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Clinical Trial

Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase III multicentre randomised controlled trial

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KEYWORDS
Locoregionally advanced nasopharyngeal carcinoma;
Induction chemotherapy;
Concurrent chemoradiotherapy;
Randomised controlled trial;
Long-term results

Abstract ***Background:*** Initial 3-year results from our clinical trial in locoregionally advanced nasopharyngeal carcinoma (NPC) patients showed that induction chemotherapy (IC) with cisplatin and fluorouracil resulted in improved disease-free survival (DFS) with a marginally significant effect on distant metastasis-free survival (DMFS), but the effect of IC on locoregional relapse-free survival and overall survival (OS) did not differ significantly. Here, we present 5-year follow-up results.

Patients and methods: Our trial was a randomised, open-label phase III trial comparing IC followed by concurrent chemoradiotherapy (CCRT) versus CCRT alone in patients with stage III-IVB (except T3N0-1) NPC. The IC followed by CCRT group received cisplatin (80 mg/m^2 d1) and fluorouracil (800 mg/m^2 d1-5) every 3 weeks for two cycles before CCRT. Both groups were treated with 80 mg/m^2 cisplatin every 3 weeks concurrently with radiotherapy. The primary end-points were DFS and DMFS. We did efficacy analyses in the 476 randomised patients (intention-to-treat population).

Results: After a median follow-up of 82.6 months, the 5-year DFS rate was 73.4% (95% confidence interval [CI] 67.7–79.1) in the IC followed by CCRT group and 63.1% (95% CI 56.8–69.4) in the CCRT alone group ($p = 0.007$). The 5-year DMFS rate was also significantly higher in the IC followed by CCRT group (82.8%, 95% CI 77.9–87.7) than in the CCRT alone group (73.1%, 95% CI 67.2–79.0, $p = 0.014$). Our updated analysis revealed an OS benefit of IC: the 5-year OS rate was 80.8% in the IC followed by CCRT group versus 76.8% in the CCRT alone group ($p = 0.040$). The proportion of patients with eye damage was significantly higher in the CCRT alone group than the IC followed by CCRT group (16.4% [39/238] versus 9.7% [23/238], $p = 0.029$).

Conclusion: IC followed by CCRT provides long-term DFS, DMFS and OS benefits compared with CCRT alone in locoregionally advanced NPC and, therefore, can be recommended for these patients.

1. Introduction

Nasopharyngeal carcinoma (NPC) accounts for more than 80, 000 newly diagnosed cancer cases per year worldwide with a unique, unbalanced endemic distribution. The highest incidences of NPC were reported in the East and Southeast Asia [1]. More than 70% of newly diagnosed NPC patients present with potentially curable, locoregionally advanced disease [2]. Historically, less than 50% of these patients live for 3 years after standard radiotherapy alone, and 40–60% eventually develop locoregional recurrences or distant metastases [3,4].

Various strategies combining chemotherapy with radiotherapy have been implemented to improve outcomes [4–13]; the updated Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma (MAC-NPC) further support the use of concomitant chemotherapy [14]. Nevertheless, the chemotherapy timing (i.e. induction chemotherapy [IC] plus concurrent chemoradiotherapy [CCRT], CCRT alone or CCRT plus adjuvant chemotherapy [AC]) remains to be defined. Recent network meta-analysis (NMA) by the MAC-NPC Collaborative Group showed that the addition of AC to concomitant chemoradiotherapy (CRT) achieved the highest survival benefit, but IC-CCRT ranked first for distant control [15]. However, the AC was often poorly tolerated leading to non-compliance [16]. Compared with CCRT-AC strategy, IC-CCRT offers the advantages of better tolerance and early eradication of micrometastases [17,18]. With encouraging results from recent randomised, controlled trials [5,6,9], IC-CCRT strategy has been clearly recommended for patients with locoregionally advanced NPC in current treatment guidelines [19].

Our previous IC trial for NPC was a randomised phase III trial to confirm the effectiveness of IC followed by CCRT compared with CCRT alone in patients with stage III-IVB (except T3N0-1) NPC [5]. Initial 3-year results showed that IC with cisplatin and fluorouracil (PF) resulted in improved disease-free survival (DFS) with a marginally significant effect on distant metastasis-free survival (DMFS), but the effect of IC on locoregional relapse-free survival (LRRFS) and overall survival (OS) did not differ significantly. Thereafter, we reported one individual patient data pooled analysis and one NMA including our trial and demonstrated the superiority of additional IC over CCRT alone in locoregionally advanced NPC with survival benefit that was mainly because of the reduction in distant metastases [20,21]. It was important to determine whether this survival benefit sustained for a longer duration, and there was no comparison of late toxicities in our initial analysis. Herein, we report the updated 5-year follow-up data of the long-term survival and late toxicities of IC in

patients with locoregionally advanced NPC to assess its therapeutic efficacy.

