5-fluorouracil (e.g., mucositis). Because TPF differs from PF in terms of docetaxel use, the TPF dose level was calculated in relation to docetaxel dosing. Patients who required a dose reduction to less than 80% of the original TPF dosage (TPF_{80}) were withdrawn from the ICT schedule. Following ICT, patients were scheduled to receive weekly cisplatin 40 mg/m^2 with concurrent RT. However, the CT regimens could be changed at the physician's discretion in patients with disease progression or poor general conditions because of ICT.

External beam RT (6 MV X-rays) was delivered through intensity-modulated techniques. Patients received 2.0 Gy/fraction once daily, 5 fractions per week. The gross target volume (GTV) was defined according to both nasopharyngolaryngoscope and imaging findings (magnetic resonance imaging, computed tomography, and ^{18}F-fluorodeoxyglucose-positron emission tomography). The prophylactic clinical target volume was initially designed to include the neck lymphatics at risk and all the tissue located within 1 cm of the GTV (dose: 46–50 Gy). Subsequently, the radiation field was restricted to the GTV, the tissue located within 0.5 cm of the GTV, and the grossly involved nodal area (dose: 70–76 Gy). The maximal dose allowed for spinal cord and brain stem irradiation was 50–60 Gy. The mean dose for parotid sparing was limited to 23 Gy, whereas uninvolved constrict muscles did not receive more than 56 Gy whenever possible.

Salvage surgery for resectable residual disease was performed between 6 weeks and 12 weeks following CCRT termination. Patients who had N2 or N3 nodal disease at the initial presentation and showed complete responses to CCRT did not undergo elective neck dissection.

Tumor clinical assessments were performed every 3 weeks throughout the entire ICT treatment period. Head and neck imaging (computed tomography or magnetic resonance imaging) was scheduled: (1) at the end of ICT TPF; (2) following CCRT; and (3) in patients who showed disease progression. Post-CCRT monitoring was performed on a monthly basis during the 1st year, every 2 months during the 2nd year, every 3 months during the 3rd year, and every 6 months thereafter (until the date of data censoring or death).

Statistical analysis

Time-to-event endpoints were calculated from the beginning of ICT TPF_{90} to the time of death from any cause (OS) or the time to disease progression, relapse, or death from any cause (progression-free survival, PFS). All time-to-event endpoints were analyzed on an intention-to-treat basis. Time-to-event data were plotted using the Kaplan–Meier method (log-rank test). Adverse events were analyzed in the safety population who received at least one ICT TPF_{90} cycle. All calculations were performed using the SPSS statistical package, version 18.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 (two tailed) was considered statistically significant.

Results

Between March 2011 and May 2014, a total of 52 consecutive patients who received ICT TPF_{90} were examined.

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Patients were censored on May 2015 (corresponding to at least 1 year of follow up for the last patient included in the study). Table 1 shows the general features of the 52 study patients. Fifty patients (96.2%) were males, and the most common primary tumor site was the oropharynx (44.2%). Forty-six patients (88.5%) had T4 disease and 44 (84.7%) patients had N2–N3 disease. All the patients had Stage IV disease. Tumors were deemed to be borderline resectable and unresectable in 18 (34.6%) and 34 (65.4%) patients, respectively.

Forty-four patients (84.6%) received at least three cycles of ICT with modified TPF (TPFm). The remaining patients received $\leq$ 2 cycles of TPFm for the following reasons: death from unknown cause (n = 1), disease progression (n = 2), neutropenic fever and fatigue (n = 1), tumor bleeding (n = 1), acute renal failure (n = 1), severe mucositis (n = 1), and patient's own decision (n = 1). Patients who received at least one cycle of TPF_{90} were included in the safety analysis (Table 2). Grade 3–4 adverse events, which occurred in at least 10% of the study patients, were as follows: neutropenia (35%), anemia (25%), stomatitis (35%), diarrhea (16%), and infections (13.5%). Five of the seven patients (13.5%) who experienced infections also had neutropenia. One patient who did not develop any obvious adverse event (as assessed in the patient's 1st clinical visit performed after the initial TPF_{90} cycle) died at home of unknown cause on the 9th day of ICT. The TPFm cycles were administered at a median interval of 23 days (range: 20–31 days). Treatment delays of $\geq$ 7 days were identified in 17 patients (32.7%). The reasons for treatment delays included the occurrence of adverse events in eight patients (15.4%) and other reasons (mainly related to administration issues) in the remaining nine patients (17.3%). Thirteen patients (25%) had their dose reduced from TPF_{90} to TPF_{80} for their second ICT cycle. Dose reductions were mainly due to the occurrence of nonhematologic adverse events. Forty-two (80.8%) patients had either gained weight or maintained their body weight at the end of ICT.

