A multicentre, phase 3, randomized trial on concurrent chemoradiotherapy plus adjuvant chemotherapy versus radiotherapy alone in patients with regionally advanced nasopharyngeal carcinoma: 10-year outcome on efficacy and toxicity

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CONFLICT OF INTEREST DISCLOSURES

None of the authors have any potential conflict of interest.

PRECIS

Compared with radiotherapy alone, concurrent chemotherapy and adjuvant chemotherapy could significantly improve overall survival for patients with regional advanced nasopharyngeal carcinoma without excessive increase in late toxicities.

ABSTRACT

Background

Concurrent-adjuvant chemoradiotherapy (CRT) became a recommended treatment for locoregionally advanced nasopharyngeal carcinoma (NPC) since the first report of significant survival benefit by the Intergroup-0099 Study. However, data on late toxicities are lacking. Previous reports from the current NPC-9901 Trial raised concerns about failure to improve overall survival (OS) due to inadequate impact on distant control, and increase in toxicities/non-cancer deaths. Validation of the long-term therapeutic ratio is needed.

Methods

In this phase 3, randomized trial, patients with non-keratinizing NPC staged T1–4N2–3M0 were randomly assigned to radiotherapy (RT) alone (176 patients) or to CRT (172 patients) using concurrent cisplatin followed by adjuvant cisplatin plus fluorouracil.

Results

The early findings of significant improvement in tumor control were maintained: the CRT group achieved significantly higher 10-year overall failure-free rate (62% *vs* 50%, *P*=0.01) and progression-free survival (56% *vs* 42%, *P*=0.006) due to superior locoregional-control (87% *vs* 74%, *P*=0.003), whilst the impact on distant-control remained insignificant (68% *vs* 65%, *P*=0.24). The initial differences in toxicities diminished with longer follow up: late toxicity rate (52% *vs* 47% at 10 years, *P*=0.20), deaths due to treatment-toxicity (4.1% *vs* 2.8%) or incidental/unknown cause (15.1% *vs* 13.1%). The OS rate in the CRT group reached statistical superiority at 10-year (62% *vs* 49%, *P*=0.047).

Conclusions

Long-term results confirmed that CRT could significantly improve OS without excessive late toxicities for patients with regionally advanced NPC. However, more potent therapy is needed for improving distant control, especially for patients with stage IVA–B disease.

Keywords

nasopharyngeal carcinoma, randomized controlled trial, radiotherapy, chemoradiotherapy, efficacy and late toxicity

INTRODUCTION

Radiotherapy (RT) has been the primary treatment modality for nasopharyngeal carcinoma (NPC) since the advent of megavoltage technology. Addition of chemotherapy to RT is an important strategy for improving tumour control of locoregionally advanced NPC because this has potential for both enhancing the local effect of RT and eradicating micro-metastases. Although NPC is relatively chemo-sensitive, survival benefit was not demonstrated until the Intergroup-0099 Study using concurrent-adjuvant chemoradiotherapy (CRT).[1] Preliminary results on patients with Stage II–IVB disease (using the staging criteria of the TNM system 5th edition) showed very impressive improvement in all endpoints, with overall survival (OS) of 78% *vs* 47% at 3 years. However, when the results were first reported in the late 1990s, there were concerns about the exact magnitude of benefit because the outcomes for their RT group were substantially worse than those by other studies in the same period. Furthermore, there were no data on late toxicities.

This led to confirmatory trials in Asia where NPC is most prevalent.[2-8] Both Wee et al.[2,3] and Chen et al.[4,5] showed that concurrent-adjuvant CRT could significantly improve both the event-free survival (EFS) and OS for patients with Stage III–IVB disease. The NPC-9901 Trial[6,7] initiated by Hong Kong Nasopharyngeal Cancer Study Group differed from the other trials as we focused on patients with T1–4N2–3 disease (the group with highest risk of distant failure). While our Trial concurred that the Intergroup-0099 regimen could significantly improve EFS, our 3-year[6] and 5-year[7] results did not show significant gain in OS, due partly to insignificant improvement in distant control and partly to increased deaths due to treatment toxicities and incidental causes.

We continued to follow-up the surviving patients to assess the late toxicities and pattern of failure. The current study provided a unique opportunity for evaluating the ultimate impact on the therapeutic ratio by the addition of concurrent-adjuvant CRT for NPC and to

identify learning points for future studies.

PATIENTS AND METHODS

Study design and patients

This multicentre, phase 3, randomized-controlled trial was participated by four centres from Hong Kong and one centre from Canada. As shown in previous reports,[6,7] the key eligibility criteria included histologically confirmed non-keratinizing (differentiated or undifferentiated) carcinoma of the nasopharynx as classified by the World Health Organization (WHO) system, and T1–4N2–3M0 disease by TNM Classification 5th edition.

All participants provided written informed consent. The protocol was approved by the institutional ethics committees of the individual participating centre. The trial was conducted in accordance with the Declaration of Helsinki, and was monitored by an independent Data Monitoring Committee.

Eligible patients were stratified by participating centre, T-category (T1–2 *vs* T3–4) and N-category (N2 *vs* N3). They were randomly assigned using a blocked randomisation scheme in a 1:1 ratio, to receive either RT alone (the RT group) or in combination with concurrent-adjuvant chemotherapy (the CRT group). Randomisation was generated by the consulting statistician in sealed envelopes labelled by stratum, which were unsealed only after patient registration. Treatment allocation was not masked, but the statisticians were blinded.

