EUROPEAN JOURNAL OF CANCER 47 (2011) 656–666

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Factors contributing to the efficacy of concurrent–adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: Combined analyses of NPC-9901 and NPC-9902 Trials

Anne W.M. Lee [a,*], *Stewart Y. Tung* [b], *Roger K.C. Ngan* [c], *Rick Chappell* [d], *Daniel T.T. Chua* [e], *T.X. Lu* [f], *Lillian Siu* [g], *Terence Tan* [h], *L.K. Chan* [a], *W.T. Ng* [a], *T.W. Leung* [b], *Y.T. Fu* [c], *Gordon K.H. Au* [e], *C. Zhao* [f], *Brian O'Sullivan* [g], *E.H. Tan* [h], *W.H. Lau* [c]

[a] *Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China*
[b] *Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong, China*
[c] *Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, China*
[d] *Department of Biostatistics, University of Wisconsin Medical School, Madison, WI, USA*
[e] *Department of Clinical Oncology, Queen Mary Hospital, Hong Kong, China*
[f] *Cancer Center, Sun Yat Sen University, Guangzhou, China*
[g] *Ontario Cancer Institute, Princess Margaret Hospital, Toronto, Canada*
[h] *Department of Clinical Oncology, National Cancer Center, Singapore*

ARTICLE INFO

Article history:
Received 10 September 2010
Accepted 27 October 2010
Available online 26 November 2010

Keywords:
Nasopharyngeal carcinoma
Concurrent-adjuvant chemotherapy

ABSTRACT

Background: The current standard treatment for locoregionally advanced nasopharyngeal carcinoma (NPC) was conventional–fractionation radiotherapy plus concurrent–adjuvant chemotherapy as recommended by the Intergroup-0099 Study. This combined analysis of the NPC-9901 and the NPC-9902 Trials aims to provide more comprehensive data to evaluate the efficacy of the Intergroup-0099 regimen and the contributing factors.

Methods: Eligible patients with stage III-IVB non-keratinizing NPC were randomly assigned to radiotherapy-alone (RT_i group: 218 patients) or chemoradiotherapy (CRT_i group: 223 patients) using cisplatin (100 mg/m^2) for three cycles in concurrence with radiotherapy, followed by cisplatin (80 mg/m^2) plus fluorouracil (1000 mg/m^2/day for 4 days) for three cycles. The median follow-up was 6.1 years.

Findings: Comparison by intention-to-treat showed that the CRT_i group achieved significant improvement in overall failure-free rate (FFR), locoregional-FFR and cancer-specific survival ($p \leqslant 0.019$); but the improvements for distant-FFR and overall survival (OS) were statistically insignificant ($p \geqslant 0.14$). Further exploratory studies based on actual treatment showed that an additional improvement achieved was a significant gain in OS (CRT_a versus RT_a group: 72% versus 63% at 5-year, $p = 0.037$). Multivariate analyses showed that the dose of cisplatin during the concurrent phase had significant impact on locoregional-FFR and OS, while that of fluorouracil during the adjuvant phase was significant for distant-FFR. The 5-year locoregional-FFR for patients who received 0–1, 2 and 3 concurrent cycles were 79%, 88% and 88%,

* *Corresponding author:* Address: Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Rd, Chai Wan, Hong Kong, China. Tel.: +852 25954173; fax: +852 29045216.
E-mail address: awmlee@ha.org.hk (A.W.M. Lee).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.10.026

respectively; the corresponding distant-FFR by adjuvant cycles were 68%, 78% and 77%, respectively.

Interpretation: Our results support the current practice of adding concurrent cisplatin plus adjuvant cisplatin-fluorouracil to radiotherapy for treating patients with locoregionally advanced NPC. The concurrent phase is important for locoregional control and survival, cisplatin 200 mg/m^2 in two concurrent cycles might be adequate. Additional chemotherapy using fluorouracil-containing combination contributed to improving distant control.

