Preliminary Results of NPC-0501 Trial to Evaluate the Therapeutic Gain by Changing Chemoradiotherapy from Concurrent-Adjuvant to Induction-Concurrent Sequence, Radiotherapy from Conventional to Accelerated Fractionation, and Fluorouracil to Capecitabine for Locoregionally Advanced Nasopharyngeal Carcinoma

Journal:	*Cancer*
Manuscript ID:	CNCR-14-2474.R1
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Lee, Anne W.M.; the Univeristy of Hong Kong (Shenzhen) Hospital, Clinical Oncology NGAN, Roger; Queen ELizabeth Hospital, Department of Clinical Oncology Tung, Stewart Y.; Tuen Mun Hospital, Clinical Oncology Cheng, Ashley; Princess Margaret Hospital, Departments of Clinical Oncology Kwong, Dora; University of Hong Kong, Clinical Oncology Lu, Taixiang; Cancer Center of Sun Yat-Sen University, ; State Key Laboratory of Oncology in Southern China, Chan, Anthony; Chinese University of Hong Kong, Clinical Oncology Chan, Lucy L K; Pamela Youde Nethersole Eastern Hospital, Departments of Clinical Oncology Yiu, Harry; Queen Elizabeth Hospital, Departments of Clinical Oncology Ng, Wai-Tong; Pamela Youde Nethersole Eastern Hospital, Wong, Frank; Tuen Mun Hospital, Clinical Oncology Yuen, Kam-Tong; Princess Margaret Hospital, Departments of Clinical Oncology Yau, Stephen; Queen ELizabeth Hospital, Department of Clinical Oncology Cheung, Foon-Yiu; Queen ELizabeth Hospital, Department of Clinical Oncology Chan, Oscar; Pamela Youde Nethersole Eastern Hospital, Choi, Horace; University of Hong Kong, School of Public Health Chappell, Rick; University of Wisconsin Medical School, Department of Biostatistics
Keywords:	nasopharyngeal carcinoma, randomized controlled trial, chemoradiotherapy, capecitabine, accelerated fractionation

Original Article

Preliminary Results of NPC-0501 Trial to Evaluate the Therapeutic Gain by Changing Chemoradiotherapy Sequence from Concurrent-Adjuvant to Induction-Concurrent, Fluorouracil to Capecitabine, and Radiotherapy Fractionation from Conventional to Accelerated for Locoregionally Advanced Nasopharyngeal Carcinoma

Anne Lee, MD[1]; Roger Ngan, FRCR[2]; Stewart Tung, FRCR[3]; Ashley Cheng, FRCR[4]; Dora Kwong, MD[5]; Tai-Xiang Lu, MD[6]; Anthony Chan, MD[7]; Lucy Chan, BSc[1]; Harry Yiu, FRCR[2]; Wai-Tong Ng, MD[1]; Frank Wong, FRCR[3]; Kam-Tong Yuen, FRCR[4]; Stephen Yau, FRCR[2]; Foon-Yiu Cheung, FRCR[2]; Oscar Chan, FRCR[1]; Horace Choi, MSc[8]; and Rick Chappell, PhD[9]

Corresponding author: Anne Lee, MD, Clinical Oncology Center, The University of Hong Kong-Shenzhen Hospital, 1 Haiyuan First Road, Futian District, Shenzhen, Guangdong Province, Postal code 518053, China. Telephone: 86-18033050750; email: annelee@hku-szh.org.

Departments of Clinical Oncology, [1]Pamela Youde Nethersole Eastern Hospital, Hong Kong; [2]Queen Elizabeth Hospital, Hong Kong; [3]Tuen Mun Hospital, Hong Kong; [4]Princess Margaret Hospital, Hong Kong; [5]Queen Mary Hospital, University of Hong Kong; [6]Sun Yat

Sen University Cancer Center, China; [7]Prince of Wales Hospital, Chinese University of Hong Kong; [8]School of Public Health, University of Hong Kong; and [9]Department of Biostatistics, University of Wisconsin Medical School, United States.

Presented in part at the European Cancer Congress, 27 September - 1 October 2013, Amsterdam, The Netherlands.

ClinicalTrials.gov identifier NCT00379262

Running head: Chemotherapy and Fractionation for NPC

Total number of text pages (including title page, references, and figure legends) = 30; tables = 5; and figures = 3

FUNDING SUPPORT

The Trial was supported by the Hong Kong Hospital Authority, Hong Kong Nasopharyngeal Cancer Study Group, Hong Kong Cancer Fund and Hong Kong Anti-Cancer Society.

CONFLICT OF INTEREST DISCLOSURES

None of the authors have any potential conflict of interest.

ACKNOWLEDGMENTS

The Trial was supported by the Hong Kong Hospital Authority, Hong Kong Nasopharyngeal Cancer Study Group, Hong Kong Cancer Fund and Hong Kong Anti-Cancer Society.

We are most grateful to Dr. Brian O'Sullivan, Dr. E.H. Tan and Dr. Rick Chappell for their guidance as our Data Monitoring Committee, Dr. Jean-Pierre Pignon (Biostatistics and Epidemiology Unit, Gustave Roussy, Villejuif) for his invaluable advices to ensure that our statistical analyses are appropriate, and colleagues of all participating centers for their contribution.

PRECIS

Preliminary results from NPC-0501 Trial showed that the benefit of changing from concurrent-adjuvant to induction-concurrent sequence remains uncertain; replacing fluorouracil by capecitabine warrants further validation in view of convenience, favorable toxicity profile and at least comparable efficacy. In concurrence with studies on other head and neck cancers, accelerated fractionation is not recommended for locoregionally advanced nasopharyngeal carcinoma treated by chemoradiotherapy.

BACKGROUND: A current recommendation for locoregionally advanced nasopharyngeal carcinoma (NPC) is conventional-fractionated radiotherapy with concurrent cisplatin plus adjuvant cisplatin and fluorouracil (PF). This randomized trial evaluates the therapeutic benefit by changing to induction-concurrent sequence, oral capecitabine (X) and/or accelerated fractionation. **METHODS:** Patients with stage III-IVB non-keratinizing NPC were randomly allocated to one of six arms. The protocol was amended in 2009 to permit confining randomization to conventional-fractionated arms. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival and safety. **RESULTS:** A total of 803 patients were accrued (706 randomly allocated to all six arms). Comparisons of Induction-PF vs adjuvant-PF did not show significant improvement. Unadjusted comparisons of Induction-PX vs adjuvant-PF showed favorable trend in PFS in the Conventional-fractionated stratum (P = .045); analyses adjusted for other significant factors and fractionation showed significant reduction of progression (hazard ratio 0.54 [0.36-0.80]) and death (0.42 [0.25-0.70]). Unadjusted comparisons of Induction vs Adjuvant sequence did not reach statistical significance, but adjusted comparisons showed favorable improvement. Comparisons of Induction-PX versus Induction-PF showed less toxicities (neutropenia and electrolyte disturbance), unadjusted comparisons of efficacy were statistically insignificant, but adjusted analyses showed lower hazard of death (0.57 [0.34-0.97]). Changing fractionation from Conventional to Accelerated did not achieve any benefit, but incurred higher toxicities (acute mucositis and dehydration). **CONCLUSIONS:** Preliminary results showed that the benefit of changing to induction-concurrent sequence

remains uncertain; replacing fluorouracil with oral capecitabine warrants further validation; accelerated fractionation is not recommended for locoregionally advanced NPC treated with chemoradiotherapy.