Assessment and Treatment

Details of the assessment, treatment and statistical methods have been described in previous reports.[6,7] Patients in both treatment groups were irradiated with megavoltage photons using the same RT technique and dose in line with the treatment policy of each individual centre. Those assigned to the CRT group were given additional chemotherapy using

the Intergroup-0099 regimen:[1] Cisplatin (100 mg/m^2) was given intravenously every 3 weeks for three cycles starting with commencement of RT, followed subsequently by a combination of cisplatin (80 mg/m^2) plus fluorouracil (1000 mg/m^2/day by 96-hour infusion) every 4 weeks for three cycles.

The first assessment of tumour response was performed 6 to 16 weeks after completion of RT. For statistical purposes, persistent primary or nodal disease at 16 weeks after completion of RT was defined as locoregional failure. Treatment of residual disease and tumour relapse (if detected) was given in line with the policy of the individual centre. Radiotherapy-related late toxicities were graded according to the Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG).

Statistical Methods

All events were measured from the date of random assignment. The primary endpoints included overall failure-free rate (FFR: time to first failure at any site) and progression-free survival (PFS: time to first failure or death from any cause). Secondary endpoints for treatment efficacy included OS, locoregional-FFR (LR-FFR) and distant-FFR (D-FFR). Secondary endpoints for safety included major toxicities (except xerostomia and dental caries) of grade 3 or greater; the current paper focused on late toxicities. For patients who had re-irradiation for treatment of locoregional relapses, events were censored at commencement of re-irradiation for assessing toxicities incurred solely by the primary treatment.

All analyses were performed on an intention-to-treat basis; statistical tests comparing treatment groups were two-sided, and *P* values less than 0.05 were considered to indicate statistical significance. Further to calculation of the hazard ratios (HR) by the Cox regression model, the assumptions of proportional hazards were confirmed basing on Schoenfeld residuals.

This trial was registered with HAREC Clinical Trial Registry by the Hong Kong Hospital Authority (ID number: HARECCTR0500023) in accordance to the WHO International Clinical Trial Registry Platform (ICTRP) requirements.

RESULTS

From March 1999 to January 2004, in compliance with the targeted accrual size of 340, 348 eligible patients were randomly assigned (Figure 1), and only 4% were lost to follow-up. All survivors had a minimum follow-up of 10 years, the median duration for the whole series was 10.7 years (range = 0.2–16.8 years).

The two treatment groups were well balanced in all patient characteristics, tumour factors and RT parameters (Table A1). Four patients had major protocol violations (Figure 1): 2 patients (1.2%) in the CRT group did not receive chemotherapy and 2 patients (1.1%) in the RT groups received chemotherapy. The compliance to chemotherapy the CRT group has been described in previous report.[6]

Efficacy

Details of outcome comparisons are shown in Table 1 and Figure 2. Altogether, 150 patients failed (at one or more sites), and 183 died (of any cause). When compared with the RT alone group, the CRT group achieved significantly higher overall-FFR (62% *vs* 50%), PFS (56% *vs* 42%), and cancer-specific survival (72% *vs* 58%) at 10-year. The improvement was strongly significant for locoregional-FFR (87% *vs* 74%), but insignificant for distant-FFR (68% *vs* 65%).

Among the patients with relapse, the majority [44/63 (70%) in the CRT group and 66/87 (76%) in the RT group] were given further treatment. Besides aggressive locoregional treatment, chemotherapy was used in 33 patients in the CRT group and in 53 patients in the

RT group. The successful salvage rates (alive without disease at last assessment) were 9% in both groups.

The OS rate of the CRT group became superior to the RT group with longer follow-up (62% *vs* 49% at 10-year, *P*=0.010). Analyses on the incidence of deaths due to different causes (Table A2) showed that the CRT group had significant reduction in deaths due to disease progression (27.3% *vs* 42.6%, *P*=0.004), without significant increase in deaths directly attributable to chemotherapy/RT toxicity (4.1% *vs* 2.8%, *P*=0.74) or incidental/unknown causes (15.1% *vs* 13.1%, *P*=0.69). Further analyses on the pattern at different period showed that excess in non-cancer deaths in the CRT group was 5.9% for patients with observation ≤5 years, but no increase for those with longer follow-up. On the other hand, deaths due to treatment toxicity increased in the RT group from 0%, 1.8% to 3.6% for patients with observation ≤5 years, >5–≤10 years, and >10 years, respectively.

Subgroup analyses (Table 1) showed a favourable trend in all endpoints (except distant failure) by adding chemotherapy for both Stage III (n=206) and Stage IVA–B (n=142), but the magnitude of hazard reduction was generally greater for Stage III. The 10-year OS in the CRT group was 74% for Stage III, but only 45% for Stage IVA–B (*P*=0.031, Figure 3).

Multivariable analyses (Table 2) based on the intention-to-treat principle showed that addition of chemotherapy is an independent factor for improving all endpoints except distant-FFR.

Further analyses of outcome based on actual treatment showed that patients who had received 2 or more cycles in the concurrent phase (n=164) achieved significantly better LR-FFR (*P*=0.001), but the impact in D-FFR was insignificant (*P*=0.15). Patients who had received 2 or more cycles in both the concurrent and the adjuvant phases (n=140) achieved significant improvement in both 10-year LR-FFR (87.9% *vs* 75.0%, *P*=0.003) and D-FFR (73.0% *vs* 61.8%, *P*<0.001).

Safety

Altogether, there were 132 incidences of late toxicity grade 3 or above (Table 3). The mean latency from commencement of RT to the manifestation of late toxicity was 4.2 years in the CRT group versus 4.7 years in the RT-alone group (P=0.40). The overall actuarial rate of grade 3 late toxicity was higher in the CRT group during the first 3 years. However, the difference gradually diminished and became insignificant: 52.3% *vs* 46.8% at 10 years (absolute difference 5.5%), P=0.20; hazard ratio (HR) 1.25 (95% confidence level [CI] 0.89–1.76) (Figure 2).