1. Introduction

Radiotherapy is the primary treatment modality for nasopharyngeal carcinoma (NPC), but the results for patients with advanced locoregional disease are unsatisfactory.[1,2] The first randomized trial that achieved significant benefit in both event-free survival (EFS) and overall survival (OS) by addition of chemotherapy was the Intergroup-0099 Study.[3] The regimen of cisplatin in concurrence with conventional–fractionated radiotherapy followed by adjuvant cisplatin plus fluorouracil has become the standard recommendation since the publication of this trial in the late nineties.

This landmark trial roused great interest but also deep concerns about exact magnitude of benefit, tolerability and toxicity because the result of their radiotherapy-alone group was substantially poorer than contemporary results.[4] Only half of the patients allocated to the chemoradiotherapy group could tolerate all scheduled courses of chemotherapy and the effect on late toxicities was unknown. Four randomized trials have since been conducted to confirm the benefit by concurrent–adjuvant chemotherapy.[5–9] In the two trials conducted by the Hong Kong Nasopharyngeal Cancer Study Group, patients with stage III-IVB disease were segregated: those with T1-4 N2-3 disease, accrued into the NPC-9901 Trial (Clinical Trial Registry ID number HARECCTR0500023),[5,6] were irradiated with conventional fractionation and randomized to chemotherapy; those with T3-4 N0-1 disease, accrued into the NPC-9902 Trial (Clinical Trial Registry ID number HARECCTR0500024),[7] were further randomly allocated to radiotherapy with conventional versus accelerated fractionation.

The NPC-9901 Trial,[5,6] together with the trials by Wee et al.[8] and Chen et al.[9] all confirmed that combined therapy could indeed significantly reduce tumour relapse and improve EFS. Only the NPC-9901 Trial[6] raised the cautionary note that the efficacy of the Intergroup-0099 regimen for reducing distant failure might be inadequate; its ultimate gain in OS was narrowed by an increase in non-cancer deaths.

One major question regarding the design of the Intergroup-0099 regimen is the contribution of the adjuvant phase because available randomized trials[10–12] and meta-analysis[13] consistently showed that adjuvant chemotherapy *per se* had no significant impact for all end-points. Better understanding about the major factors contributing to the efficacy of the Intergroup-0099 regimen is hence important. In addition, more detailed data about the magnitude of benefit for different specific subgroups are needed for informing patients about their risks and benefits by combined therapy. The current analysis, based on all patients from the NPC-9901 Trial[6] together with those irradiated with conventional–fractionated radiotherapy from the NPC-9902 Trial,[7] aims to address these important issues.

2. Methods

2.1. Patients

All patients had histologically confirmed non-keratinizing (differentiated or undifferentiated) carcinoma of the nasopharynx classified by the World Health Organization system[14] and stage III-IVB disease by the staging criteria of the 5th edition of the American Joint Committee on Cancer Staging System[15] and the International Union Against Cancer.[16] All were less than 70 years in age, with performance status of 2 or lower by the Eastern Cooperative Oncology Group System, with adequate haematologic and renal function.

All patients provided written informed consent. They were randomly assigned using a blocked randomization scheme[17] to receive radiotherapy either alone (the RT_i group) or in combination with concurrent–adjuvant chemotherapy (the CRT_i group). Randomization was generated by the consulting statistician in sealed envelopes labelled by stratum, which were unsealed only after patient registration. The suffix 'i' indicates the groups by intention-to-treat.

2.2. Treatment and assessment

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

Patients in both treatment groups were irradiated with megavoltage photons using the same radiotherapy technique and dose consistent with the treatment policy practiced by each centre. All were irradiated with conventional fractionation of 2 Gy per fraction, five daily fractions per week. A total dose of 66 Gy or greater was given to gross tumour targets and 50 Gy or greater to potential sites of local infiltration and bilateral cervical lymphatics. Technique ranged from conventional two-dimensional technique to three-dimensional conformal or intensity-modulated technique throughout. Additional boosts (not exceeding 20 Gy) could be given to the parapharyngeal space, the nasopharynx and/or nodal sites (when indicated); the boost field was confined to the involved site with the exclusion of critical structures.