2. Patients and methods

2.1. Patient eligibility and random assignment

Details of our trial protocol have been published previously [5]. Between June 2008 and February 2015, we conducted an open-label phase III multicentre randomised controlled trial at four institutions in China. Eligible patients were aged 18–60 years with previously untreated, biopsy-proven non-keratinising stage III or IVb NPC, except T3N0-1 (6th American Joint Committee on Cancer [AJCC] staging system). Written informed consent was obtained from all patients. Our trial was approved by the ethical committee or institutional review board at each centre.

Randomisation procedures were conducted by a computer-generated random number code at the Clinical Trials Centre of Sun Yat-sen University Cancer Centre. Details of the random allocations were contained in sequentially numbered, opaque, sealed envelopes prepared by a statistician with no clinical involvement in the trial. Patients were randomly assigned in a 1:1 ratio with a block size of 10 (known only to the statistician). Randomisation was stratified by treatment centre and disease stage (T4N0-1, T1-3N2–3 or T4N2-3). After informed consent was obtained from eligible patients, the investigators at each centre opened the envelopes sequentially and assigned the patients to the corresponding interventions.

2.2. Procedures

Patients received either two cycles of PF IC followed by CCRT or CCRT alone. In the IC group, PF was administered as cisplatin 80 mg/m^2 intravenously on days 1 and 22 and fluorouracil 800 mg/m^2 as a continuous 120 h infusion on days 1–5 and 22–26; the two cycles were administered at intervals of 3 weeks. The chemotherapy component of the CCRT regimen consisted of 80 mg/m^2 cisplatin every 3 weeks for three cycles, beginning on the first day of radiotherapy. All patients received external beam radiation daily fractions for a week at 2.0–2.33 Gy per fraction, using either two-dimensional radiotherapy (2DRT) or intensity-modulated radiotherapy (IMRT), consistent with the treatment policy of each centre. The details of radiotherapy techniques, dose modifications for both chemotherapy and radiotherapy and follow-up had been previously reported [5].

The primary end-points of our study were DFS and DMFS, and our secondary end-point was OS. The DFS was defined as the duration from the date of patient randomisation to the date of locoregional or distant failure or death resulting from any cause, whichever occurred first. The OS was defined as the duration from the date of patient randomisation to the date of death resulting from any cause. DMFS was defined as the duration from the date of randomisation to the date of documented distant metastasis or death from any cause; LRRFS was defined as the duration from the date of randomisation to the date of documented locoregional relapse or death from any cause. The long-term toxicities (>6 months after the completion of radiotherapy) were graded according to the Common Terminology Criteria for Adverse Events, version 4.03 [22].

2.3. Statistical analysis

We anticipated that 151 events were required in approximately 338 patients (169 patients per group) for the primary analysis of 5-year DFS. We estimated that the study would have a 90% power to detect a hazard ratio (HR) for DFS of 0.56 (two-sided log-rank test; p = 0·05). We needed to recruit a minimum of 398 patients in total (199 patients per group), assuming 15% early dropout or loss to follow-up. Similarly, we anticipated that 117 events were required in approximately 344 patients (172 patients per group) as for the primary analysis of 5-year DMFS. This yielded a final sample size of 398 (199 patients per group) [5,23].

This updated analysis was done in the intention-to-treat population, and thus, all randomised patients were included in the study. We estimated median follow-up with the reverse Kaplan–Meier method [24]. Survival curves for the time-to-event end-points were analysed by the Kaplan–Meier method and compared using the log-rank test that were stratified according to trial centre and disease stage (primary analysis). The HRs and corresponding 95% confidence intervals (CIs) were calculated using the stratified Cox proportional hazards model. We performed multivariable analyses with the Cox proportional hazard model to test the independent significance of the treatment interventions if the proportional hazard hypothesis was not violated. The incidence of late adverse events and other categorical variables were compared using the χ^2 test or Fisher's exact test as appropriate. All statistical tests were two-sided, and a p value less than 0.05 was deemed statistically significant. All analyses were done with STATA (version 12.0). This trial is registered with Clinical Trials.gov, number NCT00705627 and all data in our study have been recorded at Sun Yat-sen University Cancer Center with an Research Data Deposit (RDD) number of RDDA2019001045.

