Original Article

NPC-0501 Trial on the Value of Changing Chemoradiotherapy Sequence, Replacing 5-Fluorouracil With Capecitabine, and Altering Fractionation for Patients With Advanced Nasopharyngeal Carcinoma

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BACKGROUND: A current recommendation for the treatment of patients with locoregionally advanced nasopharyngeal carcinoma (NPC) is conventional fractionated radiotherapy (RT) with concurrent cisplatin followed by adjuvant cisplatin and 5-fluorouracil (PF). This randomized NPC-0501 trial evaluated the therapeutic effect of changing to an induction-concurrent sequence or accelerated-fractionation sequence, and/or replacing 5-fluorouracil with capecitabine (X). **METHODS:** Patients with American Joint Committee on Cancer/International Union Against Cancer stage III to stage IVB NPC initially were randomly allocated to 1 of 6 treatment arms (6-arm full-randomization cohort). The protocol was amended in 2009 to permit centers to opt out of randomization regarding fractionation (3-arm chemotherapy cohort). **RESULTS:** A total of 803 patients were accrued (1 of whom was nonevaluable) from 2006 to 2012. Based on the overall comparisons, neither changing the chemotherapy sequence nor accelerated fractionation improved treatment outcome. However, secondary analyses demonstrated that when adjusted for RT parameters and other significant factors, the induction-concurrent sequence, especially the induction-PX regimen, achieved significant improvements in progression-free survival (PFS) and overall survival. Efficacy varied among different RT groups: although no impact was observed in the accelerated-fractionation group and the 3-arm chemotherapy cohort, a comparison of the induction-concurrent versus concurrent-adjuvant sequence in the conventional-fractionation group demonstrated a significant benefit in PFS (78% vs 62% at 5 years; $P = .015$) and a marginal benefit in overall survival (84% vs 72%; $P = .042$) after adjusting for multiple comparisons. Comparison of the induction-PX versus the adjuvant-PF regimen demonstrated better PFS (78% vs 62%; $P = .027$) without an increase in overall late toxicity. **CONCLUSIONS:** For patients irradiated using conventional fractionation, changing the chemotherapy sequence from a concurrent-adjuvant to an induction-concurrent sequence, particularly using induction cisplatin and capecitabine, potentially could improve efficacy without an adverse impact on late toxicity. However, further validation is needed for confirmation of these findings. ***Cancer* 2020;126:3674-3688**. © *2020 American Cancer Society*.

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

INTRODUCTION

Since the first report of significant survival benefits by the Intergroup 0099 study,[1] the addition of concurrent cisplatin (P) plus adjuvant cisplatin and 5-fluorouracil (PF) to conventional-fractionated radiotherapy (RT) has become a standard recommendation for patients with locoregionally advanced nasopharyngeal carcinoma (NPC).[2,3] Three subsequent trials confirmed the overall efficacy of this concurrent-adjuvant strategy.[4-7] However, the NPC-9901 trial cautioned that the benefit for distant control was inadequate, particularly for patients with regionally advanced disease, partly due to poor compliance in the adjuvant phase.[8,9]

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In 2005, the Hong Kong Nasopharyngeal Cancer Study Group initiated the current multicenter randomized controlled trial to evaluate 3 promising strategies. The first is to change the chemotherapy sequence from concurrent-adjuvant to induction-concurrent, based on encouraging results reported from phase 2 studies.[10] This is theoretically advantageous because induction chemotherapy is often well tolerated, and the upfront use of cytotoxic drugs could be more efficacious in eradicating micrometastases. Furthermore, this strategy could shrink the primary tumor to allow for a wider margin for RT, which is particularly desirable for tumors infiltrating and/or abutting neurological structures.[11]

The second strategy is to improve on the PF regimen by replacing infusional 5-fluorouracil (F) with oral capecitabine (X). In addition to the obvious advantage of convenience,[12] capecitabine is potentially superior because it is metabolized to 5-fluorouracil via a 3-step enzymatic cascade with the final conversion mediated by thymidine phosphorylase, an enzyme that is present at significantly higher concentrations in a wide range of solid tumors compared with normal tissue. Furthermore, uracil analogues may have an antiangiogenic effect.[13]

The third strategy is to change RT fractionation from conventional to acceleration. The NPC-9902 trial[14] suggested that accelerated-fractionation with concurrent-adjuvant chemotherapy achieved better outcomes compared with the conventional-fractionation sequence, with a 5-year overall failure-free rate of 88% versus 65%.

To the best of our knowledge, the current trial is the only trial that has attempted to evaluate these 3 strategies compared with the Intergroup 0099 regimen. Preliminary 3-year results were reported in 2015.[15] With continual follow-up, all surviving patients have now been observed for >5 years. The objective of the current study, which has demonstrated detailed 5-year results regarding efficacy and safety, was to improve current practice and establish directions for future exploration.

MATERIALS AND METHODS

Patients

Eligible patients had histologically confirmed nonkeratinizing (differentiated or undifferentiated) NPC using the World Health Organization classification, and stage III to stage IVB disease using the 6th edition of the American Joint Committee on Cancer/International Union Against Cancer.[16,17] Other inclusion criteria were age 18 to 69 years, an Eastern Cooperative Oncology Group performance status ≤2, and adequate hematologic and renal function.

The protocol (ClinicalTrials.gov identifier NCT00379262)[18] was approved by the institutional ethics committees of the 7 individual participating centers, and the trial was monitored by an independent data monitoring committee (DMC). All patients provided written consent.

Study Design and Randomization

Eligible patients were stratified by participating center and stage of disease (stage III vs stage IV), and randomization was performed using sealed envelopes that were prepared by the DMC. The original protocol (September 2006) aimed to randomize eligible patients in equal proportions to the 6 treatment arms (the 6-arm full-randomization cohort). The protocol was amended in January 2009 following the recommendation of the DMC: individual centers who encountered logistical difficulties in arranging 6 fractions per week were allowed to opt out of the accelerated-fractionation portion of the trial to improve accrual (the 3-arm chemotherapy cohort) (Fig. 1). The protocol was amended further in February 2011, adding comparison of chemotherapy sequence (induction-concurrent by combining both induction regimen groups vs concurrent-adjuvant) as a secondary objective. These changes were made while results remained blinded.

Treatment and Assessment

Patients in all treatment arms were treated as per protocol. RT consisting of a total dose ≥70 grays (Gy) (66 Gy for patients with T1-T2a disease) was given to the macroscopic tumor targets, and a total dose ≥50 Gy was administered to potential sites of local infiltration and bilateral cervical lymphatics. Additional boosts (≤20 Gy) could be administered to the parapharyngeal space, the primary tumor, or lymph node sites (when indicated) with the exclusion of critical structures. The number of fractions per week was 5 in the conventional-fractionation group (Fr(Con); group A) and in the 3-arm chemotherapy cohort (Fr(NonR); group C). In the accelerated-fractionation group (Fr(Acc); group B), 6 fractions per week were planned, with the sixth fraction given either on Saturday or on a weekday with ≥6 hours between fractions.

Patients in all treatment arms were given concurrent cisplatin at a dose of 100 mg/m^2 by intravenous infusion