Patients assigned to the CRT_i group were given additional chemotherapy using the Intergroup-0099 regimen.[3] Cisplatin (100 mg/m^2) was given intravenously every 3 weeks for three cycles starting with commencement of radiotherapy, followed subsequently by a combination of cisplatin (80 mg/m^2) plus fluorouracil (1000 mg/m^2/d by 96-h infusion) every 4 weeks for three cycles. The scheduled number of concurrent cycles was three; for patients who completed radiotherapy before the third cycle due to delay of chemotherapy, the remaining cycle(s) of cisplatin were given in the adjuvant phase before proceeding to cisplatin plus fluorouracil. Dose modifications were permitted according to protocol-specified criteria.

The first assessment of tumour response was performed 6–16 weeks after completion of radiotherapy. All patients were assessed by complete physical examination and fiberoptic nasopharyngoscopy. Further investigations with computed tomography or magnetic resonance imaging and other tests were arranged when indicated. For statistical purposes, persistent primary or nodal disease at 16 weeks after completion of radiotherapy was taken as locoregional failure. Patients were reassessed at least every 3 months during the first 3 years and then every 6 months thereafter until death. Treatment of residual disease and tumour relapse (if detected) was given in line with the policy of individual centre.

2.3. Statistical methods

All events were measured from the date of random assignment. The current analyses focus on the following end-points: overall failure-free rate (FFR) (time to first failure at any site), locoregional-FFR (time to persistence or recurrence in the nasopharyngeal and/or cervical region), distant-FFR (time to haematogenous metastasis), cancer-specific survival (CSS) (time to death due to NPC progression) and OS (time to death due to any cause).

Comparisons of treatment group both by intention-to-treat and actual treatments were performed; statistical tests were 2-sided. Time-to-event end-points were calculated by the Kaplan–Meier method[18] and the differences compared by the log-rank test.[19] The hazard ratio (HR) and corresponding 95% confidence interval (CI) on univariate and multivariate analyses were calculated using the Cox regression model.[20] The χ^2 test was used for comparing incidence rates and categorical variables, and the Student t test was used for comparing the means of continuous variables.

2.4. Role of the funding sources

The sponsors had no role in the study design, interpretation of the data or writing of the manuscript. The corresponding author has full access to all the data and the final responsibility to submit for publication.

3. Results

3.1. Patient and treatment

From March 1999 to April 2004, 441 eligible patients (348 patients from NPC-9901 Trial[6] and 93 patients from NPC-9902 Trial[7]) were randomly assigned (Fig. 1). Participating centres