3. Results

In the initial and updated analyses, 476 patients were randomised and included on an intention-to-treat basis.

Of these patients, 78 were dead, and 398 were alive at the time of the initial analysis in May 2016. As of Jul 13, 2018, 343 patients were alive including 21 who were lost to follow-up, and 55 new patients had died (Fig. 1). For this analysis, the 21 patients lost to follow-up were deemed to be alive, and data from the 2016 initial analysis were used. Table 1 provides the baseline characteristics for the randomised patients in our study. More patients in the CCRT alone group than in the IC followed by CCRT group received 2DRT; the baseline characteristics of patients were otherwise well balanced.

After a median follow-up of 82.6 months (range 2.6–120.0 months), the DFS advantage seen in the original report was sustained: the proportion of patients with DFS at 5 years was 73.4% (95% CI 67.7–79.1) in the IC followed by CCRT group and 63.1% (95% CI 56.8–69.4) in the CCRT alone group (stratified HR 0.66 [95% CI 0.48–0.89], p = 0.007; Table 2, Fig. 2A). The 5-year DMFS rate was also significantly higher in the IC followed by CCRT group (82.8%, 95% CI 77.9–87.7) than the CCRT alone group (73.1%, 95% CI 67.2–79.0, stratified HR = 0.61 [95% CI 0.41–0.91], p = 0.014; Table 2, Fig. 2B).

Although no significant difference in OS between the two treatment groups could be detected in the initial analysis, our updated analysis revealed an OS benefit of IC followed by CCRT versus CCRT alone: the 5-year

Table 1
Baseline characteristics.

Characteristic	IC+CCRT group (n = 238) No. of patients (%)	CCRT alone group (n = 238) No. of patients (%)
Age, years		
Median	44	42
Range	19–65	21–66
Sex		
Men	173 (72.7)	190 (79.8)
Women	65 (27.3)	48 (20.2)
T classification		
T1	4 (1.7)	1 (0.4)
T2	44 (18.5)	48 (20.2)
T3	108 (45.4)	107 (45.0)
T4	82 (34.5)	82 (34.5)
N classification		
N0	12 (5.0)	8 (3.4)
N1	35 (14.7)	39 (16.4)
N2	145 (60.9)	164 (68.9)
N3	46 (19.3)	27 (11.3)
Staging		
II	1 (0.4)	0 (0.0)
III	117 (49.2)	133 (55.9)
IV	120 (50.4)	105 (44.1)
Radiotherapy technique		
2DRT	122 (51.3)	149 (62.6)
IMRT	116 (48.7)	89 (37.4)

IC = induction chemotherapy; CCRT = concurrent chemoradiotherapy; 2DRT = two-dimensional radiotherapy; IMRT = intensity-modulated radiotherapy.