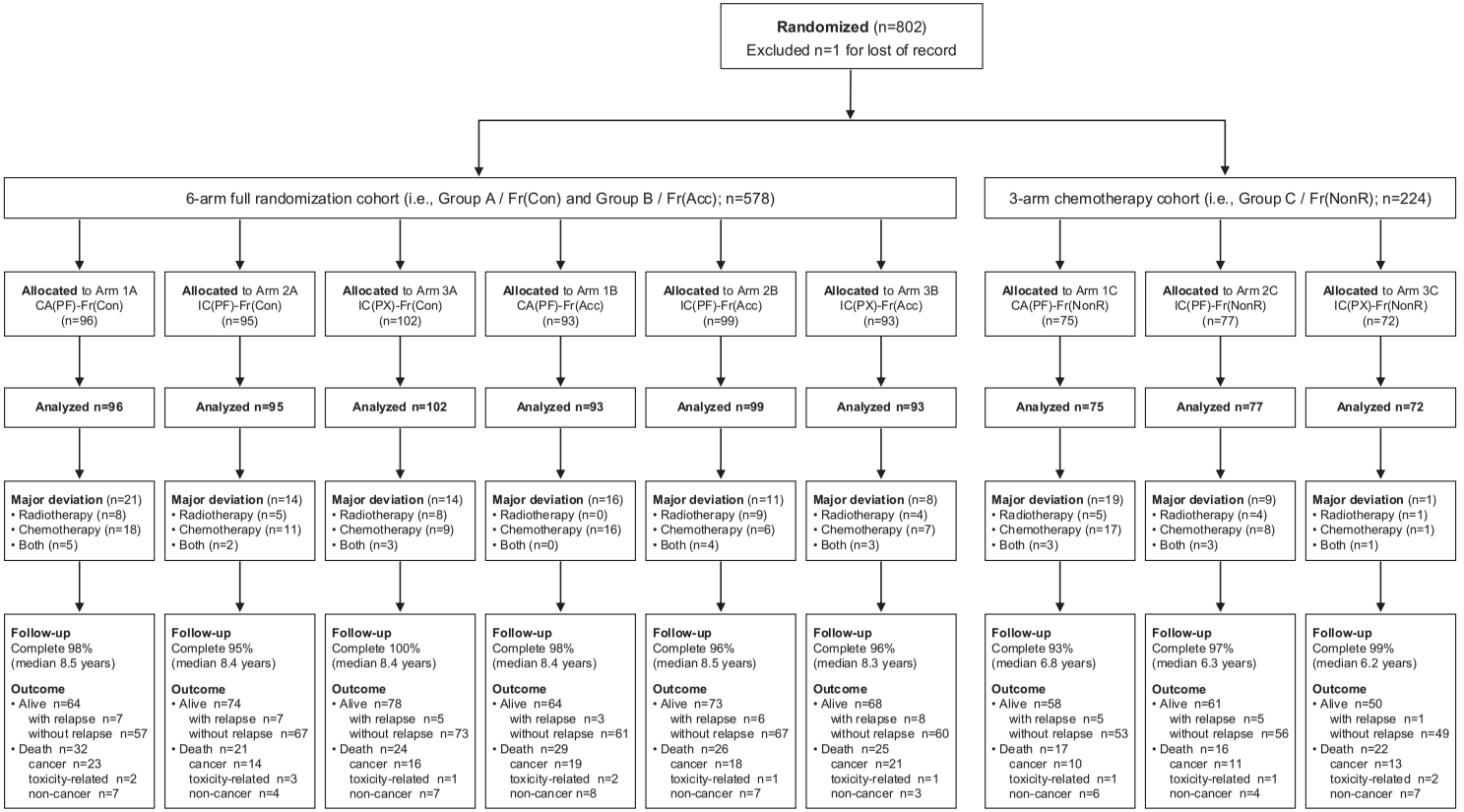

FIGURE 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of the NPC-0501 trial. CA(PF) indicates concurrent cisplatin plus adjuvant cisplatin and 5-fluorouracil regimen; Fr(Acc), accelerated-fractionation radiotherapy group; Fr(Con), conventional-fractionation radiotherapy group; Fr(NonR), nonrandomized-fractionation radiotherapy group (ie, the 3-arm chemotherapy cohort without randomization on fractionation); IC(PF), induction cisplatin and 5-fluorouracil plus concurrent cisplatin regimen; IC(PX), induction cisplatin and capecitabine plus concurrent cisplatin regimen.

every 21 days for 2 to 3 cycles (depending on overall RT time). Patients allocated to the adjuvant-PF arms (CA(PF); arm 1) were given adjuvant cisplatin at a dose of 80 mg/m^2 by intravenous infusion and 5-fluorouracil at a dose of 1000 mg/m^2/day by intravenous infusion for 96 hours every 28 days for 3 cycles. Patients allocated to the induction-PF arms (IC(PF); arm 2) were given induction cisplatin at a dose of 100 mg/m^2 by intravenous infusion and 5-fluorouracil at a dose of 1000 mg/m^2/day by intravenous infusion for 120 hours every 21 days for 3 cycles. For patients allocated to the induction-PX arms (IC(PX); arm 3), 5-fluorouracil was replaced with capecitabine at a dose of 2000 mg/m^2/day orally for 14 days per cycle. Dose modifications were permitted according to protocol-specified criteria.

The first assessment of tumor response was performed 6 to 16 weeks after the completion of RT. Persistent primary or lymph node disease at 16 weeks after the completion of RT was regarded as locoregional failure. Common Terminology Criteria for Adverse Events (version 3.0) was used to grade toxicities.

Statistical Analysis

All analyses were performed on an intention-to-treat basis and the tests were 2-sided; defining events for actuarial rates were measured from the date of randomization. The standard treatment arm was the adjuvant-PF arm with conventional-fractionation (CA(PF)-Fr(Con); arm 1A). Five-year results were estimated from previous reports.[5,6,14]

The primary endpoints were progression-free survival (PFS) (time to first failure at any disease site or death from any cause) and overall survival (OS) (time to death from any cause). Secondary endpoints for treatment efficacy included the overall failure-free rate (FFR) (time to failure at any disease site, censoring death without failure), locoregional FFR, and distant FFR. Secondary endpoints for safety included major acute and late toxicities (grade ≥3).

To detect a 10% difference in the PFS rate from 65% in the standard group to 75% in the experimental groups with a type I error of 0.05 and 80% power, the target accrual was 798 patients.

Comparisons stipulated by the protocol included a primary comparison regarding: 1) chemotherapy regimen (IC(PF) vs CA(PF) and IC(PX) vs CA(PF)); and 2) fractionation (Fr(Acc) vs Fr(Con)). Secondary comparisons were with regard to chemotherapy sequence (induction-concurrent vs concurrent-adjuvant [IC(PF/PX) vs CA(PF)]) and induction regimen (IC(PX) vs IC(PF)).

The stratified log-rank test was used: comparisons based on chemotherapy regimen and/or sequence were stratified by RT group, whereas comparisons regarding fractionation were stratified by chemotherapy regimen. In addition, univariable analyses were performed to identify other significant factors affecting outcome, and exploratory multivariable analyses using Cox regression were performed to evaluate the independent significance of treatment intervention: the hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs) were estimated.

With the inclusion of both PFS and OS as primary endpoints for this 5-year report (as stipulated by protocol), Bonferroni adjustment for multiple comparisons was applied: the 2-sided P value for statistical significance was <.025 for primary outcomes with respect to an overall 5% type I error. For secondary outcomes, explanatory analyses, and other tests, 2-sided P values <.05 were considered to be statistically significant.

Statistical analyses regarding chemotherapy regimen and/or sequence were based on the whole series because all patients were randomized for chemotherapy, including the cohort that opted out of randomization on fractionation (the 3-arm chemotherapy cohort). However, analyses concerning fractionation had to be confined to patients who were randomized equally to both chemotherapy and RT (the 6-arm full-randomization cohort) (as explained below).

RESULTS

Basic Characteristics and Treatment

From September 2006 to September 2012, a total of 803 eligible patients from 7 participating centers were accrued; all were evaluable except for 1 patient with lost records. The number of patients in the 6-arm full-randomization cohort was 578 and the number of patients in the 3-arm chemotherapy cohort was 224. Basic characteristics were found to be well balanced among all groups (Table 1).

However, analyses regarding treatment parameters demonstrated a significant imbalance with regard to RT dose and/or fraction and total dose (both $P < .001$). Detailed review of RT records demonstrated marked heterogeneity in RT prescription schedules, with the dose per fraction ranging from 1.8 to 2.27 Gy and the total dose ranging from 66 to 74 Gy. Although RT parameters were well balanced across the different arms of conventional fractionation (Fr(Con) group) and accelerated fractionation (Fr(Acc) group) in the 6-arm full-randomization cohort, they were significantly different in the