None of the damage of different normal structures showed statistically significant excess in the CRT group (Table 3). Multivariable analysis (Table 2) showed that the addition of chemotherapy did not incur significant increase in major late toxicity (HR 1.22, 95% CI 0.86–1.72). Eleven patients developed second malignancy within the irradiated areas, it is not possible to tell whether they are de-novo or radiation-induced. However, basing on the location and latency, we regard them as RT toxicity to avoid underestimating the problem.

There was no statistical difference in mortality rate due to RT toxicity between the CRT and the RT groups (3.5% *vs* 2.8%). Altogether 11 patients died of RT-induced late toxicities – including eight due to second malignancy within RT portal, and the other three due to temporal lobe necrosis, skull base necrosis, and aspiration pneumonia related to last four cranial nerve palsies, respectively.

DISCUSSION

Among the four randomized trials evaluating the addition of concurrent cisplatin plus adjuvant cisplatin-fluorouracil to conventional-fractionated RT,[1-9] our NPC-9901 Trial is the trial with the largest sample size and the only trial that focused on patients with N2–3 disease

(the group with highest metastatic risk); the current update is the first report with detailed 10-year outcome for both efficacy and late toxicities to evaluate the ultimate therapeutic ratio. Similar to the trials by Wee et al.[2,3] and Chen et al.,[4,5] the current trial is confined to patients with non-keratinizing carcinoma, the applicability to keratinizing carcinoma is uncertain. Another point to note is the RT technique used: only 51% of patients in our series were irradiated with 3-dimensional conformal technique throughout, the magnitude of benefit in the modern era of intensity-modulated RT has yet to be studied.

All four trials consistently confirmed that concurrent-adjuvant CRT could significantly improve PFS. Evaluation at 5 years showed an absolute gain of 29% by the Intergroup-0099 Study,[9] while the three confirmatory trials showed a fairly consistent absolute gain of 9–13%,[3,5,7] with reduction in hazard of failure or death at 28–35%. The current update confirmed that this significant improvement was maintained at 10 years (14% absolute gain, and 32% hazard reduction).

The impact by concurrent-adjuvant CRT on the pattern of failure is less clear; the variation might be explained at least partly by the differences in the proportion of advanced T- and N-categories among the trials. Both the preliminary reports by Intergroup-0099 Study[1] and Chen et al.[4] showed significant improvement in both locoregional-FFR and distant-FFR. However, both endpoints became insignificant in the subsequent 5-year report by Chen et al.[5] For our NPC-9901 Trial (42% with T3–4, 100% with N2–3 disease), assessments at all time-points showed significant improvement in locoregional-FFR; the current update confirmed a significant 13% absolute gain at 10 years with CRT (87% *vs* 74%). However, our trial raised the concern that the impact on distant-FFR was statistically insignificant throughout all time-points for this cohort of patients: with an absolute gain of only 3% (68% *vs* 65% at 10 years).

While the other three trials showed significant improvement in OS,[1-5,9] previous reports from our NPC-9901 Trial showed contrary results: the OS in the CRT group was almost

identical to the RT alone group at 3-year,[6] and only diverged to a 4% gain at 5-year.[7] Interestingly, this divergence steadily widened to reach statistical significance with hazard reduction of 26% and an absolute gain of 13% at 10 years (Figure 2: 62% *vs* 49%),

This trend in OS was not due to the pattern of failures, but rather the pattern of deaths from treatment toxicities and incidental/unknown causes (Table A2). Our early reports attributed the increase in deaths to incidental/unknown causes,[6,7] but these diminished with longer follow-up and became insignificant in the current analyses (19% *vs* 16%). At 3 years CRT incurred a significant 31% increase in acute toxicities and 15% increase in late toxicities of grade 3 or above when compared with RT alone, but the difference in actuarial late toxicity rate gradually narrowed to 6% at 5- and 10-year (Figure 2). In this series the deaths due to treatment toxicity steadily increased in the RT group from 0% for survivors with ≤5 years follow-up to 3.6% for those >10 years. It appeared that the latency to radiotherapy-induced toxicities was shorter in the CRT group when compared with the RT groups (4.7 vs 4.2 years), though the difference was not statistically significant (*P*=0.40).

Our current study also cautioned the predicting power of short term PFS on long term survival endpoints. The study by Rotolo et al. on NPC showed that the 3-year PFS could predict the 5-year OS [10]. In our series, while there was no difference in PFS between the RT and CRT groups at 3-year, the difference became significant at 5-year and was maintained at 10-year. This is because, in short term, the benefit of improved tumor control by CRT was offset by the death from toxicities or incidental causes, and PFS combines both the treatment failure and death by any cause. It is only when we look at just the treatment failure pattern that the overall-FFR at 3-year could really predict the final tumor control rate as indicated by the FFR at 5-year and 10-year. The pattern of failures at locoregional and distant sites at 3-year was also maintained at 5-year and 10-year.

Similarly, the difference in OS between the RT and CRT groups was statistically insignificant at both 3-year [6] and 5-year [7], but this became significant at 10-year because of the slowly increasing rate of deaths due to late toxicities in the RT group. Hence, it is important to note that for disease with notoriously high risk of late toxicities, long term follow-up is needed to fully assess the ultimate therapeutic ratio.