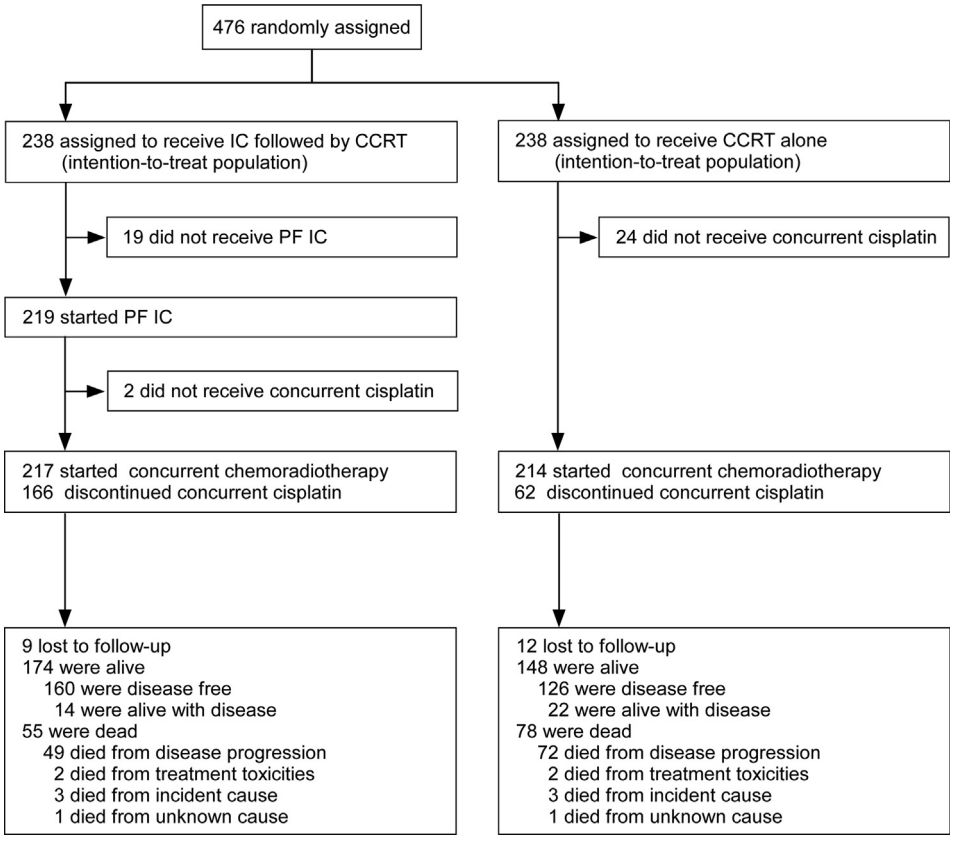


Fig. 1. **Trial profile.** IC = induction chemotherapy; CCRT = concurrent chemoradiotherapy; PF = cisplatin and fluorouracil.

Table 2
Comparison between treatment groups of the time dependent endpoints.

	IC+CCRT group (n = 238)	CCRT alone group (n = 238)	Hazard ratio[a] (95% CI)	p value
Disease-free survival				
Event no.(%)	71 (30)	103 (43)		
Rate %			0.66 (0.48–0.89)	0.007
At 3 years	81.1	74.3		
At 5 years	73.4	63.1		
Overall survival				
Event no.(%)	55 (23)	78 (33)		
Rate-%			0.69 (0.49–0.98)	0.040
At 3 years	88.7	88.2		
At 5 years	80.8	76.8		
Distant metastasis-free survival				
Event no.(%)	42 (18)	66 (28)		
Rate-%			0.61 (0.41–0.91)	0.014
At 3 years	86.1	82.0		
At 5 years	82.8	73.1		
Locoregional relapse-free survival				
Event no.(%)	32 (13)	41 (17)		
Rate-%			0.74 (0.46–1.18)	0.208
At 3 years	92.6	89.0		
At 5 years	87.9	85.0		

IC = induction chemotherapy; CCRT = concurrent chemoradiotherapy; CI = confidence interval
[a] Hazard ratios were calculated by a stratified Cox proportional-hazards model.

OS rate was 80.8% in the IC followed by CCRT group versus 76.8% in the CCRT alone group (stratified HR = 0.69 [95% CI 0.49–0.98], p = 0.040; Table 2, Fig. 2C). There was no significant difference in LRRFS for patients at 3-year follow-up as well as at 5-year follow-up (87.9% versus 85.0%, stratified HR = 0.74 [95% CI 0.46–1.18], p = 0.208; Table 2, Fig. 2D).

In multivariable analyses, treatment group was a significant predictive factor for DMFS (HR 0.65, 95% CI 0.44–0.96; p = 0.03) and DFS (HR 0.68, 95% CI 0.50–0.92; p = 0.01, Supplementary Table 1). The impact on OS remained borderline significant (p = 0.06, Supplementary Table 1), but the impact on LRRFS remained insignificant (p = 0.31, Supplementary Table 1).

We performed subgroup analyses for DMFS, DFS and OS in patients stratified by the following characteristics (covariates): sex (male, female), age (≤43, >43), tumour category (T1-2, T3-4), nodal category (N0-1, N2-3) and radiotherapy technique (2DRT, IMRT). No interactions between these covariates and treatment were observed (all p > 0.1; Fig. 3) indicating that the benefit of additional IC did not differ among specific populations.

Details of the adverse events during treatment have been previously reported [5]. In brief, the most common grade 3-4 adverse event during induction chemotherapy was neutropenia (14.7%). During CCRT, the overall incidence of grade 3-4 adverse events in the IC followed by CCRT group was significantly higher than that in the CCRT alone group (66.3% versus 49.1%, p < 0.001).