TABLE 1. Basic Characteristics

	Entire Series N = 802						
	Arm 1A and 1C N = 171	Arm 2A and 2C N = 172	Arm 3A and 3C N = 174	Arm 1B N = 93	Arm 2B N = 99	Arm 3B N = 93	
Regimen	Adjuvant-PF	Induction-PF	Induction-PX	Adjuvant-PF	Induction-PF	Induction-PX	*P*[a]
RT fraction per wk	5	5	5	6	6	6	
Patient characteristics							
Mean age (SD), y	49 (9)	49 (9)	48 (10)	49 (9)	48 (8)	49 (9)	.98
Male sex	129 (75%)	125 (73%)	139 (80%)	73 (79%)	75 (76%)	72 (77%)	.72
ECOG performance status							.80
0	122 (71%)	111 (65%)	116 (67%)	64 (69%)	62 (63%)	61 (66%)	
1	47 (28%)	60 (35%)	58 (33%)	29 (31%)	36 (36%)	31 (33%)	
2	2 (1%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	
Tumor factors							
Staging method							.29
MRI ± CT	166 (97%)	167 (97%)	167 (96%)	89 (96%)	93 (94%)	93 (100%)	
CT alone	5 (3%)	5 (3%)	7 (4%)	4 (4%)	6 (6%)	0 (0%)	
T classification							.73
T1-T2	29 (17%)	33 (19%)	37 (21%)	23 (24%)	26 (27%)	19 (20%)	
T3	115 (67%)	114 (66%)	109 (63%)	58 (63%)	57 (58%)	55 (59%)	
T4	27 (16%)	25 (14%)	28 (16%)	12 (13%)	16 (16%)	19 (20%)	
N classification							.22
N0-N1	61 (36%)	49 (28%)	39 (22%)	22 (23%)	22 (22%)	23 (25%)	
N2	85 (49%)	99 (57%)	110 (63%)	53 (57%)	60 (61%)	52 (56%)	
N3	25 (15%)	24 (14%)	25 (14%)	18 (19%)	17 (17%)	18 (19%)	
AJCC/UICC stage group							.70
III	122 (71%)	127 (74%)	124 (71%)	66 (71%)	67 (68%)	60 (65%)	
IVA-IVB	49 (29%)	45 (26%)	50 (29%)	27 (29%)	32 (33%)	33 (35%)	
Mean LDH (SD), U/L	224 (75)	235 (113)	235 (92)	241 (100)	248 (93)	255 (129)	.20

	Six-Arm Full Randomization Cohort N = 578						
	Arm 1A N = 96	Arm 2A N = 95	Arm 3A N = 102	Arm 1B N = 93	Arm 2B N = 99	Arm 3B N = 93	
Regimen	Adjuvant-PF	Induction-PF	Induction-PX	Adjuvant-PF	Induction-PF	Induction-PX	*P*[a]
RT fractionation	Conventional	Conventional	Conventional	Accelerated	Accelerated	Accelerated	
Patient characteristics							
Mean age (SD), y	47 (9)	48 (9)	48 (9)	49 (9)	48 (8)	49 (9)	.84
Male sex	65 (68%)	67 (70%)	80 (78%)	73 (78%)	75 (77%)	72 (77%)	.35
ECOG performance status							.95
0	64 (67%)	57 (60%)	66 (65%)	64 (69%)	62 (63%)	61 (66%)	
1	31 (32%)	37 (39%)	36 (35%)	29 (31%)	36 (36%)	31 (33%)	
2	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	
Tumor factor							
Staging method							.35
MRI ± CT	92 (96%)	92 (97%)	97 (95%)	89 (96%)	93 (94%)	93 (100%)	
CT alone	4 (4%)	3 (3%)	5 (5%)	4 (4%)	6 (6%)	0 (0%)	

TABLE 1. *Continued*

	Six-Arm Full Randomization Cohort N = 578						
	Arm 1A N = 96	Arm 2A N = 95	Arm 3A N = 102	Arm 1B N = 93	Arm 2B N = 99	Arm 3B N = 93	
Regimen	Adjuvant-PF	Induction-PF	Induction-PX	Adjuvant-PF	Induction-PF	Induction-PX	P^a
RT fractionation	Conventional	Conventional	Conventional	Accelerated	Accelerated	Accelerated	
T classification							.98
T1-T2	21 (22%)	21 (22%)	24 (24%)	23 (25%)	26 (26%)	19 (20%)	
T3	59 (61%)	58 (61%)	59 (58%)	58 (62%)	57 (58%)	55 (59%)	
T4	16 (17%)	16 (17%)	19 (19%)	12 (13%)	16 (16%)	19 (20%)	
N classification							.99
N0-N1	22 (23%)	19 (21%)	20 (20%)	22 (24%)	22 (22%)	23 (25%)	
N2	53 (55%)	59 (61%)	63 (62%)	53 (57%)	60 (61%)	52 (56%)	
N3	21 (22%)	17 (18%)	19 (19%)	18 (19%)	17 (17%)	18 (19%)	
AJCC/UICC stage group							.93
III	62 (65%)	65 (68%)	67 (66%)	66 (71%)	67 (68%)	60 (65%)	
IVA-IVB	34 (35%)	30 (32%)	35 (34%)	27 (29%)	32 (32%)	33 (35%)	
Mean LDH (SD), U/L	241 (91)	255 (137)	255 (103)	241 (100)	245 (88)	255 (129)	.87

Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; F, 5-fluorouracil; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; P, cisplatin; RT, radiotherapy; UICC, International Union Against Cancer; X, capecitabine.

[a]Comparison was made using the chi-square test, Fisher exact test, or analysis of variance (ANOVA) whenever appropriate.

3-arm chemotherapy cohort (see Supporting Table 1) due to changes in prescription schedules among the opt-out centers with the increasing use of a larger fractional dose (≥2.18 Gy) and higher total dose (>70 Gy). With such serious imbalances in RT prescription, the 3-arm chemotherapy cohort could not be combined with Fr(Con) group (although both were irradiated with 5 fractions per week) and had to be considered as a distinct RT stratum (Fr(NonR) group). Moreover, the comparisons regarding RT fractionation could be based only on the 6-arm full-randomization cohort.

A total of 775 patients (97%) were staged using magnetic resonance imaging and 747 patients (93%) were treated with intensity-modulated RT (IMRT) (see Supporting Table 1). Approximately 97% of patients had regular follow-up until death or the latest assessment. The median duration of follow-up was 8.4 years.

Efficacy

The comparisons based on the primary endpoints (PFS and OS) are summarized in Table 2 and those based on the secondary endpoints are summarized in Supporting Table 2.

Comparisons on Fractionation

Analyses were confined to patients who were randomized equally to both chemotherapy and RT (the 6-arm full-randomization cohort). Overall comparisons (irrespective of chemotherapy regimen) demonstrated that the Fr(Acc) group did not demonstrate improvements in any endpoint compared with the Fr(Con) group (5-year PFS: 71.3% vs 72.3% [$P = .73$] and 5-year OS: 79.7% vs 79.8% [$P = .36$]) (Fig. 2). The same pattern also was observed within each chemotherapy regimen stratum.

Comparisons Regarding Chemotherapy

The overall comparison of chemotherapy regimens irrespective of RT fractionation groups demonstrated that neither induction regimen achieved a statistically significant improvement compared with adjuvant-PF. The PFS (Fig. 3A) for induction-PF versus adjuvant-PF (IC(PF) vs CA(PF)) was 74.4% versus 69.1% at 5 years ($P = .16$), whereas that for the induction-PX versus adjuvant-PF (IC(PX) vs CA(PF)) was 74.8% versus 69.1% ($P = .14$) and the PFS for the induction-concurrent sequence compared with the concurrent-adjuvant sequence (IC(PF/PX) vs CA(PF)) was 74.6% versus 69.1% ($P = .094$).

However, the pattern varied among the 3 RT fractionation groups. In the conventional-fractionation group, improvement in PFS (overall $P = .045$) (Fig. 3B) was

TABLE 2. Comparisons Regarding Primary Efficacy Endpoints: Actuarial Results At 5 Years and HRs (95% CIs)