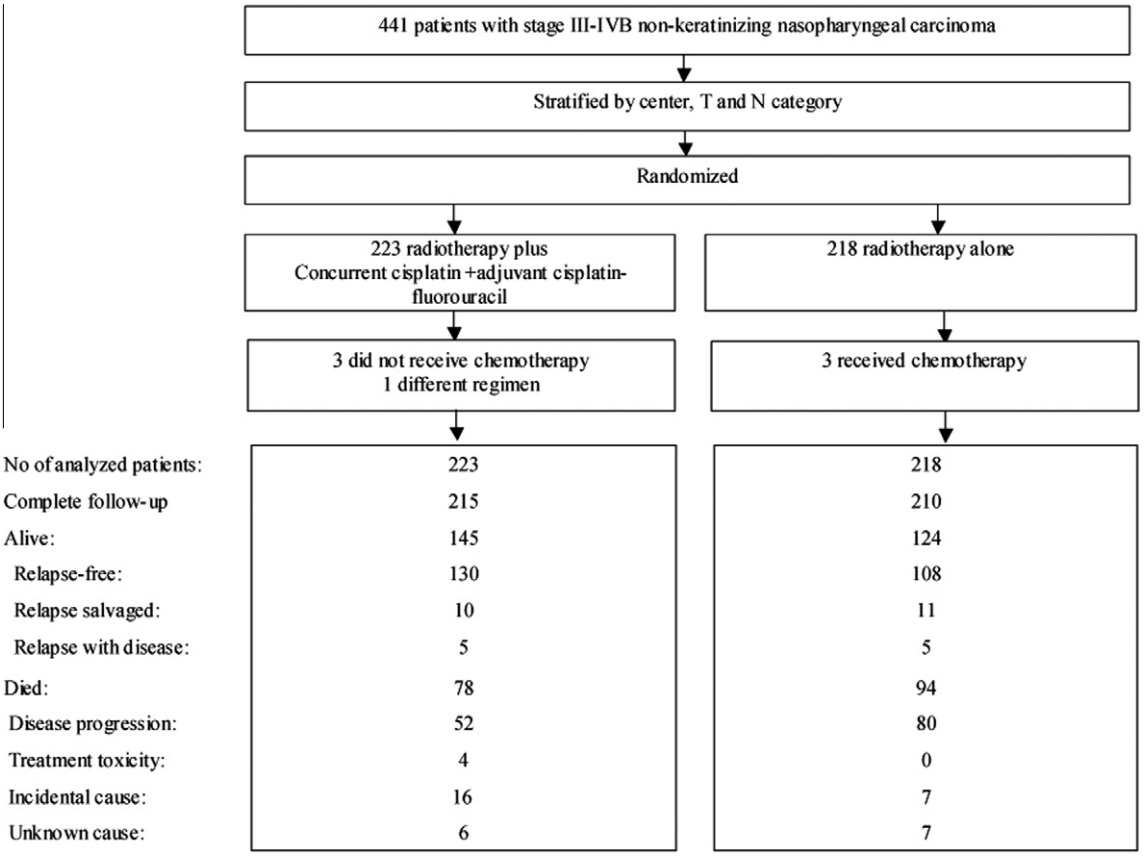

Fig. 1 – Enrollment and outcomes.

included Pamela Youde Nethersole Eastern Hospital, Tuen Mun Hospital, Queen Elizabeth Hospital, Queen Mary Hospital, and Prince of Wales Hospital from Hong Kong; Sun Yat Sen University from China; Princess Margaret Hospital from Canada and National Cancer Center from Singapore. Ninety-six percent of patients had been regularly reassessed for a median duration of 6.1 years (range, 0.2–9.9); patients alive at the time of this analysis had a minimum follow-up of 5 years.

The allocated treatment groups were well balanced in all patient characteristics, tumour factors and radiotherapy parameters (Table 1). The median total dose was 68 Gy and the overall treatment time was 46 d. For patients given an additional boost to the nasopharynx or the parapharyngeal space, the median dose was 10 Gy. Only 1.3% of patients in the CRT_i group and 0.5% in the RT_i group failed to complete the scheduled total dose.

Seven patients had major protocol violations (Fig. 1): three (1.4%) in the RT_i group received chemotherapy (because of disease progression and patient's choice); three (1.3%) in the CRT_i group did not receive chemotherapy (because of incidental cause and patient's choice) and one (0.4%) was given weekly concurrent cisplatin (because of abnormal liver function).

Altogether 62% of patients in the CRT_i group completed all six cycles of chemotherapy (Table 2), 58% patients completed all three concurrent cycles and 74% completed all three adjuvant cycles. The mean dose of cisplatin given was 82% and 80% of the scheduled dose for the concurrent and the adjuvant phase, respectively; and that of fluorouracil was 75%. In addition, three patients in the RT_i group had six cycles of chemotherapy.

3.2. *Analyses based on intention-to-treat*

Altogether 174 patients had tumour relapse (70 at locoregional and 127 at distant sites), and 172 had died (132 of disease progression, 27 of treatment toxicity or 'incidental' causes, and 13 of unknown causes).

Comparison of the treatment groups by intention-to-treat showed that the overall FFR was significantly higher in the CRT_i group as compared to the RT_i group: 66% versus 57% at 5-year, $p = 0.019$; HR 0.70 (95% CI 0.52–0.94). Locoregional-FFR was significantly higher in the CRT_i group [(Fig. 2A; 87% versus 80%, $p = 0.014$; HR 0.55 (95% CI 0.34–0.89)]. However, the corresponding improvement in distant-FFR was statistically insignificant [(Fig. 2B; 74% versus 69%, $p = 0.34$; HR was 0.84 (95% CI 0.60–1.20)].

Table 1 – Patient characteristics and radiotherapy parameters.