We assessed long-term toxicity in the updated data set according to the National Cancer Institute Common Terminology Criteria (Table 3). Two (0.8%) of 238 patients in the IC followed by CCRT group and two (0.8%) of 238 patients in the CCRT alone group died from dysphagia. Among all late radiation-related toxicities, the most common late adverse events in both groups were auditory toxicities. During follow-up, the proportion of patients with eye damage was significantly higher in the CCRT alone group than the IC followed by CCRT group (16.4% [39/238] versus 9.7% [23/238], p = 0.029, Table 3); major differences were observed in the incidences of grade 1–2 eye damage. The incidence rate of radiation-induced cranial nerve palsy was 16.0% (38/238) in the CCRT alone group versus 10.1% (24/238) in the IC followed by CCRT group, with marginal statistical significance (p = 0.057, Table 3).

4. Discussion

In this long-term analysis of our trial, with a median follow-up of 6.88 years, OS, DFS and DMSF were all significantly better in patients treated with IC followed by CCRT than in those treated with CCRT alone, thus reconfirming the conclusions reached in the early publication of the study after a median follow-up of 3 years. The absence of interactions between patient characteristics and treatment effects indicated the benefit of additional induction chemotherapy did not differ among specific populations. Long-term toxicities did not differ between treatment groups.

More than 70% of cases of newly diagnosed NPC present with locoregionally advanced disease (stage III-IV according to the 6th AJCC staging system) [2]. Despite improved locoregional control through the combined use of magnetic resonance imaging, IMRT and CCRT, long-term survival remains poor and distant metastasis is a major reason for treatment failure in long-term survivors [25–27]. Data from early trials and encouraging results from meta-analyses have revived interest in the use of induction chemotherapy before definitive radiotherapy. On the basis of initial reports of Hong Kong [9], GZ2011 [6] and our GZ2008 trial [5], induction chemotherapy followed by CCRT is now the standard treatment for locoregionally advanced NPC. Nonetheless, the contribution of induction chemotherapy is still poorly defined, and long-term results of randomised trials are expected to establish whether IC followed by CCRT is superior to CCRT alone.