Endpoints	Progression-Free Survival			Overall Survival		
	No. of Events and/or Patients	5-Year Rate	HR (95% CI)	No. of Events and/or Patients	5-Year Rate *P*	HR (95% CI)
Comparison of Fractionation in the 6-Arm Full Randomization Cohort (N = 578)						
Accelerated Versus Conventional Fractionation						
Overall comparison: arms 1-3B vs arms 1-3A	97/285 (1-3B) vs 96/293 (1-3A)	71.3% vs 72.3% .73	1.05 (0.79-1.39)	80/285 (1-3B) vs 77/293 (1-3A)	79.7% vs 79.8% .36	1.10 (0.80-1.50)
Adjuvant-PF regimen: arm 1B vs arm 1A	32/93 (1B) vs 39/96 (1A)	70.6% vs 61.5% .53	0.80 (0.50-1.27)	29/93 (1B) vs 32/96 (1A)	76.1% vs 71.9% .91	0.92 (0.56-1.53)
Induction-PF regimen: arm 2B vs arm 2A	32/99 (2B) vs 28/95 (2A)	71.7% vs 76.7% .70	1.13 (0.68-1.88)	26/99 (2B) vs 21/95 (2A)	79.4% vs 84.1% .30	1.25 (0.70-2.21)
Induction-PX regimen: arm 3B vs arm 3A	33/93 (3B) vs 29/102 (3A)	71.7% vs 78.4% .37	1.33 (0.81-2.19)	25/93 (3B) vs 24/102 (3A)	83.7% vs 83.3% .61	1.18 (0.67-2.01)
Comparison of Chemotherapy in the Entire Series (N = 802)						
Induction-PF Versus Adjuvant-PF Regimen						
Overall comparison: arms 2A-2C vs arms 1A-1C	81/271 (2A-2C) vs 93/264 (1A-1C)	74.4% vs 69.1% .16	0.82 (0.63-1.11)	63/271 (2A-2C) vs 78/264 (1A-1C)	81.7% vs 77.4% .16	0.77 (0.56-1.08)
Conventional fractionation: arm 2A vs arm 1A	28/95 (2A) vs 39/95 (1A)	76.7% vs 61.5% .061	0.65 (0.40-1.05)	21/95 (2A) vs 32/96 (1A)	84.1% vs 71.9% .079	0.62 (0.36-1.08)
Accelerated fractionation: arm 2B vs arm 1B	32/99 (2B) vs 32/93 (1B)	71.7% vs 70.6% .80	0.91 (0.56-1.49)	26/99 (2B) vs 29/93 (1B)	79.4% vs 76.1% .50	0.82 (0.48-1.39)
*3-arm chemotherapy cohort: arm 2C vs arm 1C	21/77 (2C) vs 22/75 (1C)	75.3% vs 76.9% .84	1.00 (0.55-1.82)	16/77 (2C) vs 17/75 (1C)	81.7% vs 86.3% .86	1.00 (0.51-1.99)
Induction-PX Versus Adjuvant-PF Regimen						
Overall comparison: arms 3A-3C vs arms 1A-1C	85/267 (3A-3C) vs 93/264 (1A-1C)	74.8% vs 69.1% .14	0.85 (0.63-1.14)	71/267 (3A-3C) vs 78/264 (1A-1C)	82.2% vs 77.4% .46	0.86 (0.62-1.19)
Conventional fractionation: arm 3A vs arm 1A	29/102 (3A) vs 39/96 (1A)	78.4% vs 61.5% .027	0.60 (0.37-0.97)	24/102 (3A) vs 32/96 (1A)	83.3% vs 71.9% .097	0.64 (0.38-1.08)
Accelerated fractionation: arm 3B vs arm 1B	33/93 (3B) vs 32/93 (1B)	71.7% vs 70.6% .61	0.99 (0.61-1.60)	25/93 (3B) vs 29/93 (1B)	83.7% vs 76.1% .45	0.81 (0.47-1.38)
*3-arm chemotherapy cohort: arm 3C vs arm 1C	23/72 (3C) vs 22/75 (1C)	73.6% vs 76.9% .69	1.16 (0.65-2.09)	22/72 (3C) vs 17/75 (1C)	78.8% vs 86.3% .15	1.54 (0.82-2.91)
Induction-Concurrent vs Concurrent-Adjuvant Sequence						
Overall comparison: arms 2A-2C and 3A-3C vs 1A-1C	166/538 (2A-2C and 3A-3C) vs 93/264 (1A-1C)	74.6% vs 69.1% .094	0.84 (0.65-1.08)	134/538 (2A-2C and 3A-3C) vs 78/264 (1A-1C)	81.9% vs 77.4% .23	0.82 (0.62-1.08)
Conventional fractionation: arms 2A and 3A vs 1A	57/197 (2A and 3A) vs 39/96 (1A)	77.6% vs 61.5% .015	0.62 (0.41-0.94)	45/197 (2A and 3A) vs 32/96 (1A)	83.6% vs 71.9% .042	0.63 (0.40-0.99)
Accelerated fractionation: arms 2B and 3B vs 1B	65/192 (2B and 3B) vs 32/93 (1B)	71.7% vs 70.6% .66	0.95 (0.62-1.45)	51/192 (2B and 3B) vs 29/93 (1B)	81.5% vs 76.1% .45	0.81 (0.52-1.29)
*3-arm chemotherapy cohort: Arm 2C and 3C vs 1C	44/149 (2C and 3C) vs 22/75 (1C)	74.5% vs 76.9% .91	1.08 (0.65-1.80)	38/149 (2C and 3C) vs 17/75 (1C)	80.3% vs 86.3% .36	1.26 (0.71-2.23)
Comparison of Induction Regimens PX Versus PF						
Overall comparison: arms 3A-3C vs 2A-2C	85/267 (3A-3C) vs 81/271 (2A-2C)	74.8% vs 74.4% .81	1.03 (0.76-1.40)	71/267 (3A-3C) vs 63/271 (2A-2C)	82.2% vs 81.7% .69	1.11 (0.79-1.56)
Conventional fractionation: arm 3A vs arm 2A	29/102 (3A) vs 28/95 (2A)	78.4% vs 76.7% .69	0.93 (0.55-1.56)	24/102 (3A) vs 21/95 (2A)	83.3% vs 84.1% .89	1.03 (0.57-1.85)
Accelerated fractionation: arm 3B vs arm 2B	33/93 (3B) vs 32/99 (2B)	71.7% vs 71.7% .92	1.08 (0.66-1.78)	25/93 (3B) vs 26/99 (2B)	83.7% vs 79.4% .83	0.99 (0.57-1.71)
*3-arm chemotherapy cohort: arm 3C vs arm 2C	23/72 (3C) vs 21/77 (2C)	73.6% vs 75.3% .42	1.16 (0.64-2.10)	22/72 (3C) vs 16/77 (2C)	78.8% vs 81.7% .25	1.53 (0.80-2.92)

Abbreviations: 95% CI, 95% confidence interval; arm 1, concurrent cisplatin plus adjuvant cisplatin and 5-fluorouracil regimen; arm 2: induction cisplatin and 5-fluorouracil plus concurrent cisplatin regimen; arm 3, induction cisplatin and capecitabine plus concurrent cisplatin regimen; F, 5-fluorouracil; group A, conventional fractionation group in 6-arm full-randomization cohort; group B, accelerated fractionation group; group C, *3-arm chemotherapy cohort (the group opting for comparison of chemotherapy without randomization on fractionation); HR, hazard ratio; P, cisplatin; X, capecitabine.

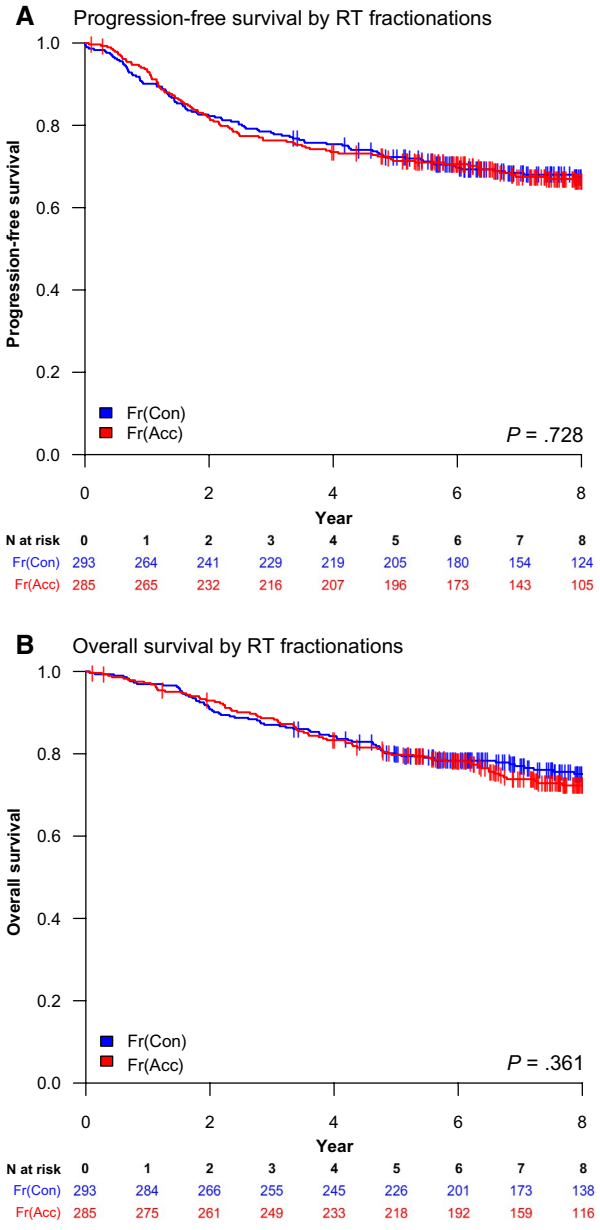

FIGURE 2. Overall comparison of radiotherapy (RT) fractionation (accelerated vs conventional) irrespective of chemotherapy regimen in terms of (A) progression-free survival and (B) overall survival. Fr(Acc) indicates accelerated-fractionation radiotherapy group; Fr(Con), conventional-fractionation radiotherapy group; N at risk, number at risk.