	CRT_i group ($n = 223$)	RT_i group ($n = 218$)	P
Patient characteristics			
Age, years			0.25
Median (range)	46 (17–69)	47 (26–69)	
Sex, *n* (%)			0.39
Male	164 (74%)	168 (77%)	
Female	59 (26%)	50 (23%)	
Performance status, *n* (%)			0.33
0	188 (84%)	185 (85%)	
1	35 (16%)	31 (14%)	
2	0	2 (1%)	
T-category, *n* (%)			0.61
T1–2	100 (45%)	103 (47%)	
T3–4	123 (55%)	115 (53%)	
N-category, *n* (%)			0.76
N0–1	51 (23%)	42 (19%)	
N2	117 (52%)	119 (55%)	
N3	55 (25%)	57 (26%)	
Stage-group, *n* (%)			0.51
III	125 (56%)	129 (59%)	
IVA-B	98 (44%)	89 (41%)	
Lactate dehydrogenase, iu/L			0.51
Median (range)	224 (24–1100)	229 (106–616)	
Radiotherapy			
Technique, *n* (%)			0.34
2-Dimensional throughout	91 (41%)	82 (38%)	
2-Dimensional + conformal	20 (9%)	29 (13%)	
Conformal throughout	112 (50%)	107 (49%)	
Total dose, Gy			0.16
Median (range)	70 (2–78)	70 (48–78)	
Overall treatment time, days			0.39
Median (range)	46 (0–58)	47 (35–59)	
Additional boost, *n* (%)			0.12
Nasopharynx/parapharynx	72 (32%)	86 (39%)	

CRT_i = Chemoradiotherapy and RT_i = Radiotherapy-alone group by intention-to treat.

Table 2 – Chemotherapy actually received.

Phase	CRT_i group (n = 223)		RT_i group (n = 218)	
	Concurrent	Adjuvant	Concurrent	Adjuvant
Number of cycles given, n (% within the allotted group)				
0	3 (1.3%)[a]	33 (14.8)	215 (98.6)	215 (98.6)
1	11 (4.9)	12 (5.4)	0	0
2	81 (36.5)	14 (6.3)	1(0.5)[a]	0
3	128 (57.4)	132 (59.2)	2 (0.9)[a]	2 (0.9)[a]
4[b]	0	32 (14.3)	0	1 (0.5)[a]
Percent of scheduled dose given: mean ± standard deviation				
Cisplatin	82 ± 22	80 ± 40	1 ± 11[a]	1 ± 11[a]
5-Fluorouracil	0	75 ± 38	0	1 ± 10[a]

CRT_i=Chemoradiotherapy and RT_i=Radiotherapy-alone group by intention-to treat.

[a] Patients with major protocol violation (see text).

[b] Patients had 2 concurrent plus 4 adjuvant cycles because the third cycle of cisplatin was given after completion of radiotherapy (due to delay during the concurrent phase).

The corresponding CSS was significantly higher in the CRT_i group [(Fig. 3A; 78% versus 67%, $p = 0.008$; HR 0.62 (95% CI 0.44–0.89)]. However, the improvement in OS was statistically insignificant [(Fig. 3B; 70% versus 64%; $p = 0.14$); HR 0.80 (95% CI 0.59–1.08)] because of significant increase in deaths due to non-cancer causes (treatment-related toxicities 1.8% versus 0 and incidental causes 7.2% versus 3.2%), $p = 0.012$ by χ^2 tests.

3.3. *Analyses based on actual treatment*

To assess the factors that affect the efficacy of chemotherapy and the magnitude of benefit for different subsets, the following analyses were based on actual treatment given. The two treatment groups (CRT_a versus RT_a, the suffice '*a*' indicates the groups by treatment actually received) were well balanced in all patient characteristics, tumour factors and radiotherapy parameters ($p \geqslant 0.12$). The CRT_a group achieved significant improvement not only in CSS, but also in OS group [Fig. 4; 72% versus 63%, $p = 0.037$; HR 0.73 (95% CI 0.54–0.98)] as compared to the RT_a group,

Table 3 summarises the multivariate analyses performed on different chemotherapy parameters together with other potential factors identified by univariate analyses (including age, sex, stage group, LDH, radiotherapy technique and total dose) as covariates. The first multivariate analysis, using chemotherapy (yes versus no) as covariate, showed that chemotherapy was a significant factor for all end-points including not only locoregional failure and cancer-specific death, but also distant failure [HR 0.67 (95% CI 0.47–0.95); $p = 0.024$] and death from all causes [HR 0.69 (95% CI 0.51–0.94); $p = 0.019$].