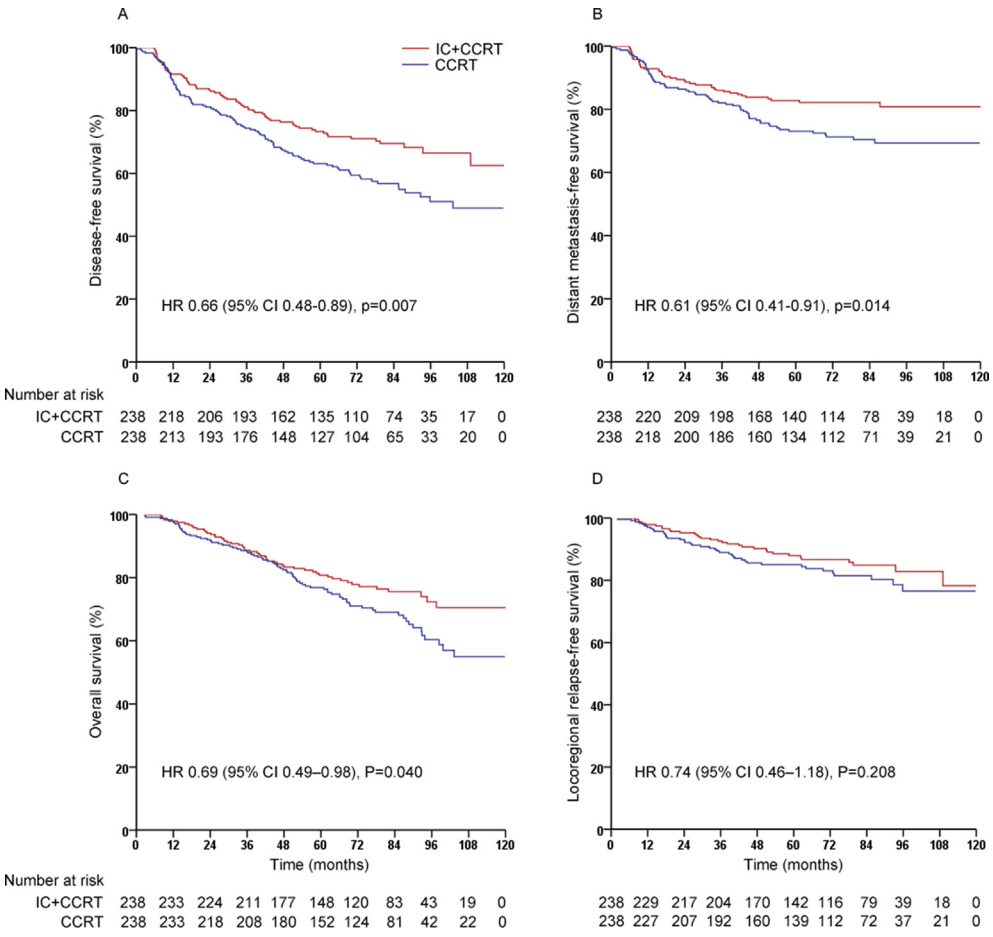


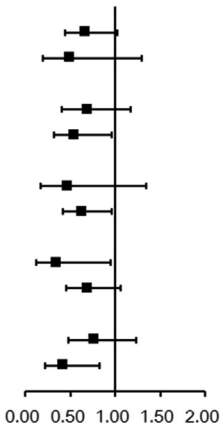
Fig. 2. **Kaplan–Meier survival curves for the IC followed by CCRT group and the CCRT alone group.** (A) Disease-free survival, (B) distant metastasis-free survival, (C) overall survival and (D) locoregional relapse-free survival. Red lines indicate the IC followed by CCRT group; blue lines indicate the CCRT alone group. Hazard ratios (HRs) were calculated with a stratified Cox proportional-hazards model. IC = induction chemotherapy. CCRT = concurrent chemoradiotherapy; CI = confidence interval.

In this context, the long-term analysis of induction chemotherapy trials, such as our GZ2008 trial, is important in establishing the long-term therapeutic efficacy as 5-year analyses can reveal changes in outcomes of trials compared with the preliminary findings. As we reported earlier, at 3 years, the difference in OS between treatment groups was not statistically significant [5]. With longer follow-up, however, the survival curves showed some separation, and the difference was significant at a median follow-up of 6.88 years. This finding could be related to the relatively low mortality rates among NPC patients. NPC responds well to chemotherapy and radiation; even patients treated with CCRT alone generally have a promising outlook [5–7]. Therefore, given the small numbers of deaths in either treatment group, an extended follow-up was needed to allow for a sufficient number of events to detect differences between two very effective treatments. Moreover, patients with disease recurrence may still be amenable to satisfactory salvage treatment such as re-irradiation, chemotherapy and surgery improving the efficacy of the regimen. The updated results of our study suggest that the improvement in DFS and DMFS of IC continued well beyond the 3 years of the original analysis and was sustained at the same level. Deaths in later years of follow-up resulted in OS changing from non-significant to significant for IC followed by CCRT compared with CCRT alone.

In this updated report, PF IC followed by CCRT improved not only DMFS and DFS but also OS at 5 years in patients with locoregionally advanced NPC. The 5-year DFS rates were 73.4% in the IC followed by CCRT group and 63.1% in the CCRT alone group. The 5-year OS rates were 80.8% and 76.8%, respectively. The treatment outcomes in both groups of our study were slightly inferior to those reported by Li *et al.* [28], which might be because 271 (56.9%) of 476 patients were treated with 2DRT. Moreover, our previous study indicated that IMRT can prolong the long-term survival of NPC patients compared with 2DRT [25,26]. Therefore, it is possible that IMRT might result in further improvements in treatment outcomes of both the IC followed by CCRT and CCRT alone groups.

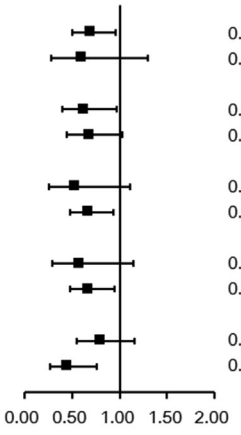
A

	No. of events/no. entered IC+CCRT	CCRT	HR	95% CI	Pinteraction
Sex					
Male	35/173	56/190	0.67	0.44-1.02	0.55
Female	7/65	10/48	0.49	0.19-1.30	
Age, years					
≤43	22/112	35/127	0.69	0.41-1.18	0.56
>43	20/126	31/111	0.55	0.31-0.96	
T classification					
T1-2	5/48	11/49	0.47	0.16-1.34	0.66
T3-4	37/190	55/189	0.64	0.42-0.96	
N classification					
N0-1	5/47	14/47	0.34	0.12-0.95	0.21
N2-3	37/191	52/191	0.69	0.45-1.05	
Radiotherapy technique					
2DRT	28/122	44/149	0.77	0.48-1.23	0.20
IMRT	14/116	22/89	0.42	0.21-0.82	