marginally significant by induction-PX (IC(PX)-Fr(Con) vs CA(PF)-Fr(Con): 78.4% vs 61.5% [$P = .027$]) and borderline by induction-PF (IC(PF)-Fr(Con) vs CA(PF)-Fr(Con): 76.7% vs 61.5% [$P = 0.061$]) after Bonferroni adjustment. The induction-concurrent sequence (IC(PF/PX)-Fr(Con) vs CA(PF)-Fr(Con)) demonstrated significant improvement in PFS (77.6% vs 61.5%; $P = .015$) (Fig. 4A) and marginal improvement in OS (83.6% vs 71.9%; $P = .042$) (Fig. 4B). However, no significant differences were observed in the Fr(Acc) and Fr(NonR) groups by either regimen ($P \geq .62$) (Fig. 3C,D) or by sequence.

The differences between the induction-PF and induction-PX groups were insignificant both by overall comparison and within each RT fractionation group ($P \geq .25$).

Multivariable Analyses of the Independent Significance of Experimental Interventions

Univariable analyses demonstrated that age, sex, stage of disease, lactate dehydrogenase, RT technique, total dose, dose per fraction, and treatment center had a significant impact on various efficacy endpoints (see Supporting Table 3), while ethnic group was not tested because all the patients were Chinese.

Exploratory multivariable analyses for RT fractionation, based on the 6-arm full-randomization cohort (see Supporting Fig. 1), confirmed that accelerated-fractionation had no beneficial effect on any endpoint, including locoregional FFR (HR, 1.33; 95% CI, 0.86-2.07 [$P = .20$]).

Another exploratory multivariable analysis of chemotherapy regimen and/or sequence, based on the entire series (Fig. 5), demonstrated that induction-PF resulted in a borderline improvement in OS when compared with adjuvant-PF (IC(PF) vs CA(PF): HR, 0.71; 95% CI, 0.50-1.01 [$P = .055$]), whereas induction-PX achieved marginal improvement in overall comparisons (IC(PX) vs CA(PF)) for both PFS (HR, 0.72; 95% CI, 0.53-0.99 [$P = .040$]) and OS [HR, 0.71; 95% CI, 0.50-1.00 [$P = .048$]) after adjustment for multiple comparisons. The resulting impact by induction-concurrent sequence (IC(PF/PX) vs CA(PF)) was significant for OS (HR, 0.71; 95% CI, 0.53-0.95 [$P = .022$]) and marginal for PFS (HR, 0.74; 95% CI, 0.57-0.97 [$P = .029$]). In the conventional-fractionation group, significant improvements were achieved not only with regard to PFS and OS, but also with regard to distant FFR by induction-PX (IC(PX)-Fr(Con) vs CA(PF)-Fr(Con): HR, 0.38; 95% CI, 0.19-0.75 [$P = .005$]) and by the induction-concurrent sequence (IC(PF/PX)-Fr(Con) vs CA(PF)-Fr(Con): HR, 0.47; 95% CI, 0.27-0.82 [$P = .008$]).

Safety

Comparison of fractionation (irrespective of chemotherapy regimen) demonstrated no significant difference in the overall actuarial rate of all late toxicities (grade

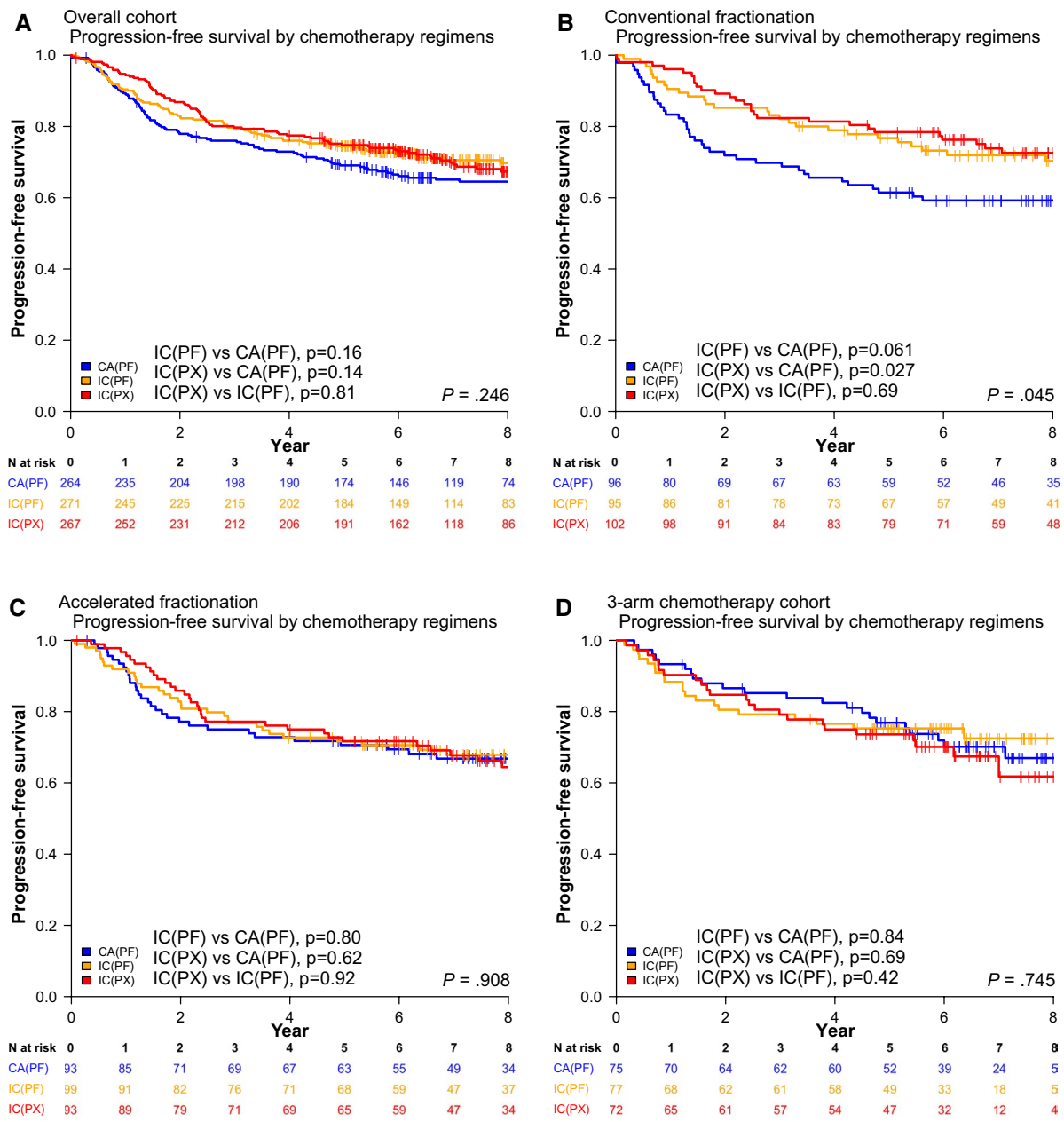

FIGURE 3. Comparison of chemotherapy regimens (induction cisplatin and 5-fluorouracil [PF] vs induction cisplatin and capecitabine [PX] vs adjuvant PF) for (A) the entire series irrespective of radiotherapy, (B) the conventional-fractionation group, (C) the accelerated-fractionation group, and (D) the 3-arm chemotherapy cohort in terms of progression-free survival. CA(PF) indicates concurrent cisplatin plus adjuvant cisplatin and 5-fluorouracil regimen; IC(PF), induction cisplatin and 5-fluorouracil plus concurrent cisplatin regimen; IC(PX), induction cisplatin and capecitabine plus concurrent cisplatin regimen; N at risk, number at risk.