Repeating the multivariate analysis using the percent of scheduled dose of each drug as covariates showed that the dose of concurrent cisplatin was a significant factor not only for locoregional failure and cancer-specific death, but also for death from all causes [HR 0.996 (95% CI 0.992–0.999) per% dose increase; $p = 0.019$]. The only significant chemotherapy parameter that affected distant failure was the dose of adjuvant fluorouracil [HR 0.995 (95% CI 0.991–0.999) per% dose increase; $p = 0.012$].

The 5-year locoregional-FFR for patients who received 0–1, 2 and 3 concurrent cycles were 79%, 88% and 88%, respectively (Fig. 5A; $p = 0.006$). When compared with 229 patients who received 0–1 cycle of concurrent cycles, significant improvement was achieved in both the 82 patients with two cycles ($p = 0.040$) and the 130 patients with three cycles ($p = 0.006$); the difference between two and three cycles was insignificant ($p = 0.83$). The same pattern was observed when the comparison was based on the % of scheduled dose of concurrent cisplatin: the 5-year locoregional-FFR for patients who received <67%, ⩾67% to <100% and 100% doses were 79%, 87% and 88%, respectively.

The 5-year distant-FFR for patients who received 0–1, 2 and 3–4 adjuvant cycles were 68%, 78% and 77%, respectively (Fig. 5B; $p = 0.063$). When compared with 260 patients who received 0–1 cycle of adjuvant cycles, significant improvement was achieved in the 167 patients with 3–4 cycles ($p = 0.019$). Only 14 patients had two adjuvant cycles, differences from other groups were statistically insignificant ($p \geqslant 0.62$). Similar pattern was observed when the comparison was based on the % of scheduled dose of adjuvant fluorouracil: the 5-year distant-FFR for patients who received <67%, ⩾67 to <100% and 100% doses were 68%, 80% and 76%, respectively.

Among the other potential factors, those with a statistically significant impact on OS include stage group, LDH, age, sex and radiotherapy dose. The values for HR based on the first multivariate analysis using chemotherapy as covariate are listed in Table 3. The individual values varied slightly in the multivariate analysis using % scheduled doses of drugs as covariates, but the conclusions about their respective statistical significance were the same. Patients with stage III disease had significantly better outcome than those with stage IVA-B in all end-points, increases in LDH and age were associated with significantly poorer distant control, male patients had significantly poorer locoregional control, patients with radiotherapy total dose <70 Gy had poorer control at both locoregional and distant sites.

Table 4 shows the differences in outcome for different prognostic groups. Subset by stage group showed that for the patients with stage III diseases, the CRT_a group achieved significant improvement not only in FFR, but also in OS [82% versus 70%, $p = 0.047$; HR 0.63 (0.401–0.998)]. For patients with stage IVA-B disease, the CRT_a group also achieved significant