B

	No. of events/no. entered IC+CCRT	CCRT	HR	95% CI	Pinteraction
Sex					
Male	59/173	89/190	0.69	0.50-0.96	0.71
Female	12/65	14/48	0.60	0.28-1.30	
Age, years					
≤43	31/112	53/127	0.62	0.40-0.97	0.76
>43	40/126	50/111	0.68	0.45-1.03	
T classification					
T1-2	11/48	20/49	0.53	0.25-1.11	0.61
T3-4	60/190	83/189	0.67	0.48-0.94	
N classification					
N0-1	13/47	22/47	0.57	0.29-1.14	0.63
N2-3	58/191	81/191	0.68	0.48-0.95	
Radiotherapy technique					
2DRT	46/122	68/149	0.80	0.55-1.16	0.12
IMRT	25/116	35/89	0.45	0.27-0.76	



C

	No. of events/no. entered IC+CCRT	CCRT	HR	95% CI	Pinteraction
Sex					
Male	43/173	65/190	0.74	0.50-1.08	0.78
Female	12/65	13/48	0.66	0.30-1.45	
Age, years					
≤43	23/112	38/127	0.68	0.40-1.14	0.87
>43	32/126	40/111	0.72	0.45-1.14	
T classification					
T1-2	10/48	12/49	0.81	0.35-1.89	0.68
T3-4	45/190	66/189	0.68	0.47-1.00	
N classification					
N0-1	10/47	18/47	0.64	0.30-1.40	0.65
N2-3	45/191	60/191	0.74	0.50-1.08	
Radiotherapy technique					
2DRT	36/122	54/149	0.81	0.53-1.23	0.33
IMRT	19/116	24/89	0.55	0.30-1.01	

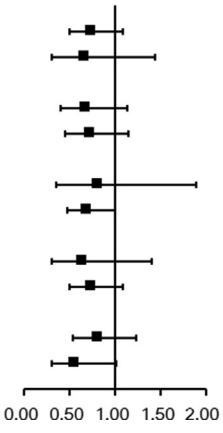


Fig. 3. **Subgroup analysis: distant metastasis-free survival (A), disease-free survival (B) and overall survival (C) for eligible population.** IC = induction chemotherapy. CCRT = concurrent chemoradiotherapy; 2DRT = two-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy; CI = confidence interval. Hazard ratios (HRs) were calculated with the unadjusted Cox proportional-hazards model.

Table 3
Late adverse events.

Toxicity, No(%)	IC+CCRT group (n = 238)			CCRT alone group (n = 238)			p value (grade ≥1)	p value (grade ≥3)
	Grade 1	Grade 2	Grade 3-4	Grade 1	Grade 2	Grade 3-4		
Auditory/hearing	47 (19.7)	38 (16.0)	32 (13.4)	47 (19.7)	41 (17.2)	34 (14.3)	0.647	0.791
Bone necrosis	6 (2.5)	1 (0.4)	3 (1.3)	5 (2.1)	2 (0.8)	5 (2.1)	0.662	0.721
Cranial nerve palsy	10 (4.2)	8 (3.4)	6 (2.5)	18 (7.6)	14 (5.9)	6 (2.5)	0.057	1.000
Dysphagia	22 (9.2)	6 (2.5)	4 (1.7)	32 (13.4)	11 (4.6)	3 (1.3)	0.083	1.000
Eye damage	14 (5.9)	6 (2.5)	3 (1.3)	25 (10.5)	10 (4.2)	4 (1.7)	0.029	1.000
Neck fibrosis	29 (12.2)	10 (4.2)	3 (1.3)	28 (11.8)	15 (6.3)	6 (2.5)	0.415	0.501
Trismus	10 (4.2)	8 (3.4)	1 (0.4)	14 (5.9)	11 (4.6)	3 (1.3)	0.167	0.616
Xerostomia	47 (19.7)	24 (10.1)	12 (5.0)	50 (21.0)	28 (11.8)	11 (4.6)	0.567	0.831

IC = induction chemotherapy, CCRT = concurrent chemoradiotherapy.
Differences in adverse events were analysed using χ^2 test. For adverse events that did not meet the requirement for χ^2 analysis (absolute count was <1), Fisher's exact test was used.