≥3) between the 2 RT fractionation groups (Fr(Con) vs Fr(Acc)) (see Supporting Table 2). Overall comparison of different chemotherapy regimens and sequences (irrespective of RT fractionation groups) also demonstrated no significant difference in the overall actuarial toxicity rate ($P \geq .44$) (see Supporting Table 2). However, the pattern was found to be affected by fractionation. In the conventional-fractionation group, the induction-concurrent sequence was found to have a significantly lower late toxicity rate compared with the concurrent-adjuvant sequence (IC(PF/PX)-Fr(Con) vs CA(PF)-Fr(Con): 15.0% vs 26.5% [$P = .006$]), but the pattern was found to be reversed in the accelerated-fractionation group (IC(PF/PX)-Fr(Acc) vs CA(PF)-Fr(Acc): 22.3% vs 10.5% [$P = .016$]).

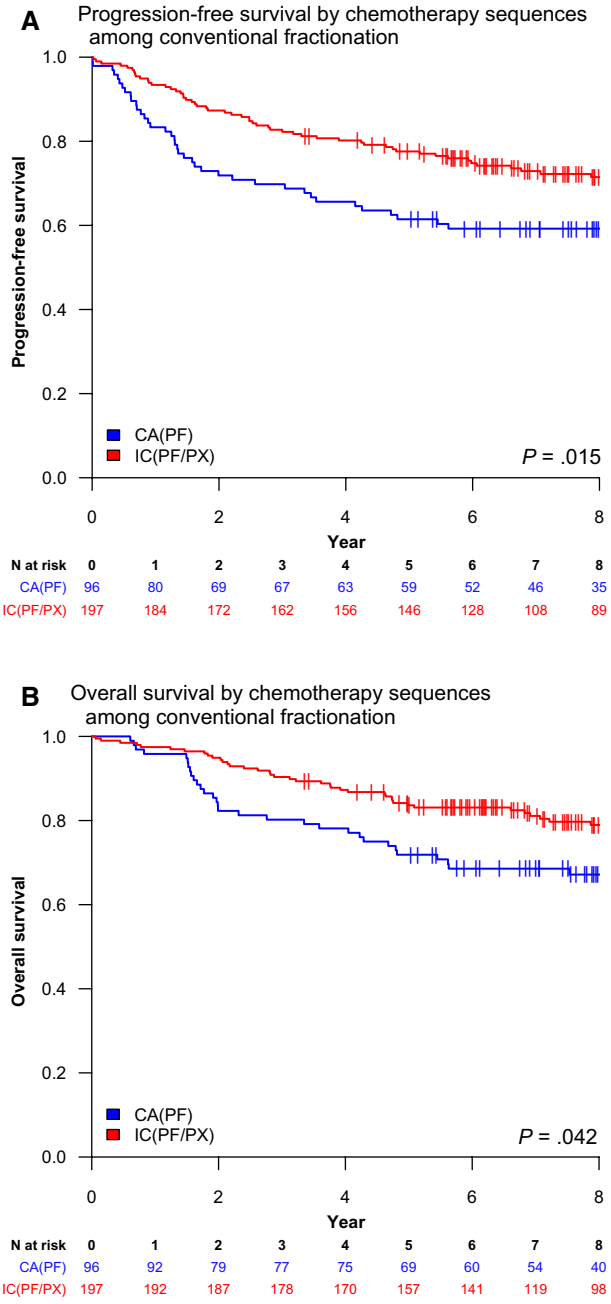

FIGURE 4. Comparison of chemotherapy sequence (combined induction cisplatin and 5-fluorouracil [PF] and/or cisplatin and capecitabine [PX] vs adjuvant PF) for the conventional-fractionation group in terms of (A) progression-free survival and (B) overall survival. CA(PF) indicates concurrent cisplatin plus adjuvant cisplatin and 5-fluorouracil regimen; IC(PF/PX), induction-concurrent sequence (inclusive of both induction cisplatin and 5-fluorouracil or cisplatin and capecitabine regimens); N at risk, number at risk.

The cumulative incidence counts of major toxicities at different sites are summarized in Supporting Table 4. In the conventional-fractionation group, the induction-concurrent sequence (IC(PF/PX)-Fr(Con) vs CA(PF)-Fr(Con)) resulted in a significantly lower incidence of cranial neuropathy (0.5% vs 4.1%; $P = .041$) and hearing loss and/or otitis (13.2% vs 24.0%; $P = .032$) but a higher incidence of peripheral neuropathy (8% vs 1%; $P = .040$) compared with concurrent-adjuvant chemotherapy.

DISCUSSION

As it is always a tremendous challenge to conduct a multicenter randomized trial, we ambitiously aimed to make use of this valuable opportunity to address as many issues as possible. Back in 2005, apart from the interest in evaluating the induction-concurrent chemotherapy sequence, the potential for accelerated fractionation and substituting 5-fluorouracil with more potent and/or convenient drugs were strategies to be explored. Hence, the NPC-0501 trial was planned with a complex 6-arm factorial design. The analyses were complicated further by the change of protocol in 2009: on the recommendation of the DMC to expedite accrual, centers with logistical difficulties in administering 6 RT fractions per week were allowed to opt out of randomization regarding fractionation. However, the 3-arm chemotherapy cohort caused a major imbalance in RT parameters due to changes in prescription schedules among the opt-out centers (see Supporting Table 1), with dose painting by IMRT using acceleration by fractional dose ≥2.18 Gy and higher total dose ($P < .001$). Hence, this cohort had to be taken as a distinct RT stratum in the analyses concerning chemotherapy sequence to eliminate the possibility of bias from this source.

Based on overall comparisons regarding RT fractionation (irrespective of chemotherapy regimen) (Fig. 2) and chemotherapy regimen and/or sequence (irrespective of RT fractionation) (Fig. 3) by log-rank tests as stipulated in the trial protocol, the experimental interventions did not demonstrate a significant impact on any efficacy endpoint (Table 2) (see Supporting Table 2). However, secondary analyses demonstrated that, when adjusted for RT fractionation groups and other significant factors, the improvement achieved by the induction-concurrent sequence was significant for OS and marginal for PFS when compared with adjuvant-PF (Fig. 5).

The current study findings confirmed that coupling accelerated-fractionation with chemoradiotherapy is not beneficial for patients with advanced NPC (Fig. 2) (see Supporting Fig. 1). This observation also is in keeping with the GORTEC (Groupe d'Oncologie Radiothérapie Tête Et Cou) 99-02 trial[19] and the Radiation Therapy