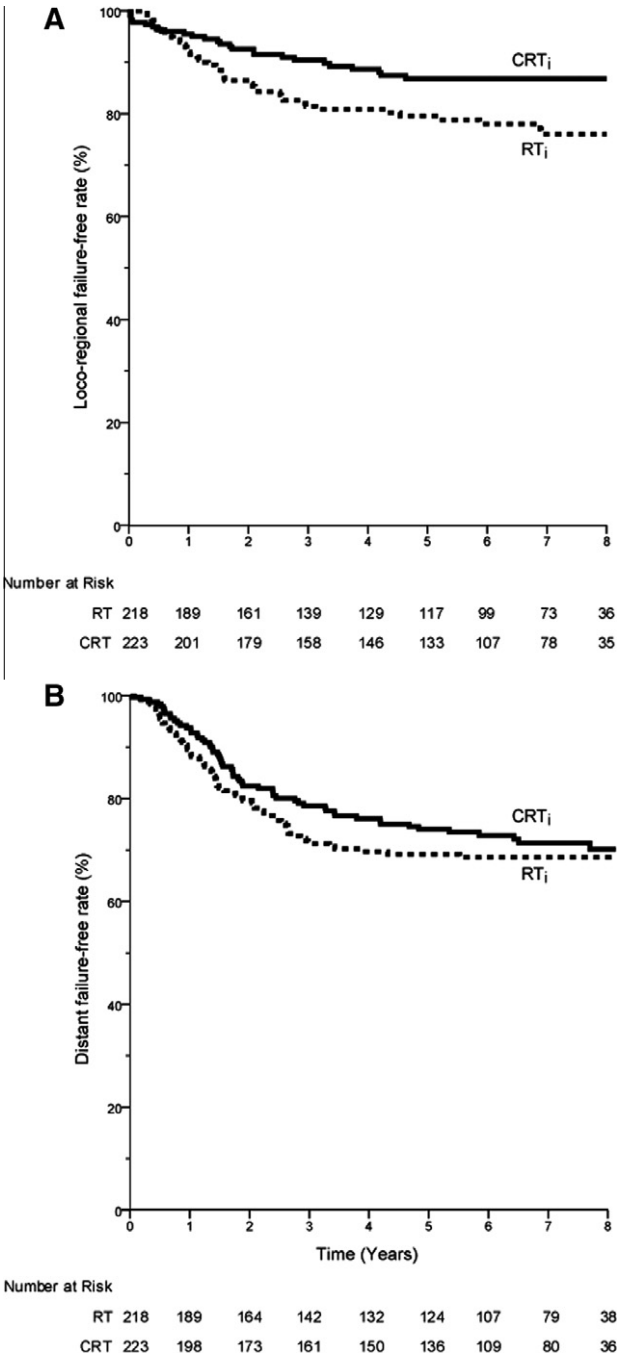

Fig. 2 – Kaplan–Meier estimates of (A) loco-regional failure-free rate and (B) distant failure-free rate. CRT_i = chemoradiotherapy group versus RT_i = radiotherapy-alone group by intention-to-treat.