Hence, it is reassuring that all four randomized trials consistently confirmed that concurrent-adjuvant chemotherapy could significantly improve both PFS and OS. More importantly, the current update with a median observation period of 10.7 years showed that this treatment was safe: with no significant increase in late toxicity or non-cancer deaths. Study by the MAC-NPC Collaborative Group,[11] with a median follow-up of 7.7 years, similarly showed that addition of concurrent-adjuvant chemotherapy (total of 1267 patients) could significantly reduce the hazard of all deaths by 35% [HR 0.65 (0.56–0.76)], without significant increase in non-cancer deaths (HR 1.19 (0.77–1.85)]. This favorable long-term therapeutic ratio for NPC is contrary to the RTOG 91-11 Trial for laryngeal cancer,[12] which showed loss of survival gain by concurrent cisplatin (OS 28% *vs* 32% at 10 years) due to significant increase in non-cancer deaths (31% *vs* 17%).

One unresolved uncertainty is the exact magnitude of contribution by the adjuvant phase. Results from the randomized trial by Chen et al. comparing concurrent-adjuvant chemotherapy versus concurrent chemotherapy showed that the concurrent-adjuvant group did not achieve significant increase in estimated 5-year FFR [HR 0.88 (0.64–1.22)].[13] However, it should be cautioned that the impact on outcome for NPC could take a prolonged period to manifest (as shown by our study), long-term follow-up is needed for definitive conclusion.

The analyses by the MAC-NPC Collaborative Group favored additional chemotherapy.[11,14] The comparisons on concurrent chemotherapy were more heterogeneous:

review of individual trials showed that only the trial using concurrent cisplatin for patients largely with stage II disease treated by 2-dimensional RT achieved significant benefit in both PFS and OS.[15] Ranking of different treatment strategies by network analyses showed that the concurrent-adjuvant chemotherapy group achieved the highest benefit on OS and PFS when compared with RT alone: the P-Scores were 96% and 94% respectively, while the corresponding P-Scores by concurrent chemotherapy group was 70% and 52% (P-score is the statistical score to indicate the extent of certainty that a treatment is better than other competing treatments, higher P-Score means greater probability of being the best).[14] The concurrent-adjuvant group achieved significantly better PFS than the concurrent group [HR 0.81 (0.66–0.98)].

Although the current concurrent-adjuvant chemotherapy is consistently superior to RT alone, our trial showed that further improvement in efficacy for distant control is needed, especially for patients with Stage IVA–B disease. A major reason for inadequate impact on distant control is the poor tolerance in the adjuvant phase. Analyses of outcome based on actual treatment showed that patients who had received 2 or more cycles in both the concurrent and the adjuvant phases achieved significant improvement not only in LR-FFR but also in D-FFR.

One potential strategy for improvement is to change the time sequence to induction-concurrent as early administration of potent chemotherapy combination at full dose could be more effective for eradication of micro-metastases.[16] Indeed, the network analyses by the MAC-NPC Collaborative Group[14] showed that the induction-concurrent group achieved the highest benefit on D-FFR as compared with concurrent-adjuvant and concurrent-alone groups: the P-scores were 95%, 72% and 48% respectively.

Early trials evaluating induction-concurrent versus concurrent-alone chemotherapy showed conflicting outcome, but promising 3-years result were recently reported by Sun et al.

using induction cisplatin, fluorouracil, and docetaxel followed by concurrent cisplatin (80% vs 72%, *P*=0.034),[17] and Cao et al. using induction cisplatin and fluorouracil followed by concurrent cisplatin (82% vs 74%, *P*=0.028).[18] The NPC-0501 Trial by The Hong Kong Nasopharyngeal Cancer Study Group was the only trial that aimed to evaluate induction-concurrent versus concurrent-adjuvant chemotherapy: preliminary results showed that the group randomized to receive induction cisplatin-capecitabine followed by cisplatin in concurrence with conventional-fractionated RT achieved better PFS than the concurrent-adjuvant group (81% vs 75% at 3-years, *P*=0.045).[19] Longer follow-up of these trials are needed for confirmation, especially as there is concern that the induction chemotherapy may affect the tolerability of chemotherapy at the concurrent phase.

Another key focus for future trial is personalized refinement of treatment strategy. An on-going NRG trial (NCT02135042) attempts to use post-RT EBV-DNA level for tailoring adjuvant chemotherapy. Furthermore, we should explore the possibility of identifying patients who could be safely treated with RT alone. Current guidelines recommend CRT for all Stage II–IVB patients, but even for the current cohort with suboptimal RT technique by modern standard, 50% of Stage III and 29% Stage IVA–B treated by RT alone were progression-free at 10-year. Further clinical and translational studies are needed to identify good-risk patients who can be spared of unnecessary chemotherapy.

Conclusion

Long-term results of the NPC-9901 Trial confirm that adding concurrent cisplatin plus adjuvant cisplatin-fluorouracil to conventional-fractionated RT could significantly improve both PFS and OS at 10 years, without significant increase in late treatment toxicities and non-cancer deaths. However, exploration for more potent regimen for distant control is needed, especially for patients with Stage IVA–B disease. Further clinical and translational studies are

also needed to work towards personalised medicine and spare good-risk patients of over-treatment.