The intention-to-treat overall response rate (RR) after ICT TPF_{90} was 73.1%, with the complete response (CR) and partial response (PR) rates being 13.5% (7 patients) and 59.6% (31 patients), respectively.

Eight patients (15.4%) did not receive the originally scheduled RT following ICT TPF_{90} for the following reasons: consent withdrawal (n = 5), suspected lung metastasis (n = 1), surgery (n = 1), and death (n = 1). Forty-four patients (84.6%) received post-ICT CCRT. The median time interval between the finish of the last ICT TPF to the start of RT was 20.5 days (range, 0–56 days). The CT schemes

Table 1 Characteristics of TPF_{90} intention-to-treat population.

Characteristics	n	Percentage
Sex		
Male	50	96.2
Female	2	3.8
Age (y)		
Median (range)	48 (33–66)	
ECOG performance status		
0	9	17.3
1	40	76.9
2	3	5.8
Tumor site		
Oropharynx cancer	23	44.2
Oral cavity cancer	16	30.8
Hypopharynx cancer	10	19.2
Paranasal sinus cancer	3	5.8
Pathologic differentiation		
Well	5	9.6
Moderate	26	50.0
Poor	7	13.5
NA	14	26.9
Tumor status		
T1	3	5.8
T2	2	3.8
T3	1	1.9
T4A	24	46.2
T4B	22	42.3
Node status		
N0	4	7.7
N1	4	7.7
N2	33	63.5
N3	11	21.2
Stage		
IVA	22	42.3
IVB	30	57.7
Resectability		
Borderline resectable	18	34.6
Unresectable	34	65.4

ECOG = Eastern Cooperative Oncology Group; NA = not assessed; TPF_{90} = 90% dose of the original docetaxel–cisplatin–fluorouracil regimen.

Table 2 Adverse events observed in the study.

Event/NCI CTCAE 3.0 grading	0	1	2	3	4
During induction chemotherapy (n = 52; %)					
Neutropenia	23	14	28	14	21
Anemia	2	46	27	19	6
Thrombocytopenia	73	27	0	0	0
Vomiting	67	12	12	9	0
Stomatitis	21	6	38	33	2
Diarrhea	42	21	21	16	0
Renal insufficiency	73	15	6	2	4
Liver dysfunction	31	52	11	6	0
During radiotherapy concomitant with cisplatin 40 mg/m^2 weekly (n = 27; %)					
Neutropenia	37	18	26	15	4
Anemia	4	26	40	26	4
Thrombocytopenia	18	56	15	11	0
Vomiting	74	11	11	4	0
Stomatitis	0	0	22	63	15
Dermatitis	8	44	33	15	0
Diarrhea	96	4	0	0	0
Renal insufficiency	66	30	4	0	0
Liver dysfunction	70	22	4	4	0

NCI CTCAE 3.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

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Table 3 Postinduction chemoradiotherapy and the compliance ($n = 44$).