KEYWORDS: nasopharyngeal carcinoma, randomized controlled trial, chemoradiotherapy, capecitabine, accelerated fractionation

INTRODUCTION

Since the first report of significant survival benefits by the Intergroup-0099 Study,[1] addition of concurrent cisplatin plus adjuvant cisplatin and fluorouracil (PF) to conventional-fractionated radiotherapy (RT) has become a standard recommendation in National Comprehensive Cancer Network (NCCN) practice guideline[2] for patients with locoregionally advanced nasopharyngeal carcinoma (NPC). Three subsequent trials confirmed the efficacy of this concurrent-adjuvant strategy.[3-5] However, distant control remains a key problem, more efficacious regimen is needed.

The Hong Kong Nasopharyngeal Cancer Study Group initiated this multi-center randomized controlled trial to evaluate three promising strategies. The first strategy is to change the chemotherapy sequence from concurrent-adjuvant to induction-concurrent. An exploratory study[6] based on patients from the NPC-9901[4] and NPC-9902[7] Trials showed that the number of adjuvant cycles and the dose of fluorouracil given had significant impact on distant control. However, the adjuvant phase is often poorly tolerated. Changing to induction, with better tolerance[8] and upfront use of cytotoxic drug combination, could theoretically be more effective for eradicating potent micro-metastases. In addition, this could shrink the primary tumor to give wider margin for RT, an advantage that is particularly needed for tumors infiltrating/abutting critical neurological structures.[8] With encouraging results extensively reported from Phase II studies since the first report by Rischin et al,[9] this has been included as an option (Category 3 evidence) in NCCN guideline[2] and (II, B evidence) in European guideline.[10]

Our second strategy is to improve the current PF regimen by replacing fluorouracil (given by infusion) with capecitabine (Xeloda, oral preparation manufactured by Roche). Besides obvious advantage of convenience,[11] potential improvement in efficacy and safety[12-15] could be achieved because capecitabine is metabolized to fluorouracil via a three-step enzymatic cascade with final conversion mediated by thymidine phosphorylase, an enzyme present at significantly increased concentrations in a wide range of solid tumors compared with normal tissue; furthermore, uracil analogues may have anti-angiogenic effect.[16]

NPC-9902 Trial[7] suggested that combining concurrent-adjuvant chemotherapy with accelerated fractionation could improve tumor control for advanced local diseases. However, this can only be taken as hypothesis-generating because the trial was terminated early due to slow accrual. Our third strategy is to re-evaluate the potential benefit by changing RT fractionation from conventional to acceleration.

MATERIALS AND METHODS

Patients

Eligible patients had histologically confirmed non-keratinizing (differentiated or undifferentiated) NPC by World Health Organization Classification; Stage III-IVB (tumor with bony structure, paranasal sinuses [T3], or intracranial extension, cranial nerve, hypopharynx, orbit, infratemporal fossa (masticator space) involvement [T4]; cervical lymph node metastasis with bilateral involvement [N2], greatest dimension >6 cm [N3a] or

extension into supraclavicular fossa [N3b]; and no distant metastasis [M0]) by American Joint Committee on Cancer Staging System (6th edition).[16] Other inclusion criteria were age 18-69 years, performance status of 2 or lower by the Eastern Cooperative Oncology Group System, adequate hematologic and renal functions. The exclusion criteria were pregnancy or lactation, history of previous treatment, or prior malignancy.

The protocol was approved by the institutional ethics committees of individual participating center, and the trial was monitored by an independent Data Monitoring Committee. All patients provided written informed consent.

All patients were assessed by complete physical examination, fibreoptic nasopharyngoscopy, magnetic resonance imaging and/or computed tomography of the nasopharyngeal region, chest radiograph, complete blood count, renal and liver function tests, and lactate dehydrogenase (LDH). Additional investigations were performed for those with suspicious findings or abnormal biochemical profile.

Study Design and Randomization

Eligible patients were stratified by participating center and stage (III vs IV), and randomly allocated in equal proportions to six arms. Blocks of variable size were chosen randomly by the designing statistician to ensure both randomness and investigator blinding; sealed envelopes for each stratum (defined by center and stage) were sequentially numerated and sent to the randomization office in each center, where patient eligibility is confirmed and the sealed envelope with the next number in the corresponding stratum is opened to allocate

treatment.

In accordance with the original protocol (September 2006), eligible patients were initially randomized in equal proportions to one of the six arms (Fig. 1). The protocol was amended in January 2009 following the recommendation of the independent Data Monitoring Committee: individual centers with logistical difficulty to arrange six RT fractions per week were allowed to opt out of the accelerated fractionation portion of the trial in order to improve accrual.

The protocol specified two reporting: a preliminary report after the closure of the study (regardless of their significance) and the final report after 5-year follow-up for all surviving patients.

Treatment and Assessment

Patients in all arms were irradiated with megavoltage photons using the same RT technique and dose in line with the policy of individual center. A total dose of 70 Gy or greater (66 Gy for T1-2a) was given to the gross tumor targets, and 50 Gy or greater to potential sites of local infiltration and bilateral cervical lymphatics. Additional boosts (not exceeding 20 Gy) could be given to the parapharyngeal space, the primary or nodal sites (when indicated); the boost field was confined to the involved site with exclusion of critical structures. The number of fractions per week was 5 in the Conventional group, and 6 in the Accelerated group (the sixth fraction was given either on Saturday or on a weekday with $\geq$ 6 hours between fractions).