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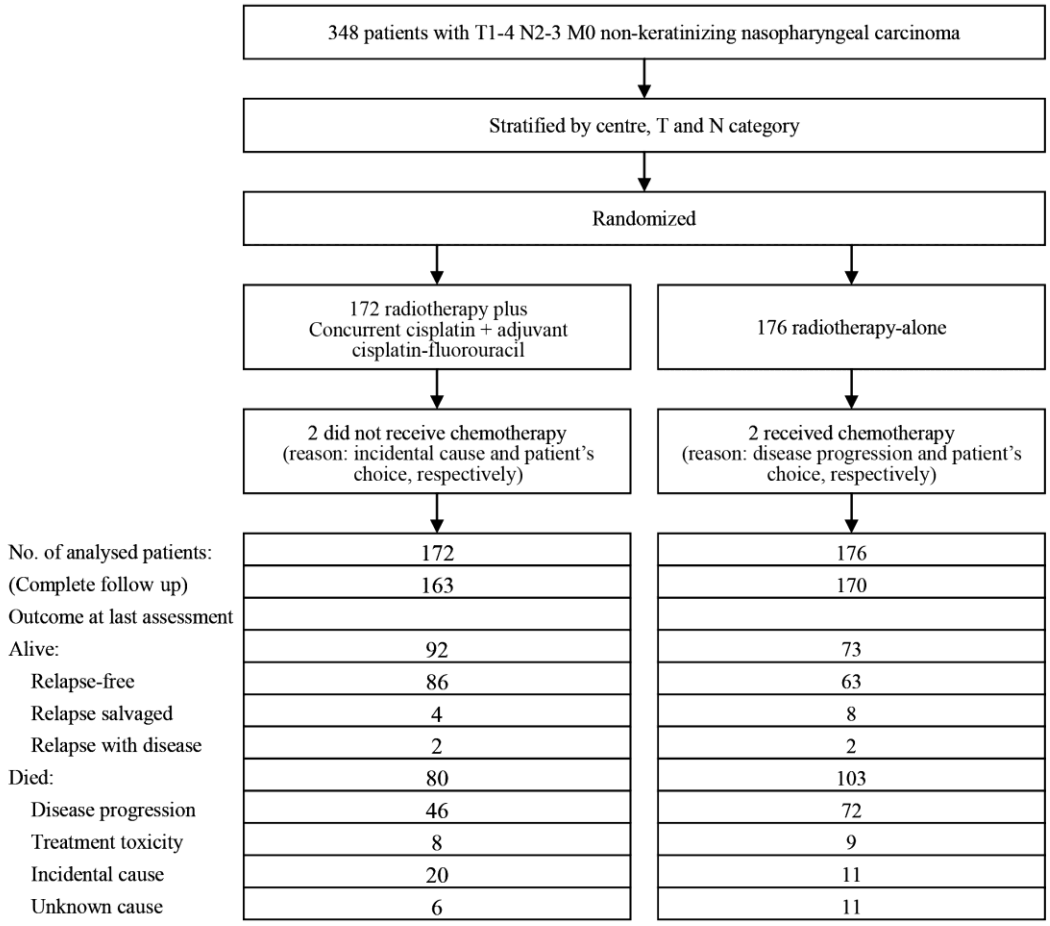
Figure Legends

Figure 1. CONSORT flow diagram showing design, enrolment and outcomes of this study (NPC-9901 Trial). Patients with T1–4N2–3M0 nasopharyngeal carcinoma were randomly assigned to radiotherapy either alone or with addition of concurrent-adjuvant chemotherapy.

Figure 2. Comparisons of the chemoradiotherapy (CRT) group versus the radiotherapy-alone (RT) group in terms of (a) overall failure-free rates, (b) progression-free survival, (c) overall survival, (d) locoregional failure-free rate, (e) distant failure-free rate, and (f) major late toxicity grade 3 or above. The vertical solid lines showed the 95% CI of the Kaplan-Meier estimates at 5, 10 and 15 years.

Figure 3. Subgroup analyses – Comparisons on efficacy of the chemoradiotherapy (CRT) group versus the radiotherapy-alone (RT) group in the Stage III and Stage IVA–B Subgroups in terms of (i) locoregional failure-free rate, (ii) distant failure-free rate, and (iii) overall survival.

Figure 1. CONSORT flow diagram showing design, enrolment and outcomes of this study (NPC-9901 Trial). Patients with T1–4N2–3M0 nasopharyngeal carcinoma were randomly assigned to radiotherapy either alone or with addition of concurrent-adjuvant chemotherapy.



No. of analysed patients:	172	176
(Complete follow up)	163	170
Outcome at last assessment		
Alive:	92	73
Relapse-free	86	63
Relapse salvaged	4	8
Relapse with disease	2	2
Died:	80	103
Disease progression	46	72
Treatment toxicity	8	9
Incidental cause	20	11
Unknown cause	6	11

Figure 2. Comparisons of the chemoradiotherapy (CRT) group versus the radiotherapy-alone (RT) group in terms of (a) overall failure-free rates, (b) progression-free survival, (c) overall survival, (d) locoregional failure-free rate, (e) distant failure-free rate, and (f) major late toxicity grade 3 or above. The vertical solid lines showed the 95% CI of the Kaplan-Meier estimates at 5, 10 and 15 years.