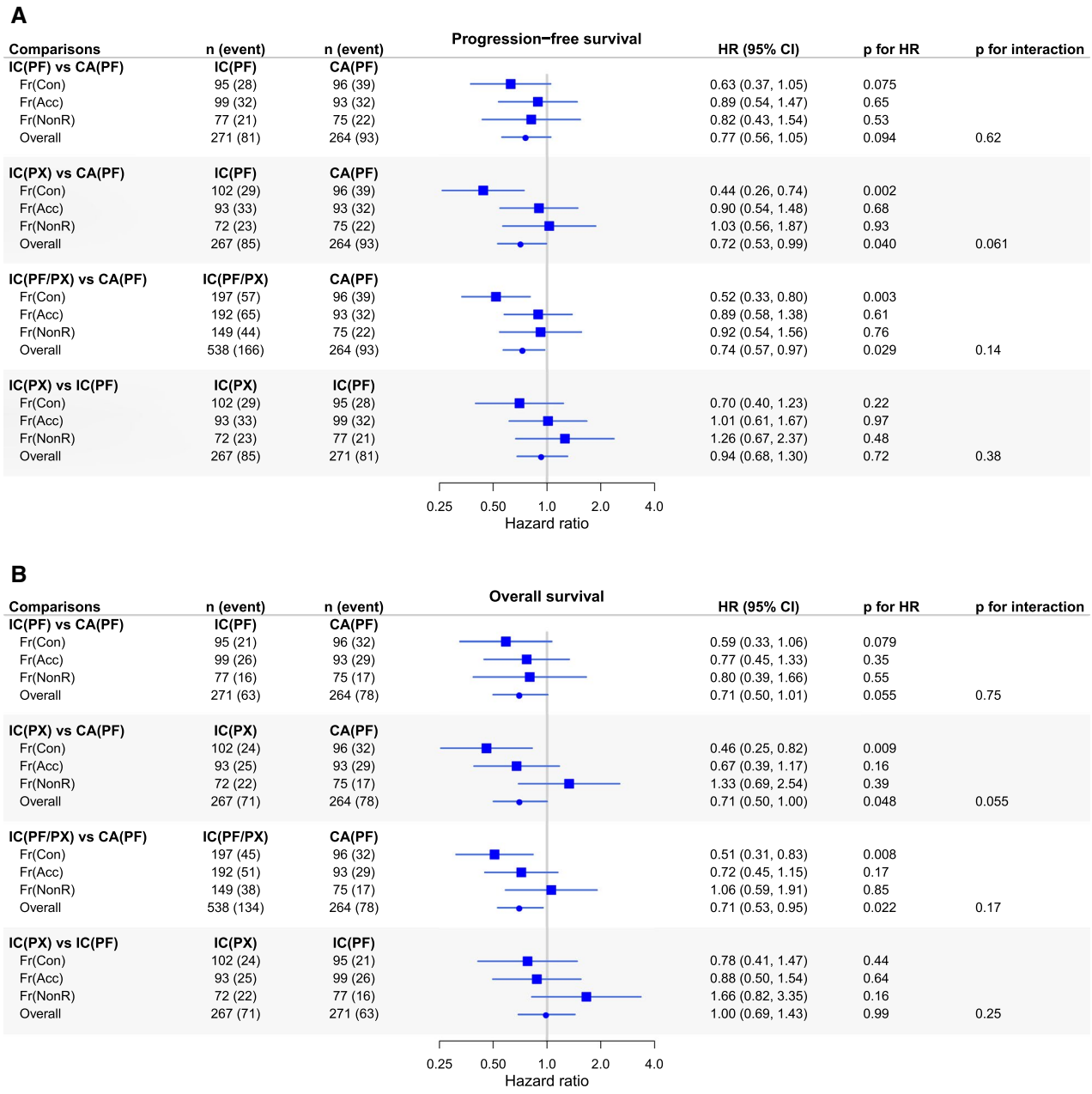

FIGURE 5. Forest plot of the independent significance of chemotherapy in the entire series by multivariable analyses in terms of (A) progression-free survival, (B) overall survival, (C) distant failure-free rate, and (D) locoregional failure-free rate. The analyses were adjusted for radiotherapy groups together with other significant factors including age, sex, stage of disease, lactate dehydrogenase, radiotherapy (technique, total dose, and dose per fraction), and treatment center. CA(PF) indicates concurrent cisplatin plus adjuvant cisplatin and 5-fluorouracil regimen; Fr(Acc), accelerated-fractionation group; Fr(Con), conventional-fractionation group; Fr(NonR), nonrandomized-fractionation group (ie, the 3-arm chemotherapy cohort without randomization on fractionation); HR, hazard ratio; IC(PF), induction cisplatin and 5-fluorouracil plus concurrent cisplatin regimen; IC(PF/PX), induction-concurrent sequence (inclusive of both induction regimens); IC(PX), induction cisplatin and capecitabine plus concurrent cisplatin regimen.

Oncology Group (RTOG)–0129 Study[20] on other head and neck cancers. However, what to our knowledge is less well recognized is the potential interaction between fractionation and chemotherapy. To our knowledge, the current trial is the first to indicate that acceleration could negate the potential benefit of changing from a concurrent-adjuvant sequence to an induction-concurrent sequence (Fig. 3). Hence, we concur with the National

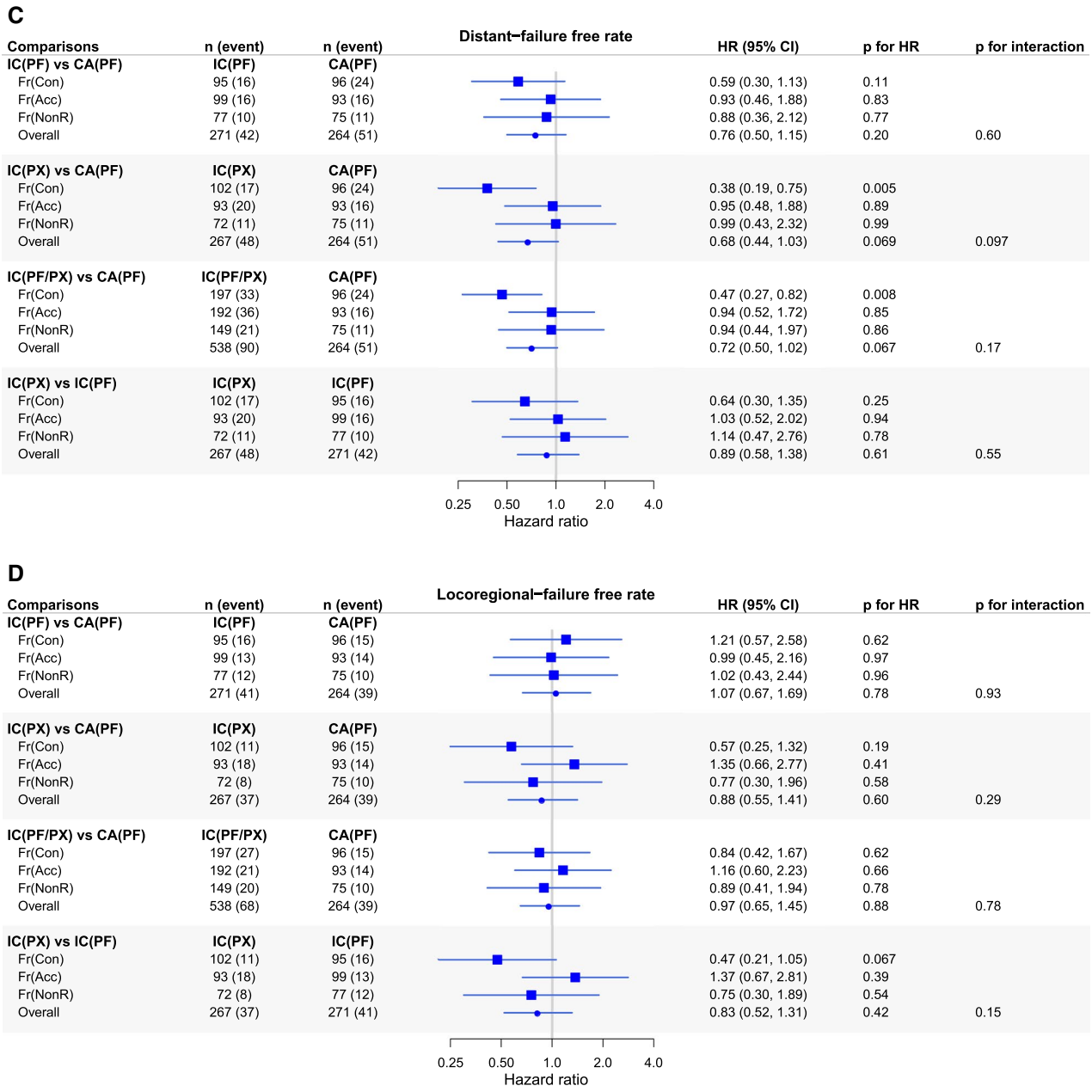

FIGURE 5. *Continued.*

Comprehensive Cancer Network guideline that treatment with 70 to 70.2 Gy, at 1.8 to 2 Gy per fraction, for 5 fractions per week is the preferred concurrent RT regimen.[2]

For the conventional-fractionation group in the current study, the induction-concurrent sequence (IC(PF/PX)-Fr(Con) vs CA(PF)-Fr(Con)) achieved a significant benefit in PFS (78% vs 62%; $P = .015$) (Fig. 4A) and a marginal benefit in OS (84% vs 72%; $P = .042$) (Fig. 4B) when compared with the concurrent-adjuvant sequence. The impact on efficacy was attributed entirely to improvements in distant control (Fig. 5) (see Supporting Table 2). Although there was no significant differences in efficacy noted between the 2 induction regimens, only induction-PX achieved a significant reduction in distant failure when adjusted for other significant factors (HR, 0.38; 95% CI, 0.19-0.75) (Fig. 5). The current long-term results demonstrated that there was no significant difference in the overall late toxicity

TABLE 3. Summary of Randomized Phase 2 to 3 Trials Evaluating Induction-Concurrent Chemotherapy With Conventional-Fractionation Radiotherapy