Patients in all arms were given concurrent cisplatin 100 mg/m^2 intravenous infusion (IVI) every 21 days for 2-3 cycles (depending on overall RT time). Patients allocated to the Adjuvant-PF group were given adjuvant cisplatin 80 mg/m^2 IVI + fluorouracil 1000 mg/m^2/day IVI for 96 hours every 28 days for 3 cycles. Patients allocated to the Induction-PF group were given induction cisplatin 100 mg/m^2 IVI + fluorouracil 1000 mg/m^2/day IVI for 120 hours every 21 days for 3 cycles. For patients allocated to the Induction-PX group, fluorouracil was replaced by capecitabine 2000 mg/m^2/day orally for 14 days per cycle. Dose modifications were permitted according to protocol-specified criteria.

The intended total dose of chemotherapy per treatment arms are as follows:

Arm 1A: Cisplatin 540mg/m^2, 5-Fluorouracil 12,000 mg/m^2

Arm 1B: Cisplatin 440mg/m^2, 5-Fluorouracil 12,000 mg/m^2

Arm 2A: Cisplatin 600mg/m^2, 5-Fluorouracil 15,000 mg/m^2

Arm 2B: Cisplatin 500mg/m^2, 5-Fluorouracil 15,000 mg/m^2

Arm 3A : Cisplatin 600mg/m^2, Capecitabine 84,000 mg/m^2

Arm 3B : Cisplatin 500mg/m^2, Capecitabine 84,000 mg/m^2

The first assessment of tumor response was performed 6 weeks to 16 weeks after completion of RT. All patients were assessed by complete physical examination and fiberoptic nasopharyngoscopy. Further investigations with computed tomography/MRI or other tests were arranged when indicated (regular imaging assessment was not routinely performed due to limitation of resources). Persistent primary or nodal disease at 16 weeks after completion of RT was taken as locoregional failure. Persistent disease and relapse were

treated with the policy of individual center. Common Toxicity Criteria for Adverse Events version 3.0 was used to gauge toxicities (both acute and late).

Statistical Analysis

All analyses were performed on an intent-to-treat basis, the tests are two-sided, and events for actuarial rates were measured from the date of randomization as the starting date. For the preliminary report, the primary endpoint is progression-free survival (PFS, time to first failure at any site or death due to any cause). The standard group is the Adjuvant-PF group with Conventional-fractionated RT, 5-year results were estimated from previous reports.[4, 5,7,18] The following sets of hypotheses and assumptions are used for power calculation:

H0: The null hypotheses of no difference in treatment efficacy: 5-year PFS is 65% in all groups;

HA: The alternative hypotheses of treatment efficacy: the 5-year PFS is 65% in the standard group and 75% in the experimental groups.

For detecting this 10% difference in PFS with alpha error of 0.05 and 80% power, the target accrual is 798 patients.

Secondary endpoints for treatment efficacy in the preliminary report included overall survival (OS, time to death due to any cause). Secondary endpoints for safety included major toxicities (grade 3 or above) both acute (incidence rates compared by Chi-square) and late (time to toxicities compared by log-rank test).

Primary comparisons include comparisons of each induction regimen to the adjuvant

regimen (Induction-PF vs Adjuvant-PF, Induction-PX vs Adjuvant-PF) and fractionation (Accelerated vs Conventional). Secondary comparisons include comparisons of sequence (Induction vs Adjuvant) and induction regimens (Induction-PX vs Induction-PF group).

Stratified log-rank test was used: comparisons on regimen groups and sequence were stratified by fractionation (Accelerated, Conventional), while comparisons on fractionation were stratified by regimen groups (Adjuvant-PF, Induction-PF, Induction-PX). In addition, multivariate analyses by Cox regression were performed to evaluate independent significance of intervention and other potential prognostic factors.

RESULTS

Basic Characteristics and Radiotherapy

From September 2006 to 2012, 803 eligible patients from seven participating centers were randomly allocated (Fig 1): 706 patients were randomly allocated to all six arms and 97 patients to Conventional-fractionated arms only. All except one patient with lost record were analyzed.

The six treatment arms were well balanced in all patient characteristics, tumor factors, RT technique and total dose (Table 1). The median duration of follow-up for the whole series was 3.3 years (range 0.1-7.1).

Chemotherapy Tolerance

The number of concurrent cycles varied with both chemotherapy sequence and fractionation

(Table 2). As the mean overall RT time for the Accelerated group was shorter than the Conventional group (mean 40 vs 47 days), the proportion of patients with 3 concurrent cycles was correspondingly lower (11% vs 43%, $P < .001$), but the proportion with at least 2 concurrent cycles was identical (92% in both). Significantly higher proportion of patients in the Induction group completed 3 non-concurrent cycles as compared with the Adjuvant group (88% vs 64%, $P < .001$), but lower proportion had ≥2 concurrent cycles (90% vs 95%, $P = .009$). There were no significant differences between the two induction regimens (PX vs PF) in the mean number of cycles given during both phases ($P > .47$).

Efficacy

In this preliminary study, the core analyses on efficacy were based on the 706 patients randomized to all six arms as planned in the original study design: 171 patients had progression (failure or death) and 116 had death due to any cause. Table 3 summarized the comparisons of PFS and OS rates by stratified log-rank test; Fig. 2-3 showed the actuarial PFS curves for each stratum. Univariate analyses showed significant impact by other factors (including stage, LDH, age, sex, RT technique and center), the independent effect of intervention methods were analyzed by Cox regression with adjustment for these factors (Table 4).

Comparisons of regimen Induction-PF vs Adjuvant-PF did not show statistically significant improvement. Unadjusted comparisons of Induction-PX vs Adjuvant-PF showed favorable trend in PFS in the Conventional stratum (Fig. 2A, 81% vs 75% at 3-year, $P = .045$),

but insignificant differences in the Accelerated stratum. When adjusted for other significant factors and fractionation, Induction-PX achieved significant reduction in hazard of progression (hazard ratio [HR] 0.54, [95% confidence interval 0.36-0.80], *P* = .002) and death (HR 0.42 [0.25-0.70], *P* = .001). When the two induction regimens were combined for evaluation of Induction vs Adjuvant sequence, unadjusted comparisons did not reach statistical significance, but adjusted comparisons showed reduction in hazard of progression (HR 0.67, [0.48-0.93], *P* = .016) and death (HR 0.57 [0.39-0.86], *P* = .006).

For comparisons of capecitabine vs fluorouracil, unadjusted comparisons of Induction-PX vs Induction-PF did not show significant improvement, but adjusted analyses showed lower hazard of death (HR 0.57 [0.34-0.97], *P* = .037). Finally, all comparisons (both adjusted and unadjusted) of fractionation Accelerated vs Conventional did not show any benefit.