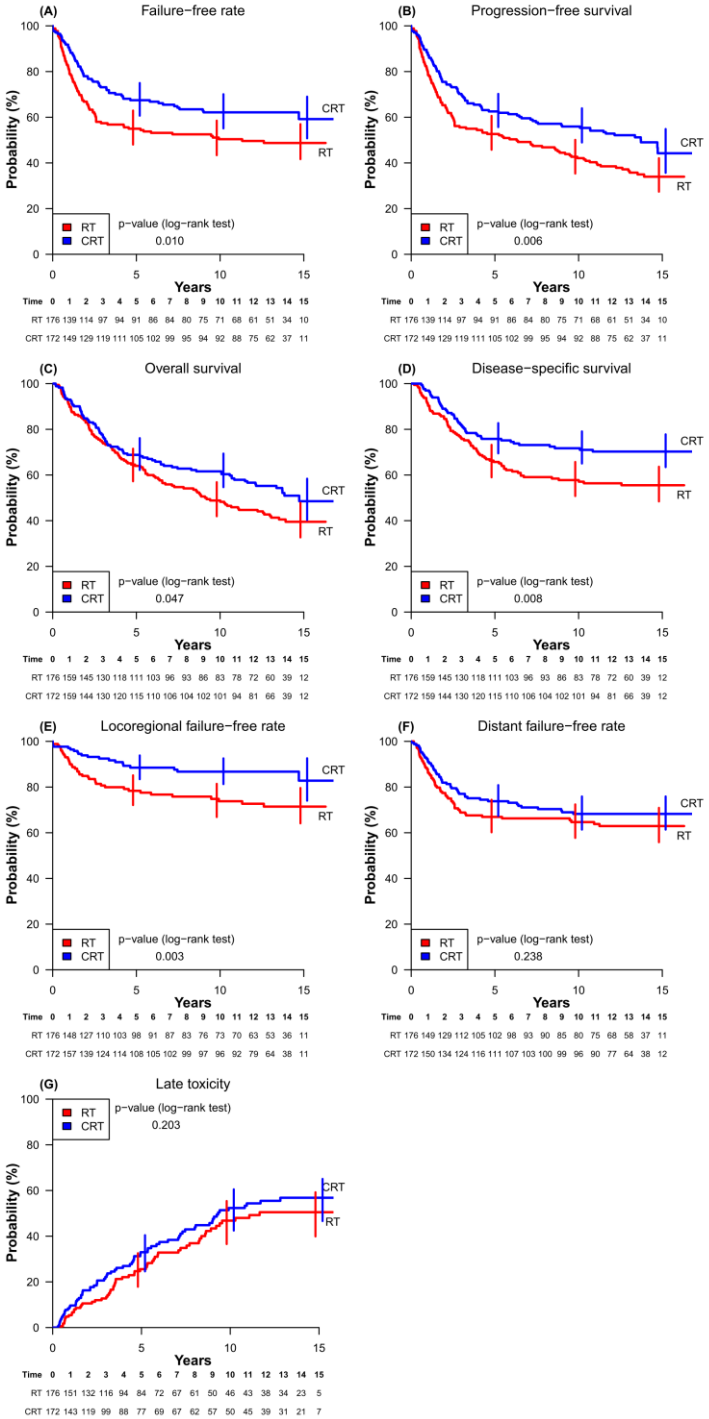


Figure 3. Subgroup analyses – Comparisons on efficacy of the chemoradiotherapy (CRT) group versus the radiotherapy-alone (RT) group in the Stage III and Stage IVA–B Subgroups in terms of (i) locoregional failure-free rate, (ii) distant failure-free rate, and (iii) overall survival.

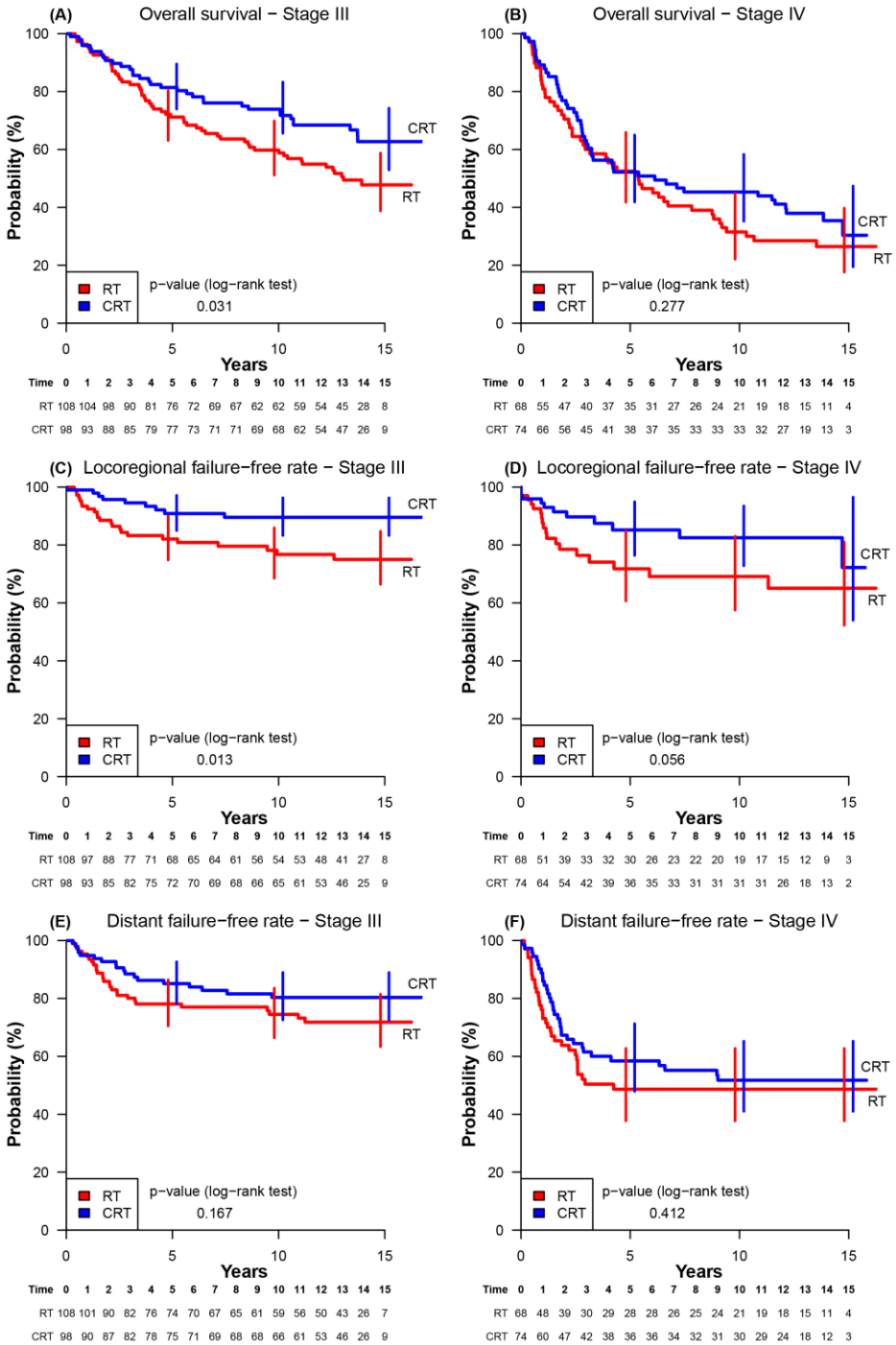


Table 1: **Comparison of efficacy outcome - Chemoradiotherapy group versus radiotherapy-alone group**