		Stage				Progression-Free Survival		Overall Survival	
Study	No.[a]	Inclusion	% Stage IV	Induction Regimen	Time	Actuarial Rate *P*	HR (95% CI)	Actuarial Rate *P*	HR (95% CI)
Induction Plus Concurrent Cisplatin Versus Concurrent Cisplatin									
Hui 2009[21]	65	III-IVB	41.5	PT	3 y	88% vs 60% .12	0.49 (0.20-1.19)	94% vs 68% .012	0.24 (0.078-0.73)
Fountzilas 2012[22]	141	IIB-IVB	41.1	PEPa	3 y	65% vs 64% .71	0.71 (0.36-2.44)	67% vs 72% .65	1.05 (0.53-2.08)
Tan 2015[23]	172	T3-T4 or N2-N3	40.1	GCPa	3 y	75% vs 67%[b] NR	0.77[b] (0.44-1.35)	94% vs 92% NR	1.05 (0-2.19)[c]
Li 2019[24]	480	III-IVB	46.5	Modified TPF	5 y	77% vs 66%[b] .019	0.67[b] (0.49-0.94)	86% vs 78% .042	0.65 (0.43-0.98)
Cao 2017[25]	476	III-IVB	47.3	PF	3 y	82% vs 74%[b] .028	0.67[b] (0.47-0.95)	88% vs 89% .82	0.90 (0.57-1.42)
Frikha 2018[26]	83	T2b-T4 or N1-N3	NR	TPF	3 y	74% vs 57% .042	0.44 (0.20-0.97)	86% vs 69% .059	0.40 (0.15-1.04)
Hong 2018[27]	479	IVA-IVB	100	MEPFL	5 y	61% vs 50%[b] .026	0.74[b] (0.57-0.97)	72% vs 68% .62	0.92 (0.67-1.27)
Zhang 2019[28]	480	III-IVB	52	GP	3 y	85% vs 77% .002	0.51 (0.34-0.77)	95% vs 90% NR	0.43 (0.24-0.77)
Induction Plus Concurrent Cisplatin Versus Concurrent Cisplatin Plus Adjuvant Cisplatin and 5-Fluorouracil With Conventional Fractionation									
Current study	191[d]	III-IV	34	PF	5 y	77% vs 62% .061	0.65 (0.40-1.05)	84% vs 72% .079	0.62 (0.36-1.08)
	198[e]		35	PX	5 y	78% vs 62% .027	0.60 (0.37-0.97)	83% vs 72% .097	0.64 (0.38-1.08)
	293[f]		34	Combined PF/PX	5 y	78% vs 62% .015	0.62 (0.41-0.94)	84% vs 72% .042	0.63 (0.40-0.99)

Abbreviations: 95% CI, 95% confidence interval; C, carboplatin; E, epirubicin; F, 5-fluorouracil; G, gemcitabine; HR, hazard ratio; L, leucovorin; M, mitomycin; NR, not reported; P, cisplatin; Pa, paclitaxel; T, docetaxel; X, capecitabine.
[a]Number of patients in the experimental arm and the standard arm.
[b]Disease-free survival.
[c]One-sided 95% CI.
[d]Standard arms 2A plus 1A in the current study.
[e]Standard arms 3A plus 1A in the current study.
[f]Standard arms 2A to 3A plus 1A in the current study.

rate between induction-PX and adjuvant-PF among the conventional-fractionation group (IC(PX)-Fr(Con) vs CA(PF)-Fr(Con): 19.1% vs 26.5% [$P = .095$]) (see Supporting Table 2). Taken together with the obvious advantage of the convenience of using capecitabine (given orally) compared with 5-fluorouracil (given by infusion), induction-PX is favored.

Although the conventional-fractionation group only was considered as a stratum by protocol, information regarding the therapeutic benefit in this group is most relevant and important in clinical practice. To the best of our knowledge, all other randomized trials and meta-analyses regarding the evaluation of chemoradiotherapy were based on patients who were irradiated using the conventional-fractionation sequence. On the other hand, 8 other randomized trials regarding induction-concurrent chemoradiotherapy have been published to date, all of which used the concurrent-alone sequence as the standard treatment arm (Table 3).[21-28] Although conflicting results initially were reported,[21-23] all recent trials demonstrated consistent improvements in disease-free survival.[24-28] In a systematic review focused on the comparison of the induction-concurrent versus concurrent-alone sequences of chemoradiotherapy,[29] based on 2802 patients from 6 randomized trials and 5 observational studies, the induction-concurrent scheme was confirmed to be superior for both PFS and OS.

A randomized trial by Chen et al[30] demonstrated no significant differences in efficacy between concurrent alone versus concurrent-adjuvant chemoradiotherapy, but in the individual patient data network meta-analysis by the Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma (MAC-NPC),[31] based on 5144 patients from 20 trials, concurrent-adjuvant chemotherapy was found to achieve the greatest survival benefit and consistent improvement in all endpoints. Hence, the current study, which to our knowledge is the only study to date that used the Intergroup 0099 concurrent-adjuvant regimen

as the standard treatment arm, is particularly valuable for assessing the chemotherapy sequence. We concur with the findings of the MAC-NPC[31] that induction-concurrent chemotherapy achieved better distant control, as well as the results of the publication-based network meta-analysis by You et al[32] that demonstrated that induction-concurrent chemotherapy was effective for OS, PFS, and distant FFS.

One major strength of the current trial was that approximately 97% of patients had regular follow-up, and the median duration was 8.4 years. The pattern of care nearly matched the current standard with approximately 96% of patients staged with magnetic resonance imaging and 92% irradiated with IMRT. However, a major weakness of the current study was inadequacy in central monitoring and quality assurance. We relied on the site investigators of the participating centers to ensure quality and we allowed for flexibility for centers to establish department policy regarding RT schedules. Although this reflects reality in the clinical world, more stringent control and standardization of the fractional dose and total dose should be considered in future trials, particularly with a better understanding of the impact of altered fractionation on chemotherapy. Another weakness is the complex multiple comparisons: the number accrued in each group was underpowered to reach statistical significance. Last, the main results of the current study regarding chemotherapy were based on subgroup and exploratory analyses, and therefore further validation is needed.

The current study focused on results based on intention-to-treat as per protocol, but further analyses with which to study the relative impact of different treatment factors on locoregional and distant failures will be valuable for generating potential hypotheses for future improvements. We currently are preparing an additional exploratory study based on actual treatment to evaluate: 1) whether the observed benefit in distant control observed with induction-PX is attributed to the timing and relative dose intensity of chemotherapy, and/or intrinsic differences in efficacy between 5-fluorouracil and capecitabine; 2) whether induction chemotherapy may lead to a deleterious effect on local control; and 3) the correlation between local control and RT factors. The full exploratory analyses will be presented in a separate article.

Conclusions

To the best of our knowledge, the NPC-0501 trial is the only randomized trial to date to evaluate the therapeutic ratio of the induction-concurrent versus concurrent-adjuvant sequences and accelerated versus conventional fractionation. The results of the current study demonstrated that coupling chemoradiotherapy with accelerated fractionation is not recommended. For patients treated with conventional fractionation, although further validation is needed, the data from the current study favored changing from the concurrent-adjuvant to the induction-concurrent sequence because this could achieve significant improvements in PFS and marginal improvements in OS without an adverse impact on late toxicity.

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CONFLICT OF INTEREST DISCLOSURES

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Anne W.M. Lee, **Roger K.C. Ngan**, **Stewart Y. Tung**, and **Rick Chappell** designed the study. **Anne W.M. Lee**, **Roger K.C. Ngan**, **Wai-Tong Ng**, **Stewart Y. Tung**, **Ashley A.C. Cheng**, **Dora L.W. Kwong**, **Tai-Xiang Lu**, **Anthony T.C. Chan**, **Henry C.K. Sze**, **Harry H.Y. Yiu**, **Frank C.S. Wong**, and **Kam-Tong Yuen** participated in data collection. **Rick Chappell** and **Horace C.W. Choi** performed the statistical analyses. **Anne W.M. Lee**, **Roger K.C. Ngan**, **Wai-Tong Ng**, **Rick Chappell**, and **Horace C.W. Choi** participated in data interpretation and writing the article. All authors gave final approval for publication.

DATA AVAILABILITY

The data set will be shared with the Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma (MAC-NPC) collaborative group.

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