Safety

Table 5 summarizes major toxicities grade 3 or above. The Induction group had higher incidence of chemotherapy-related toxicities including neutropenia, thrombocytopenia, renal impairment and peripheral neuropathy, but less weight loss than the Adjuvant group. Comparison of the two induction regimens showed that induction-PX had less neutropenia and electrolyte disturbance. The Accelerated group had significantly higher incidence of acute mucositis and dehydration than the Conventional group.

Majorities of toxicities are uneventful; treatment mortality for the whole series was

1.2%. There were no significant differences in late toxicities and non-cancer deaths among the groups.

DISCUSSION

There is little controversy that addition of chemotherapy could achieve significant survival benefit for patients with locoregionally advanced NPC, and concurrent sequence is the most efficacious for combining with RT.[19] There are differences of opinion as to whether concurrent alone or concurrent-adjuvant chemotherapy should be recommended. Preliminary results from a randomized trial by Chen et al.[20] comparing concurrent-adjuvant vs concurrent alone chemoradiotherapy showed no statistically significant differences in 2-year results: HR for failure-free survival was 0.74 (0.49-1.10), $P = .13$. However, it must be cautioned that the follow-up was too short for definitive confirmation. Data from the second patient-data based meta-analysis by MAC-NPC Collaborative Group[21] showed that both groups achieved significant benefit in OS: the concurrent-adjuvant group showed robust long-term results (HR = 0.65 [0.56-0.76], with 5/6 comparisons individually significant); the corresponding results in the concurrent alone group was HR = 0.80 [0.70-0.93] (2/7 comparisons individually significant, the greatest benefit was observed in a trial aimed for Stage II). Concurrent-adjuvant chemotherapy remains a recommendation with Level 1A evidence; the use of this sequence as the standard arm in the current trial is relevant.

All the reported trials on Concurrent-adjuvant chemotherapy used concurrent cisplatin and adjuvant PF; hence PF is used as the standard non-concurrent chemotherapy in the

current trial. Unlike other head and neck cancers, no trial has yet been conducted on non-keratinizing NPC to evaluate the benefit of adding taxane or compare the efficacy of taxane versus fluorouracil. As our previous exploratory study on NPC-9901 and NPC-9902 Trials[6] showed dose-dependent effect of fluorouracil on distant failure, we focus on exploring for better uracil agent.

As explained in the Introduction, the current trial is designed to evaluate three potential strategies: induction-concurrent sequence, use of capecitabine, and accelerated fractionation. In concurrence with a review[18] of reported studies, patients treated with induction-concurrent regimens had excellent tolerance in the non-concurrent phase, but decreased tolerance in the concurrent phase. Acceleration further affected the proportion of patients with 3 concurrent cycles. Such interacting variations (Table 2) may affect the ultimate efficacy of the induction and the acceleration strategies.

Regarding the change to induction-concurrent sequence, there are five randomized studies by other groups, all used concurrent alone chemotherapy as the standard arm. Despite the encouraging results of single-arm studies, three reported randomized studies showed conflicting results. Hui et al.[22] (adding induction cisplatin and docetaxel, n = 65) showed significantly better 3-year OS, but both Fountzilas et al.[23] (adding cisplatin, epirubicin and paclitaxel, n = 141) and Tan et al.[24] (adding carboplatin, gemcitabine and paclitaxel, n = 172) did not achieve OS benefit. Two trials are still on-going.

Preliminary results from the current trial (Tables 3 and 4, Fig. 2) showed that changing the sequence per se, as shown by comparison of Induction-PF versus Adjuvant-PF,

did not achieve statistically significant improvement in efficacy. More encouraging results were achieved by changing both the sequence and the induction regimen: unadjusted comparison of induction-PX versus Adjuvant-PF showed favorable trend in PFS when given with Conventional-fractionated RT (P = .045). Multivariate analyses further showed that when adjusted for other significant factors and fractionation, PX group had significantly lower hazard in progression (P = .002) and death (P = .001). When the two induction groups were combined for evaluation of sequence Induction versus Adjuvant, unadjusted comparisons did not reach statistical significance, but adjusted analyses also showed lower hazard in progression (P = .016) and death (P = .006).

The change from fluorouracil to capecitabine has been extensively studied in other solid cancers. Studies comparing capecitabine versus fluorouracil in gastrointestinal cancers consistently confirmed that capecitabine is a favorable alternative with at least equivalent efficacy, lower toxicities and better patient acceptance.[10-14] However the conclusion on survival benefit is less definitive. Two large trials on metastatic colorectal cancer[12,13] showed superior response rates, but only equivalent PFS and OS. The X-ACT Trial on adjuvant therapy for colon cancer[14] showed significant survival benefit on preplanned multivariate analyses, but only borderline benefit on unadjusted comparisons. A meta-analysis comparing capecitabine- versus fluorouracil-containing chemotherapy for colorectal and gastric cancers[15] showed that unadjusted HR for OS was 0·94 (P = ·049).

Promising efficacy of capecitabine has been reported in a phase II study[25] on patients with recurrent and metastatic NPC: 24% showed overall response with significant tumor

regression after 3 cycles despite heavy pretreatment with cisplatin-based chemotherapy. The current trial is the first randomized trial to evaluate this uracil agent for NPC. Replacing fluorouracil (given by intravenous infusion) by capecitabine (given orally) is obviously more convenient and welcomed by patients. In addition, this regimen incurred less neutropenia and electrolyte disturbance (Table 5). In terms of efficacy, unadjusted comparison of Induction-PX versus Induction-PF did not show significant difference, but adjusted analysis showed that Induction-PX had lower hazard in death (P = .038).

Regarding the change to accelerated fractionation, a meta-analysis[26] showed that altered fractionation, particularly hyper-fractionation, can improve survival. However, both the GORTEC 99-02 trial[27] and the RTOG-0129 Study[28] showed that acceleration is not beneficial for patients with concurrent chemoradiotherapy. It should be noted that all these studies only focused on other head and neck cancers. The only trial that specifically focused on NPC is the NPC-9902 Trial,[7] which in contrast suggested that acceleration combined with concurrent-adjuvant chemoradiotherapy could further improve the failure-free rate for T3-4N0-1 disease. However, it must be cautioned that this finding can only be taken as hypothesis-generating as the trial was terminated early due to slow accrual, the sample size (189 patients) is smaller than the planned target, possibility of subtle biases and chance findings cannot be totally excluded.