Endpoints	**Whole cohort**	**Subgroup analysis**	
Actuarial rate at 10 years	**T1–4N2–3**	**III**	**IVA–B**
HR of defining events (95% CI)	(n=348)	(n=206)	(n=142)
Overall failure-free rate	62% *vs* 50%	75% *vs* 59%	44% *vs* 37%
	P=0.010	*P*=0.008	*P*=0.12
	0.66 (0.47–0.91)	0.51 (0.31–0.85)	0.71 (0.46–1.10)
Progression-free survival	56% *vs* 42%	70% *vs* 50%	38% *vs* 29%
	P=0.006	*P*=0.004	*P*=0.13
	0.68 (0.51–0.90)	0.55 (0.36–0.83)	0.74 (0.50–1.09)
Overall survival	62% *vs* 49%	74% *vs* 60%	45% *vs* 31%
	P=0.047	*P*=0.031	*P*=0.28
	0.74 (0.56–0.997)	0.62 (0.40–0.96)	0.80 (0.54–1.20)
Cancer-specific survival	72% *vs* 58%	83% *vs* 68%	56% *vs* 42%
	P=0.008	*P*=0.009	*P*=0.11
	0.61 (0.43–0.88)	0.46 (0.26–0.84)	0.68 (0.42–1.09)
Locoregional failure-free rate	87% *vs* 74%	90% *vs* 77%	83% *vs* 69%
	P=0.003	*P*=0.013	*P*=0.06
	0.45 (0.26–0.77)	0.39 (0.18–0.84)	0.49 (0.23–1.04)
Distant failure-free rate	68% *vs* 65%	80% *vs* 74%	52% *vs* 49%
	P=0.24	*P*=0.17	*P*=0.41
	0.80 (0.55–1.16)	0.66 (0.37–1.19)	0.82 (0.50–1.32)

HR = hazard ratio; CI = confidence interval; *P* values were calculated by log-rank test

Table 2: **Multivariable analysis on significance of treatment group (based on intention-to-treat) and other potential covariates: Hazard ratio (95% Confidence Interval)**

Factor	Locoregional failure	Distant failure	All failure	Failure or death	All death	Cancer-specific survival	Late toxicity
Treatment group: CRT *vs* RT alone	0.41 (0.23–0.72) *P*=0.002	0.71 (0.48–1.04) *P*=0.08	0.58 (0.42–0.81) *P*=0.002	0.61 (0.46–0.82) *P*=0.001	0.68 (0.50–0.92) *P*=0.013	0.56 (0.39–0.81) *P*=0.002	1.22 (0.86–1.72) *P*=0.27
Stage group: IV *vs* III	1.55 (0.91–2.63) *P*=0.11	2.39 (1.61–3.54) *P*<0.001	2.18 (1.56–3.06) *P*<0.001	1.91 (1.43, 2.55) *P*<0.001	1.77 (1.31–2.40) *P*<0.001	2.20 (1.51–3.20) *P*<0.001	1.52 (1.03–2.23) *P*=0.034
Lactate dehydrogenase: per 10 iu/L increase	1.004 (0.973–1.036) *P*=0.78	1.019 (0.9997–1.038) *P*=0.54	1.019 (1.002–1.036) *P*=0.031	1.023 (1.008–1.038) *P*=0.002	1.034 (1.018–1.049) *P*<0.001	1.030 (1.012–1.049) *P*=0.001	1.021 (1.001–1.042) *P*=0.042
Age: per year increase	1.02 (0.99–1.04) *P*=0.23	1.01 (0.99–1.03) *P*=0.19	1.01 (0.996–1.03) *P*=0.12	1.02 (1.01–1.04) *P*=0.002	1.03 (1.01–1.05) *P*<0.001	1.03 (1.01–1.05) *P*=0.006	1.02 (1.01–1.04) *P*=0.013
Gender: female *vs* male	0.40 (0.18–0.88) *P*=0.023	0.72 (0.43–1.19) *P*=0.20	0.59 (0.37–0.92) *P*=0.021	0.57 (0.39–0.84) *P*=0.005	0.56 (0.37–0.85) *P*=0.007	0.66 (0.40–1.08) *P*=0.10	1.70 (1.17–2.48) *P*=0.005
Radiotherapy technique:	1.09 (0.48–2.49)	1.01 (0.57–	1.18 (0.72–	1.29 (0.83–	1.57 (0.98–	1.25 (0.70–	1.30 (0.66–

3D vs	*P*=0.84	1.79)	1.95)	2.01)	2.52)	2.22)	2.56)
2D±boost		*P*=0.98	*P*=0.51	*P*=0.25	*P*=0.06	*P*=0.45	*P*=0.45
Radiotherapy	0.92 (0.90–	0.94	0.94	0.94	0.95	0.96	1.06
dose:	0.95)	(0.91–	(0.91–	(0.92–	(0.92–	(0.92–	(0.94–
per Gy	*P*<0.001	0.98)	0.96)	0.97)	0.97)	1.01)	1.20)
increase		*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*=0.09	*P*=0.34

*Statistically significant factors on univariable analyses: age, gender, stage group, lactate dehydrogenase, radiotherapy technique and total dose.