Clinical scenario	n	Drugs during radiotherapy	Drugs cycles	Radiotherapy > 60 Gy (n)
Per protocol	27	Cisplatin 40 mg/m^2/wk	4.5 (median)	26
Fatigue	6	Cisplatin 30 mg/m^2/wk	1, 1, 2, 3, 5, 8	6
Renal insufficiency	4	Carboplatin (AUC = 2)[a]	2, 2, 5, 6	4
Neuropathy	2	Cetuximab[b]	5, 8	2
Postsurgery	1	Cetuximab[b] + docetaxel[c]	7	1
Physician's discretion	4	Others[d]	1, 5, 5, 7	4

[a] Area under curve (AUC) used in the Calvert's formula to calculate the dose of carboplatin.
[b] Initial dose of 400 mg/m^{2}followed by subsequent doses of 250 mg/m^2/wk.
[c] Docetaxel 15 mg/m^2/wk.
[d] Others: methotrexate or paclitaxel.

and therapeutic compliance are summarized in Table 3. The median duration of RT was 52 days (range: 38–75 days) with a median dosage of 72 Gy (range: 56–80.2 Gy). Only one patient who died of pneumonia within 30 days of the end of CCRT received an RT dose of < 60 Gy.

The intention-to-treat overall RR after CCRT was 65.3%. The CR and PR rates were 28.8% (15 patients) and 36.5% (19 patients), respectively. Seven patients (13.5%) received salvage surgery for the presence of residual disease (2 patients at lymph nodes only and 5 patients at both the primary tumor and the nodes). After salvage surgery, the intention-to-treat overall RR was 67.3%, with CR and PR rates being 42.3% (22 patients) and 25.0% (13 patients), respectively.

In the last survival analysis performed in May 2015, the median follow-up time of the 21 surviving patients was 34 months. The median OS and PFS durations were 21 months (95% CI: 14–28 months) and 16 months (95% CI: 11–21 months), respectively (Figures 1 and 2). The estimated 3-year OS and PFS rates were 41% (95% CI: 25–56%) and 23% (95% CI: 10–39%), respectively. Treatment failures occurred in 34 patients (65%). Initial failures had the following distribution: locoregional failure ($n = 20$; 38%); locoregional and distant failure ($n = 4$; 8%); distant failure only ($n = 6$; 11%);

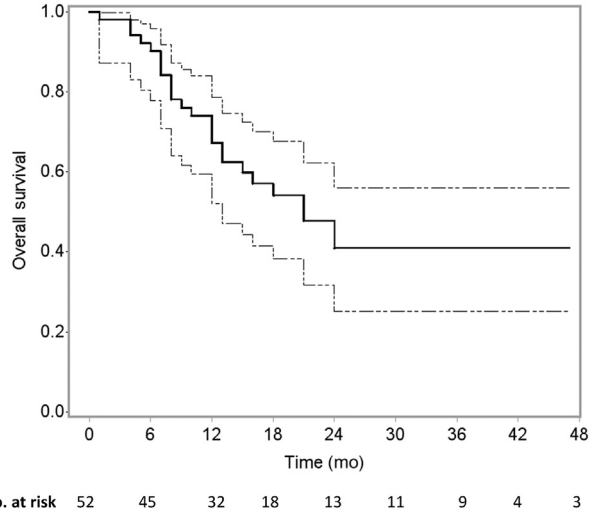

Figure 1 Kaplan–Meier plots of overall survival (patients at risk and 95% confidence intervals are depicted).

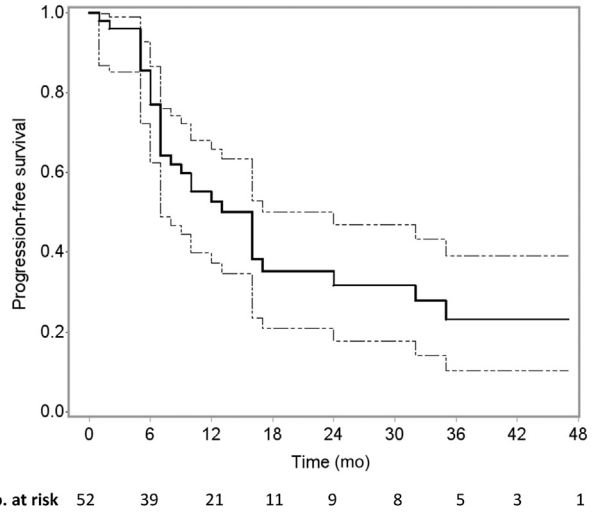

Figure 2 Kaplan–Meier plots of progression-free survival (patients at risk and 95% confidence intervals are depicted).

second primary tumor failure ($n = 1$; 2%); and early withdrawal according to the study protocol ($n = 3$; 6%).