The current trial is the only trial that attempted to confirm this potential strategy. With shorter overall RT time, the proportion of patients with 3 concurrent cycles was inevitably low in the Accelerated group. With further lowering of tolerance by induction chemotherapy,

even the proportion with ≥2 concurrent cycles was affected. In concurrence with trials[27,28] on other head and neck cancers, the current finding showed that acceleration did not improve efficacy (Tables 3 and 4, Fig. 3). In addition, acceleration incurred significantly higher incidence of acute mucositis and dehydration (Table 5). Together with the logistic difficulty for arranging six fractions per week, acceleration is not recommended for patients treated with chemoradiotherapy, particularly those with induction-concurrent regimens.

The current NPC-0501 Trial is a trial with largest sample size for NPC (802 evaluable patients), however, the trial is possibly still under-powered. A major weakness is that the trial design is too complex with inclusion of multiple arms and strata. This is further complicated by the change in protocol after the first interim analysis allowing centers with logistical difficulty to opt out of the Accelerated arms. To be pertinent, all comparisons on efficacy related to fractionation were based only on the 706 patients randomly assigned to all six arms. Another point that may further lead to difficulty in proving statistical difference is that 90% of patients in the current trial were irradiated with modern intensity-modulated technique; the magnitude of benefit contributed by chemotherapy is likely to be lower than past series irradiated with less optimal techniques. Lastly, the median follow-up for this preliminary analysis is 3.3 years; longer observation is needed to confirm the long-term therapeutic ratio. Nonetheless, the current findings provide valuable data for guiding clinical practice and future trials.

In conclusion, our preliminary results showed that the benefit of changing to induction-concurrent sequence remains uncertain; the Induction-PF regimen did not achieve

statistical significant improvement in efficacy. Changing both the sequence and regimen to Induction-PX achieved more favorable trends in efficacy. In view of convenience, favorable toxicity profile and at least comparable efficacy, replacing fluorouracil with capecitabine warrants further validation. Accelerated fractionation is not recommended for NPC patients treated by chemoradiotherapy.

REFERENCES

1. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup Study 0099. *J Clin Oncol.* 1998;16:1310-1317.
2. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology – Head and Neck Cancers, version 2.2014. Available from URL: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#head-and-neck [accessed June 24, 2014].
3. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union Against Cancer Stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol.* 2005;23:6730-6738.
4. Lee AWM, Tung SY, Chua DTT, et al. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally-advanced nasopharyngeal carcinoma. *J NCI.* 2010;102:1188-1198.
5. Chen Y, Sun Y, Liang SB, et al. Progress report of a randomized trial comparing long-term survival and late toxicity of concurrent chemoradiotherapy with adjuvant chemotherapy versus radiotherapy alone in patients

with stage III to IVB nasopharyngeal carcinoma from endemic regions of China. *Cancer*. 2013;119:2230-2238.

6. Lee AWM, Tung Y, Ngan RKC, et al. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 Trials. *Eu J Cancer*. 2011;47:656-666.
7. Lee AWM, Tung Y, Chan ATC, et al. A randomized trial on addition of concurrent-adjuvant chemotherapy and/or accelerated fractionation for locally-advanced nasopharyngeal carcinoma. *Radiother Oncol*. 2011;98:15-22.
8. Lee AWM, Lau KY, Hung WM, et al. Potential improvement of tumor control probability by induction chemotherapy for advanced nasopharyngeal carcinoma. *Radiother Oncol*. 2008;87:204-210.
9. Rischin D, Corry J, Smith J, et al. Excellent disease control and survival in patients with advanced nasopharyngeal cancer treated with chemoradiation. *J Clin Oncol*. 2002;20:1845-1852.
10. Chan ATC, Grégoire V, Lefebvre JL, et al. Nasopharyngeal cancer: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23 (Supplement 7):vii83-85.
11. Twelves C, Boyer M, Findlay M, et al. Capecitabine (Xeloda) improves medical resource use compared to 5-fluorouracil plus leucovorin in a phase III trial conducted in patients with advanced colorectal carcinoma. *Eu J Cancer*. 2001;37:597-604.
12. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous 5-fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol*. 2001;19:2282-2292.

13. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous 5-fluorouracil plus leucovorin (Mayo Clinic regimen) in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol*. 2001;19: 4097-4106.

14. Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. *Ann Oncol.* 2012;23:1190-1197.

15. Cassidy J, Saltz L, Twelves C, et al. Efficacy of capecitabine versus 5-fluorouracil in colorectal and gastric cancers: a meta-analysis of individual data from 6171 patients. *Ann Oncol*. 2011;22:2604-2609.

16. Basaki Y, Aoyagi K, Chikahisa L, et al. UFT and its metabolites inhibit cancer-induced angiogenesis via a VEGF-related pathway. *Oncol*. 2000;10 (Suppl 9):68-71.

17. Greene F, Page D, Fleming I. AJCC Cancer Staging Manual. 6th ed. New York: Springer-Verlag, 2002.

18. Lee AWM, Ng WT, Chan OSH, et al. If concurrent-adjuvant chemoradiotherapy is beneficial for locoregionally advanced nasopharyngeal carcinoma, would changing the sequence to induction-concurrent achieve better outcome? *J Radiat Oncol*. 2012;1:107-115.

19. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: An individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys*. 2006;64:47-56.

20. Chen L, Hu CS, Chen XZ, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomized control trial. Lancet Oncol. 2012;13:163-171.

21. Blanchard P, Lee A, Leclercq J, et al. Meta-analysis of chemotherapy in nasopharyngeal carcinoma (MAC-NPC): An update on 4,806 patients. Presented at the 50th Annual Meeting of ASCO, San Francisco, June 2014.

22. Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol*. 2009;27:242-249.

23. Fountzilas G, Ciuleanu E, Bobos M, et al. Induction chemotherapy followed by concomitant radiotherapy and weekly cisplatin versus the same concomitant chemoradiotherapy in patients with nasopharyngeal carcinoma: a randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation. *Ann Oncol*. 2011;23:427-435.

24. Tan T, Lim WT, Fong KW, et al. Randomized phase III trial of concurrent chemoradiation with or without neoadjuvant gemcitabine, carboplatin, and paclitaxel in locally advanced nasopharyngeal cancer. *J Clin Oncol. 2014*;32:5s(suppl; abstr 6003).

25. Chua DTT, Sham JST, Au GKH. A phsase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. *Oral Oncol*. 2003;39:361-366.

26. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet*. 2006;368:843-854.

27. Bourhis J, Sire C, Graff P, et al. concomitant chemoradiotherapy versus acceleration with or without concomitant chemootherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open label phase 3 randomized trial. *Lancet Oncol*. 2012;13:145-153.

28. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. NEJM 2010;363:24-35.