***Table 3*: Late Toxicities**

Toxicity grade, No. (%)	Chemoradiotherapy (N = 172)			Radiotherapy (N = 176)			*P* value
	3	4	5	3	4	5	
Neurological structures	11 (6.4)	1 (0.6)	2 (1.2)	15 (8.5)	0 (0)	0 (0)	0.32
Temporal lobe necrosis	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	0 (0)	0 (0)	0.75
Brainstem damage	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)	0 (0)	1.00
Brachial plexopathy	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)	0 (0)	1.00
Cranial Neuropathy[a]	7 (4.1)	0 (0)	1 (0.6)	13 (7.4)	0 (0)	0 (0)	0.25
Peripheral neuropathy	4 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.06
Soft tissue and bone	13 (7.6)	6 (3.5)	4 (2.3)	18 (10.2)	5 (2.8)	5 (2.8)	0.85
Bone necrosis	0 (0)	1 (0.6)	0 (0)	0 (0)	1 (0.6)	1 (0.6)	1.00
Soft tissue damage[b]	12 (7.0)	4 (2.3)	0 (0)	17 (9.7)	1 (0.6)	0 (0)	0.27
Dysphagia	2 (1.2)	0 (0)	0 (0)	4 (2.3)	0 (0)	0 (0)	0.68
Vascular (bleeding)	2 (1.2)	2 (1.2)	0 (0)	1 (0.6)	1 (0.6)	0 (0)	0.57
Radiation-induced malignancy[c]	0 (0)	1 (0.6)	4 (2.3)	0 (0)	2 (1.1)	4 (2.3)	1.00

Ear (hearing impairment / otitis)	39 (22.7)	8 (4.7)	0 (0)	32 (18.2)	4 (2.3)	0 (0)	0.26
Eye	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.49
Endocrine dysfunction	17 (9.9)	0 (0)	0 (0)	13 (7.4)	0 (0)	0 (0)	0.45
Late toxicity at any structure (max grade)	54 (31.4)	12 (7.0)	6 (3.5)	46 (26.1)	9 (5.1)	5 (2.8)	0.52

P values were calculated across toxicity grades (grades 0-2, 3, 4 and 5) by $\chi 2$ test (or Fisher's exact test when appropriate).

[a] Patients with toxicities in cranial neuropathies: XII (19), XII + VI (1) and VII (1). Optic nerve damage was not reported in this study; [b] Soft tissue damage included head and neck tissue necrosis, fibrosis and trismus; [c] Patients with radiation-induced malignancy: squamous cell carcinoma of the oral cavity (5), soft tissue sarcoma over the irradiated area (5), and thyroid cancer (1).

Additional Tables (Online only)

Table A1. Baseline characteristics and primary radiotherapy

Table A2. Incidence of deaths due to different causes at different time-point

Table A1. Baseline characteristics and primary radiotherapy

	Chemoradiotherapy (n=172)	**Radiotherapy (n=176)**	***P* value**
Patient Characteristics			
Age, years			
Mean ± SD	46 ± 10	47 ± 10	0.42
Gender, No. (%)			
Male	124 (72)	139 (79)	0.14
Female	48 (28)	37 (21)	
Performance status, No. (%)			
0	148 (86)	151 (86)	0.37
1	24 (14)	23 (13)	
2	0	2 (1)	
T-category, No. (%)			
T1-2	100 (58)	103 (59)	0.94
T3-4	72 (42)	73 (41)	
N-category, No. (%)			
N2	117 (68)	119 (68)	0.94
N3	55 (32)	57 (32)	
Stage group, No. (%)			
III	98 (57)	108 (61)	0.41
IVA-B	74 (43)	68 (39)	
Lactate dehydrogenase, IU/L			
Mean ± SD	282 ±152	271 ± 128	0.45

Radiotherapy			
Technique, No. (%)			0.89
2-dimensional throughout	69 (40)	73 (41)	
2 dimensional + conformal	13 (8)	15 (9)	
Conformal throughout	90 (52)	88 (50)	
Total dose, Gy			
Mean ± SD	67.8 ± 7.4	68.5 ± 2.7	0.28
Overall treatment time, days			
Mean ± SD	46 ± 6	46 ± 3	0.59
Additional boost, No. (%)			
Nasopharynx / parapharyngeal space	59 (34)	72 (41)	0.20

SD = standard deviation; IU = international units; Gy = gray (radiation units).

P values were calculated by two-sided t-test or $\chi 2$ test.

Performance status: 0 = fully active, 1 = ambulatory but restricted by physically strenuous activity, 2 = ambulatory >50% of waking hours, but unable to work

Table A2. Incidence of deaths due to different causes at different time-point

Cause of deaths	**Pattern at different time-points**							
	Overall		**≤5 years**		**>5 to ≤10 years**		**>10 years**	
	CRT (n=172)	RT (n=176)	CRT (n=172)	RT (n=176)	CRT (n=115)	RT (n=111)	CRT (n=101)	RT (n=83)
Cancer	47 (27.3%)	75 (42.6%)	39 (22.7%)	59 (33.5%)	6 (5.2%)	13 (11.7%)	2 (2.0%)	3 (3.6%)
Toxicity of chemotherapy / radiotherapy	7 (4.1%)	5 (2.8%)	3 (1.7%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	3 (3.0%)	3 (3.6%)
Incidental / unknown cause	26 (15.1%)	23 (13.1%)	11 (6.4%)	4 (2.3%)	5 (4.3%)	11 (9.9%)	10 (9.9%)	8 (9.6%)