Discussion

A proper selection of candidates is paramount to optimize the success of ICT. In accordance with our treatment guideline, ICT TPF was specifically focused on patients with borderline resectable or unresectable HNSCC because they can potentially benefit from this approach.[18] However, the classification of a tumor as either borderline resectable or unresectable is not univocal and may be physician dependent. Herein, our multidisciplinary tumor board considered a tumor as borderline resectable or unresectable when the following criteria were met: (1) presence of very advanced local disease according to the American Joint Committee on Cancer 2010 staging criteria (pharyngeal tumors)[16]; (2) tumor invasion occurring above the mandibular notch in patients with oral cancer[19]; (3) marked central compartment involvement; and (4) presence of N3 disease. Patients who met such stringent criteria are deemed to have a poor prognosis.

Another critical issue is the proper selection of the TPF regimen. Two different ICT TPF dosages have been reported in the literature.[2,17] The combined regimen of docetaxel

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75 mg/m^2 on Day 1, cisplatin 75 mg/m^2 on Day 1, and 5-fluorouracil 750 mg/m^2/d on Days 1–5 was used by the TAX 323 study group.[2] However, the TAX 324 study group utilized the following scheme: docetaxel 75 mg/m^2 on Day 1, cisplatin 100 mg/m^2 on Day 1, and 5-fluorouracil 1000 mg/m^2/d on Days 1–4.[17] As 5-fluorouracil at a dose of 1000 mg/m^2/d has been shown to cause a high incidence of stomatitis at 96–120 hours of infusion in our patients,[14,15] we selected the TAX 323 trial dosage as the reference regimen (TPF$_{100}$). TPF$_{90}$ was then selected as the optimal dosage for ICT TPF in our clinical scenario. The observation that 25% ($<$ 33%) of the treated patients required a dose reduction from TPF$_{90}$ to TPF$_{80}$ during the second ICT cycle supported the clinical feasibility of TPF$_{90}$ as an ICT regimen.

The exact number of ICT cycles to be conducted before locoregional therapy has not been clearly established. In general, three to four cycles of ICT are required to ensure optimal clinical results,[20] but the total number may vary according to the RRs and the incidence of adverse events. Herein, 44 patients (84.6%) received $\geq$ 3 ICT TPFm cycles. The methodology used in the current study (including the patient population and the TPF regimen) is similar to that of the TAX 323 trial.[2] The major Grade 3–4 adverse events observed in our study and in the TAX 323 trial were as follows: neutropenia 35% versus 77%; anemia 25% versus 9%; stomatitis 35% versus 5%; diarrhea 16% versus 3%; and infections 13.5% versus 6.9%. Despite a lower incidence of neutropenia, severe stomatitis and diarrhea occurred at a relatively high frequency in our patients. As betel quid chewing-related changes in the oral mucosa cannot easily explain these observations, we believe that they may be dependent on ethnic or genetic factors that warrant further scrutiny.

In this study, TPF$_{90}$ cycles were administered at a median interval of 23 days from each other (range: 20–31 days), and the dose intensity was 82% of the original TPF regimen. The dose intensity of cisplatin can have an impact on the clinical outcomes of HNSCC patients undergoing CCRT.[21,22] However, the question as to whether the dose intensity of ICT TPF can affect the therapeutic results remains open. Despite using an ICT TPF regimen with a lower dose intensity, the CR and PR rates observed in our intention-to-treat population (13.5% and 59.6%, respectively) were similar to those reported in the TAX 323 trial (8.5% and 59.3%, respectively).