TABLE 1. Basic Characteristics and Radiotherapy of the Whole Series (n = 802)

	Arm 1A (n=160)	Arm 2A (n=161)	Arm 3A (n = 165)	Arm 1B (n=104)	Arm 2B (n = 110)	Arm 3B (n = 102)
Fractionation	Conventional	Conventional	Conventional	Accelerated	Accelerated	Accelerated
Regimen	Adjuvant-PF	Induction-PF	Induction-PX	Adjuvant-PF	Induction-PF	Induction-PX
Patient						
Age: mean (SD) years	48 (9)	48 (9)	48 (9)	49 (8)	48 (10)	49 (9)
Sex - Male	117 (73%)	116 (72%)	133 (81%)	85 (82%)	84 (76%)	78 (76%)
Performance status						
0	116 (73%)	106 (66%)	112 (68%)	70 (67%)	67 (61%)	65 (64%)
1	43 (27%)	54 (34%)	53 (32%)	33 (32%)	42 (38%)	36 (35%)
2	1 (0.6%)	1 (0.6%)	0 (0%)	1 (1.0%)	1 (0.9%)	1 (1.0%)
Tumor factor						
Staging method						
MRI ± CT	155 (97%)	156 (97%)	158 (96%)	100 (96%)	104 (95%)	102 (100%)
CT alone	5 (3%)	5 (3%)	7 (4%)	4 (4%)	6 (5%)	0 (0%)
T-classification						
T1-2	24 (15%)	33 (20%)	35 (21%)	28 (27%)	26 (24%)	21 (21%)
T3	113 (71%)	105 (65%)	103 (62%)	60 (58%)	66 (60%)	61 (60%)
T4	23 (14%)	23 (14%)	27 (16%)	16 (15%)	18 (16%)	20 (20%)
N-classification						
N0-1	58 (36%)	46 (29%)	37 (22%)	25 (24%)	25 (23%)	25 (25%)
N2	77 (48%)	92 (57%)	104 (63%)	61 (59%)	67 (61%)	58 (57%)
N3	25 (16%)	23 (14%)	24 (15%)	18 (17%)	18 (16%)	19 (19%)
Stage-group						
III	114 (71%)	118 (73%)	117 (71%)	74 (71%)	76 (69%)	67 (66%)

TABLE 1. Continued.

Stage-group						
IVA - IVB	46 (29%)	43 (27%)	48 (29%)	30 (29%)	34 (31%)	35 (34%)
LDH: mean (SD) iu/L	226 (79)	237 (115)	236 (93)	236 (94)	244 (91)	252 (126)
Radiotherapy						
Technique						
2DRT	3 (2%)	5 (3%)	5 (3%)	7 (7%)	2 (2%)	2 (2%)
3DRT	6 (4%)	2 (1%)	2 (1%)	3 (3%)	0 (0%)	4 (4%)
IMRT	148 (93%)	152 (94%)	154 (93%)	94 (90%)	104 (95%)	94 (92%)
Total Dose: mean (SD) Gy	69.7 (2.2)	69.6 (3.2)	69.9 (1.7)	69.6 (1.7)	69.3 (5.8)	69.6 (1.9)
Overall time: mean (SD) day	47 (2.7)	47 (3.0)	47 (2.8)	42 (3.3)	41 (4.4)	41 (3.1)

Abbreviations: SD, standard deviation; P, cisplatin; F, fluorouracil; X, capecitabine; MRI, magnetic resonance imaging; CT, computed tomography; LDH, lactate dehydrogenase; 2DRT, 2-dimensional; 3DRT, 3-dimensional conformal; IMRT, intensity-modulated radiotherapy technique.

TABLE 2. Tolerance to Chemotherapy

Chemotherapy	Conventional Fractionation			Accelerated Fractionation		
	Adjuvant-PF (Arm 1A)	Induction-PF (Arm 2A)	Induction-PX (Arm 3A)	Adjuvant-PF (Arm 1B)	Induction-PF (Arm 2B)	Induction-PX (Arm 3B)
Concurrent						
None	3%	7%	5%	0	3%	5%
1 cycle	3%	3%	4%	3%	6%	7%
2 cycles	40%	49%	58%	75%	85%	83%
3 cycles	55%	40%	33%	22%	6%	5%
Non-Concurrent						
None	19%	1%	1%	17%	1%	0%
1 cycle	8%	6%	7%	12%	8%	3%
2 cycles	8%	4%	7%	8%	0	9%
3 cycles	65%	89%	85%	63%	91%	88%

Abbreviations: P, cisplatin; F, fluorouracil; X, capecitabine.

TABLE 3. Efficacy – Tumor Control Rates and Stratified Comparisons

Factor	Strata	Progression-Free Survival	Overall Survival
Actuarial Rate at 3-year			
Arm 1A		75%	83%
Arm 2A		79%	85%
Arm 3A		81%	91%
Arm 1B		79%	87%
Arm 2B		77%	90%
Arm 3B		76%	88%
Arm 2-3A		80%	88%
Arm 2-3B		76%	89%
P Value on Comparison by Stratified Log Rank Test			
Regimen group			
Induction-PF vs Adjuvant PF	Conventional (Arm 2A vs 1A)	.30	.30
	Accelerated (Arm 2B vs 1B)	.75	.73
	Overall	.33	.33
Induction-PX vs Adjuvant PF	Conventional (Arm 3A vs 1A)	.045	.12
	Accelerated (Arm 3B vs 1B)	.66	.24
	Overall (Arms 3A-B vs 1A-B)	.079	.055
Induction-PX vs Induction-PF	Conventional (Arm 3A vs 2A)	.34	.61
	Accelerated (Arm 3B vs 2B)	.90	.34
	Overall	.44	.30
Sequence			
Induction vs Adjuvant	Conventional (Arms 2-3A vs 1A)	.073	.12
	Accelerated (Arms 2-3B vs 1B)	.66	.39
	Overall	.11	.089
Fractionation			
Accelerated vs Conventional	Adjuvant-PF (Arm 1B vs 1A)	.68	.96
	Induction-PF (Arm 2B vs 2A)	.84	.44
	Induction-PX (Arm 3B vs 3A)	.31	.81
	Overall	.68	.55

Abbreviations: P, cisplatin; F, fluorouracil; X, capecitabine.