The dose of PF IC in this study was based on Al-Sarraf regime (Study 0099) [3], with cisplatin given at a dose of 80 mg/m^2 and fluorouracil of 4 g/m^2 every 3 weeks. We employed two cycles instead of three cycles, considering the compliance of the subsequent radiotherapy and additional toxicity. The encouraging results from Hui *et al.*, in which the addition of two cycles of induction docetaxel and cisplatin to CCRT achieved significant improvement in OS, provide further evidence about the efficacy, compliance and toxicity of our choice of IC cycles [9]. During PF IC in this study, 65 (27.3%) of 238 patients had grade 3 or 4 adverse events, which was lower than that (43–97%) reported in former studies wherein other induction regimens were administered [6–9,29]. For late toxicities, the incidence of late radiation-related toxicities was similar between IC followed by CCRT and CCRT alone group in our long-term analysis. Therefore, PF IC followed by CCRT is a highly feasible sequential strategy with satisfactory efficacy and less toxicity for advanced NPC. Although Zhang *et al.* reported that gemcitabine plus cisplatin (GP) achieved better PFS than the PF regimen in the first-line setting of recurrent or metastatic NPC [30], it still needs further head-to-head study to compare the efficacy and toxicity of induction GP and PF regimens in advanced NPC by our ongoing trial (NCT03840421). Meanwhile, Sun et al. proved that cisplatin/fluorouracil/docetaxel (TPF) significantly improved 5-year FFS (failure-free survival), OS, DFFS (distant failure-free survival) and LR-FFS (locoregional failure-free survival) in patients with locoregionally advanced NPC. In other two retrospective studies, TPF was superior to PF for patients while the addition of docetaxel produced more grade 3–4 toxicities. A recent randomised non-inferiority trial reported that PF was not superior to TPF induction chemotherapy in patients with locoregionally advanced NPC. Further studies are needed to establish the optimal IC regimen with better efficacy and less toxicity. Several ongoing trials are also conducting to assess the efficacy and safety of different IC regimens in locoregionally advanced NPC (e.g. NCT01872962, NCT02512315, NCT03503136, NCT03604965), and confirmation of the value of such strategies is awaited.

During follow-up, the proportion of patients with eye damage was significantly higher in the CCRT alone group than the IC followed by CCRT group (16.4% [39/238] versus 9.7% [23/238], p = 0.029); major differences were observed in the incidences of grade 1–2 eye damage. Of the patients with grade 1–2 eye damage, the most common chief complaint in patients' routine follow-up visits was a decline of vision in one or both eyes mainly due to the radiation-induced optic neuropathy, a late adverse event that manifests months to years after radiotherapy [31]. Besides, the comparison of radiation-induced cranial nerve palsy occurrences between two groups reached marginal statistical significance. Previous studies have indicated that IC could shrink tumour volume to provide a wider margin for RT, which is essential to ensure safe doses to normal tissues, particularly for patients with extensive locoregional infiltration adjacent to critical neurological structures [18,32]. Our long-term analyses provide evidence that IC might reduce late adverse events by decreasing the dose to critical normal structures.

The strengths of our study are its large trial size, long-term follow-up and consistency of the results with the different end-points. At the time of this update, our trial had a follow-up as long as 10 years. Although our subgroup analyses provide useful information, the data should be interpreted with caution for the following reasons. First, the study was not powered to test statistical differences between patient subgroups. Second, all associations between the covariates and treatment were not significant. The point estimates of the HRs were consistent across various subgroups, but the CIs included 1 in some subgroups because of lack of statistical power. Third, the number of events, particularly for the analysis of DMFS, was small even with 5 years of follow-up. The findings of subgroup analyses need to be replicated in future studies.

A potential limitation of our study as stated in the initial analysis is that not all patients received IMRT. However, we did exploratory subset analyses by radiotherapy techniques (IMRT versus 2DRT), and the results showed that the effect of induction chemotherapy did not differ within specific patient subgroups and the test of interaction was not significant in both the IMRT and 2DRT subgroups. Our pooled analysis further confirmed the non-significant results [20]. Therefore, different radiotherapy techniques had a limited effect on our long-term results.

In conclusion, our long-term analysis confirmed that IC followed by CCRT improved DFMS, DFS and OS at 5 years in patients with locoregionally advanced NPC. The addition of PF induction chemotherapy did not significantly increase late toxicities. Therefore, IC followed by CCRT can be recommended for patients with locoregionally advanced NPC.

Conflict of interest statement

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.07.007.

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