In general, disease control is largely dependent on an effective post-ICT locoregional therapy (mainly RT or CCRT for unresectable HNSCC). However, a substantial proportion of patients with unresectable disease did not receive RT in the current study (mainly because of disease progression or the onset of ICT TPF-related adverse events). It is nonetheless worth noting that only 15.4% of our patients were not treated with RT, a substantially lower proportion than those reported (27–31%) in previous ICT TPF trials conducted in patients with unresectable HNSCC.[2,23]

The CT regimen used for post-ICT CCRT is another critical determinant of outcomes in patients with advanced HNSCC. In the current study, weekly cisplatin 40 mg/m^2 was used in combination with RT (a commonly used alternative to 3-weekly cisplatin 100 mg/m^2 in Asian countries).[24] Using weekly cisplatin 40 mg/m^2, the major Grade 3–4 adverse events of CCRT observed after ICT TPF compared with our postsurgery adjuvant setting were as follows: neutropenia 29% versus 12%, anemia 30% versus 9%, stomatitis 78% versus 67%, and dermatitis 15% versus 6%.[25] These data suggest that ICT TPF may increase the severity of adverse events of the following CCRT. Although previous studies utilized different approaches (i.e., RT alone, CCRT with various CT regimens, and bioradiotherapy with cetuximab),[2,5,6,17,26,27] the optimal strategy for minimizing treatment-related morbidity has not been yet identified.

Herein, the estimated 3-year OS and PFS rates were 41% and 23%, respectively (Figures 1 and 2), with the median OS and PFS durations being 21.0 months and 16.0 months, respectively. The ICT TPF arm included in the TAX 323 trial showed an OS rate of 37% and a median OS of 18.8 months.[2] Moreover, the Spanish Head and Neck Cancer Cooperative Group (TTCC) trial reported median OS and PFS durations of 27.0 months and 14.6 months, respectively.[23] The different number and characteristics of the study patients may, at least in part, explain the observed differences in survival rates. In the current study, 13.5% of patients who underwent ICT TPF were surgically salvaged. The use of salvage surgery in the TAX 323 and TTCC trials was 15.3% and 27.1%, respectively, suggesting important differences in the study participants. A previous Taiwanese retrospective study conducted in patients with unresectable tumors or candidates for organ preservation who were treated with ICT at a dose similar to TPF$_{80}$ reported a median PFS of 435 days.[12]

Twenty-three (44%) of our patients had oropharyngeal cancer. Twelve patients were examined for p16 expression by immunohistochemistry, and three (25%) of them had strong diffuse nuclear and cytoplasmic immunohistochemistry staining of p16 in more than 70% of tumor cells. Such patients were considered to have human papillomavirus (HPV)-related HNSCC.[28] No positive p16 staining was observed in the remaining nine patients. The three HPV-positive patients had T4 disease, ultimately being at high risk according to the refined American Joint Committee on Cancer criteria for HPV-related oropharyngeal squamous cell carcinoma.[29] All of them died of disease with an OS of 4 months, 8 months, and 21 months. In Taiwan, the incidence of HPV-related site HNSCC (1.3/100,000 in 1995 to 3.3/100,000 in 2009, annual percentage change 56.9, $p < 0.0001$) has increased more rapidly than that of HPV-unrelated site HNSCC (10.4/100,000 in 1995 to 21.7/100,000 in 2009, annual percentage change 55.0, $p < 0.0001$).[30] However, the HPV-positive rates in Taiwan (13–17%) remain significantly lower than those reported in industrialized countries.[31,32] In this context, optimization of intensive therapeutic approaches with an acceptable burden of adverse events is paramount, especially for HPV-unrelated HNSCC patients.

In conclusion, our experience indicates that TPF$_{90}$ is a suitable option for Asian patients with borderline resectable or unresectable HNSCC who are scheduled for ICT TPF. Despite the reduced dosage, such an approach allowed us to achieve survival figures similar to those reported for the original dose regimen. However, we acknowledge the shortcomings of our report. The dose reduction to 90% was not through a Phase I study and was chosen in accordance with the adverse events in a small number of patients. Can a dose reduction of more than 10% further reduce the

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adverse effects and have a comparative efficacy? Future studies aiming at both identifying the ideal candidates for ICT TPF and optimizing the balance between its efficacy and toxicity are needed.

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