TABLE 4. Multivariate Analyses on Independent Significance of Experimental Intervention on Tumor Control: Hazard Ratio (95% Confidence Interval) and *P* Value

	Progression-Free Survival	Overall Survival
Part I: Regimen Groups and Fractionation in Patients Randomized to All Six Arms (n = 706)		
Regimen Groups	.009	.003
Induction-PF vs Adjuvant-PF	0.82 (0.57-1.19)	0.76 (0.48-1.19)
	.29	.23
Induction-PX vs Adjuvant-PF	0.54 (0.36-0.80)	0.42 (0.25-0.70)
	.002	.001
Fractionation: Acceleration vs Conventional	1.13 (0.82-1.54)	1.11 (0.75-1.62)
	.46	.61
Part II: Chemotherapy Sequence and Fractionation in Patients Randomized to All Six Arms (n = 706)		
Sequence: Induction vs Adjuvant	0.67 (0.48-0.93)	0.57 (0.39-0.86)
	.016	.006
Fractionation: Acceleration vs Conventional	1.14 (0.83-1.56)	1.12 (0.76-1.64)
	.41	.57
Part III: Regimen and Fractionation in Patients Randomized to Induction Arms (n = 473)		
Regimen: Induction-PX vs Induction -PF	0.67 (0.44-1.02)	0.57 (0.34-0.97)
	.059	.038
Fractionation: Acceleration vs Conventional	1.34 (0.90-2.01)	1.31 (0.80-2.18)
	.16	.30

The above analyses were adjusted for other significant covariates including stage, lactic dehydrogenase, radiotherapy technique, center, gender and age.

Abbreviations: P, cisplatin; F, fluorouracil; X, capecitabine.

TABLE 5. Safety – Major Toxicity (Grade 3 or Above)

	Regimen group Induction-PX vs Induction-PF vs Adjuvant-PF	Sequence Induction vs Adjuvant	Fractionation Accelerated vs Conventional
Acute Toxicity (grade ≥3): cumulative rate %			
Concurrent phase			
Mucositis (radiation-induced)	30% vs 33% vs 32%	31% vs 32%	38%[1] vs 27%
Dermatitis (radiation-induced)	3% vs 4% vs 3%	3% vs 3%	3% vs 4%
Dysphagia	8% vs 5% vs 6%	7% vs 6%	8% vs 6%
Dehydration	3% vs 3% vs 3%	3% vs 3%	4%[1] vs 2%
Neutropenia	6%[1] vs 4%[1,2] vs 8%	5%[1] vs 8%	4% vs 8%
Anemia	8% vs 8% vs 1%	8% vs 1%	5% vs 6%
Thrombocytopenia	4%[1] vs 2% vs 0%	3%[1] vs 0%	2% vs 2%
Infection	3% vs 2% vs 4%	2% vs 4%	4% vs 3%
Vomiting	2% vs 2% vs 9%	2% vs 9%	4% vs 5%
Gastrointestinal	1% vs 0.4% vs 2%	0.7% vs 2%	2% vs 0.8%
Renal impairment	3% vs 3%[1] vs 1%	3%[1] vs 1%	3% vs 2%
Electrolyte disturbance	2% vs 2%[2] vs 3%	2% vs 3%	3% vs 2%
Peripheral neuropathy	0.4%[1] vs 0%[1] vs 0%	0.2%[1] vs 0%	0% vs 0.2%
Weight loss	2% vs 2% vs 2%	2% vs 2%	2% vs 2%
Others	0.4% vs 0.4% vs 1.1%	0.4% vs 1.1%	0.6% vs 0.6%
Any acute toxicity	26%[1] vs 26%[1] vs 45%	26%[1] vs 45%	32% vs 32%
Sequential phase			
Mucositis (radiation-induced)	4% vs 4% vs 5%	4% vs 5%	7%[1] vs 3%
Dermatitis (radiation-induced)	5% vs 3% vs 6%	4% vs 6%	7% vs 4%
Dysphagia	1% vs 2% vs 1%	2% vs 1%	2% vs 1%
Dehydration	3% vs 2% vs 1%	3% vs 1%	3%[1] vs 1%
Neutropenia	28%[1] vs 39%[1,2] vs 13%	33%[1] vs 13%	31% vs 24%
Anemia	6% vs 5% vs 8%	5% vs 8%	7% vs 6%
Thrombocytopenia	5%[1] vs 2% vs 2%	3%[1] vs 2%	3% vs 3%
Infection	6% vs 3% vs 3%	5% vs 3%	6% vs 3%
Vomiting	10% vs 4% vs 1%	7% vs 1%	7% vs 4%
Gastrointestinal	5% vs 7% vs 4%	6% vs 4%	7% vs 5%
Renal impairment	3% vs 4%[1] vs 1%	3%[1] vs 1%	3% vs 2%
Electrolyte disturbance	4% vs 7%[2] vs 3%	5% vs 3%	6% vs 4%
Peripheral neuropathy	10%[1] vs 6%[1] vs 2%	8%[1] vs 2%	7% vs 6%
Weight loss	1% vs 2% vs 8%	1% vs 8%	3% vs 4%
Others	5% vs 3% vs 1%	4% vs 1%	2% vs 3%
Any acute toxicity	48%[1] vs 52%[1] vs 19%	50%[1] vs 19%	44% vs 37%
Late Toxicity (grade ≥3): actuarial rate at 3-year			
Central nervous system	0.9% vs 0.8% vs 0.8%	0.9% vs 0.8%	1.0% vs 0.7%

Ear toxicity	8% vs 6% vs 8%	7% vs 8%	6% vs 10%
Soft tissue/bone damage necrosis	1.2% vs 0.4% vs 1.7%	0.8% vs 1.7%	0.4% vs 1.6%
Others	1.5% vs 0.4% vs 2.0%	0.9% vs 2.0%	2.1% vs 0.6%
Any late toxicity	10% vs 7% vs 12%	9% vs 12%	8% vs 12%

Abbreviations: P, cisplatin; F, fluorouracil; X, capecitabine;

Peripheral neuropathy (sensory and/or motor) irrespective of persistence;

Ear toxicity (hearing impairment and/or otitis) irrespective of time of onset;

Central nervous system (temporal lobe necrosis, brainstem damage and/or cranial neuropathy);

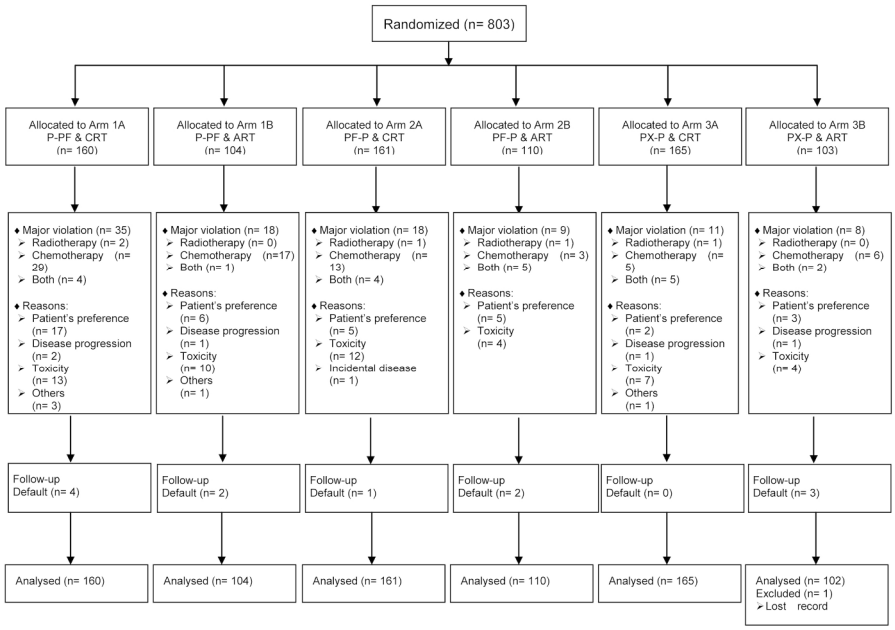
Significantly higher toxicity ($P < .05$): [1]Experimental vs standard group, [2]Induction-PF vs Induction-PX

FIGURE LEGENDS

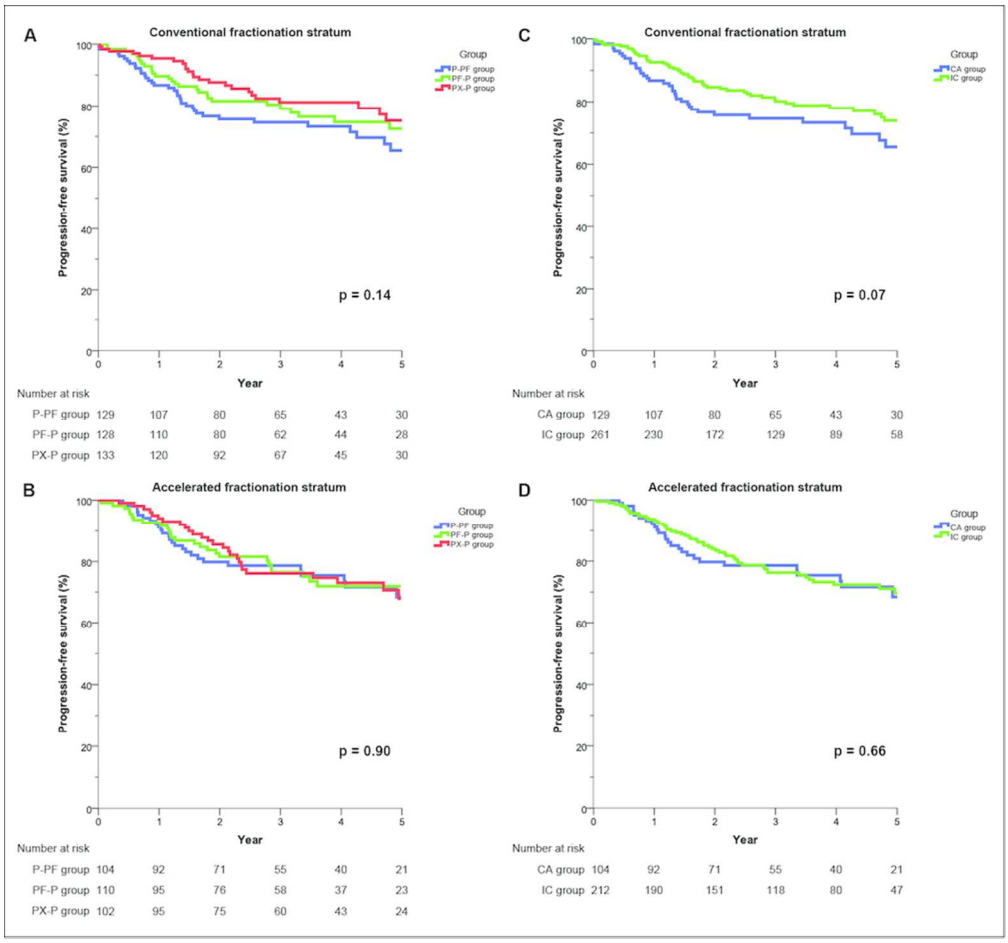
FIGURE 1. CONSORT diagram of the whole series in NPC-0501 Trial.

FIGURE 2. Comparison of progression-free survival by (A) regimen groups in patients with conventional-fractionation; (B) regimen groups in patients with accelerated -fractionation; (C) chemotherapy sequence in patients with conventional-fractionation; and (D) chemotherapy sequence in patients with accelerated -fractionation.

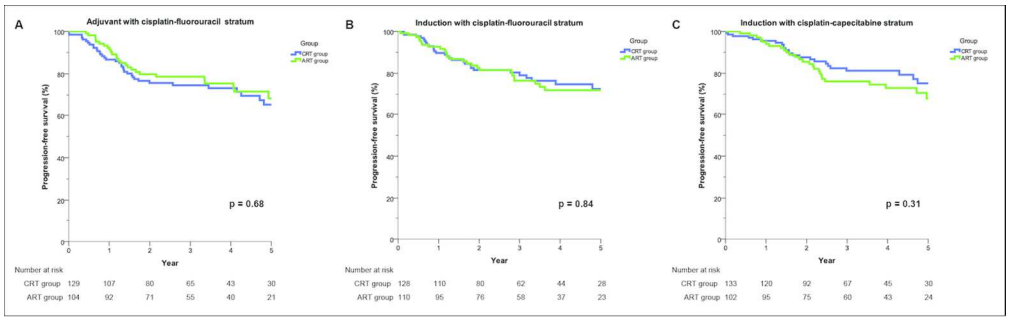
FIGURE 3. Comparison of progression-free survival by fractionation (A) adjuvant cisplatin-fluorouracil group; (B) induction cisplatin-fluorouracil group; and (C) induction cisplatin-capecitabine group.



CONSORT diagram of the whole series in NPC-0501 Trial.
211x147mm (300 x 300 DPI)



Comparison of progression-free survival by (A) regimen groups in patients with conventional-fractionation; (B) regimen groups in patients with accelerated -fractionation; (C) chemotherapy sequence in patients with conventional-fractionation; and (D) chemotherapy sequence in patients with accelerated -fractionation.
254x236mm (100 x 100 DPI)



Comparison of progression-free survival by fractionation (A) adjuvant cisplatin-fluorouracil group; (B) induction cisplatin-fluorouracil group; and (C) induction cisplatin-capecitabine group.
380x118mm (100 x 100 DPI)