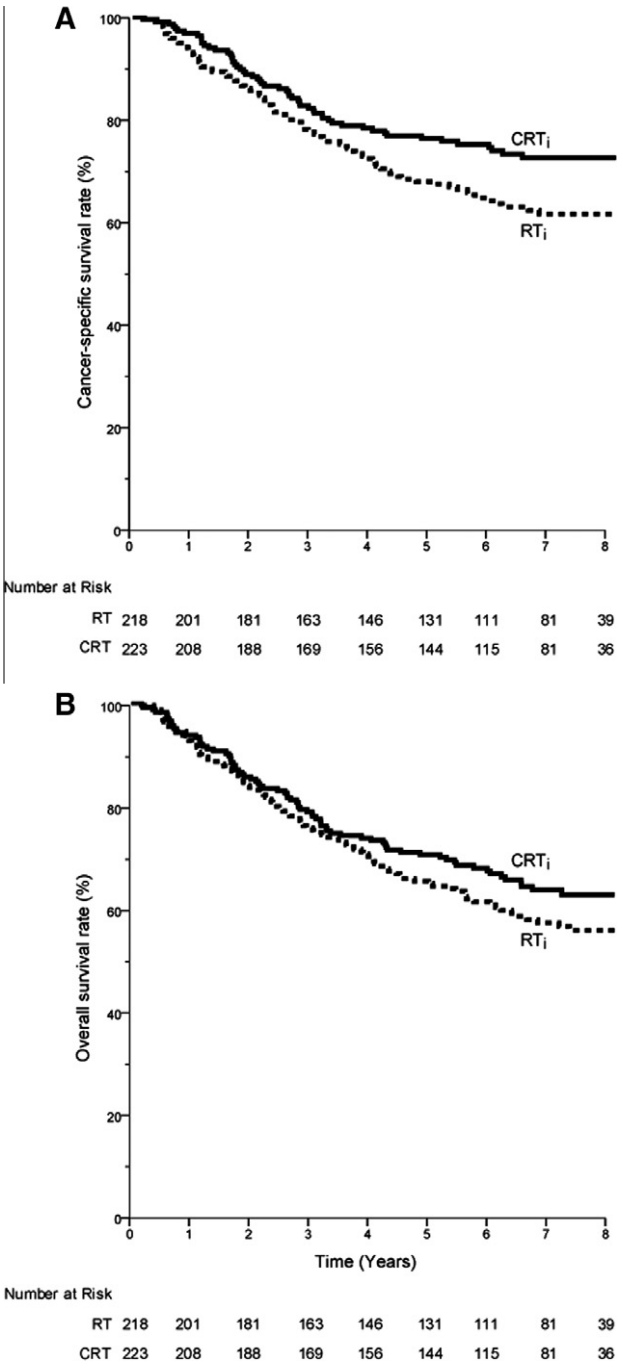

Fig. 3 – Kaplan–Meier estimates of (A) cancer-specific survival and (B) overall survival. CRT_i = chemoradiotherapy group versus RT_i = radiotherapy-alone group by intention-to-treat.

improvement in FFR, but the improvement in OS was statistically insignificant ($p = 0.19$). Subset analysis by LDH showed that for both the patients with LDH <200 iu/L and with LDH ⩾200 iu/L, the CRT_a group achieved significantly higher FFR, but the improvement in OS reached borderline significance only in those with low LDH [83% versus 73%, $p = 0.054$; HR 0.59 (0.34–1.02)].

Subset by age showed that for patients 45–69 years old, the CRT_a group achieved significantly higher FFR and borderline improvement in OS [68% versus 58%, $p = 0.059$; 0.70 (0.48–1.02)]; but for patients aged <45 years, even the improvement in FFR only reached borderline significant statistically ($p = 0.049$ by log-rank, $p = 0.051$ by Cox regression). Subset by sex showed that for male patients, the CRT_a group achieved significantly higher FFR and borderline improvement in OS [69% versus 59%, $p = 0.062$; 0.73 (0.52–1.02)]; but for female patients, the improvement in both FFR and OS were statistically insignificant ($p \geqslant 0.45$).

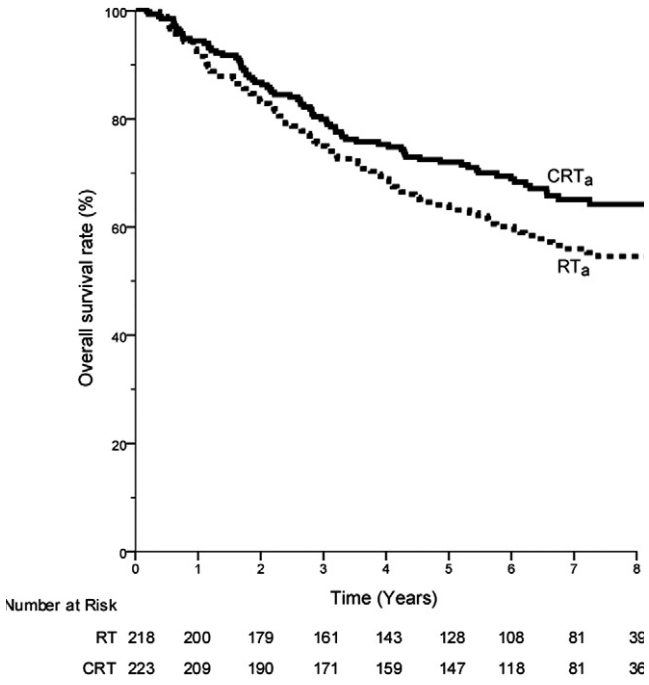

Fig. 4 – Kaplan–Meier estimates of overall survival. CRT_a = chemoradiotherapy group versus RT_a = radiotherapy-alone group by actual treatment.

Subset by radiotherapy total dose showed that for patients with less than 70 Gy, the CRT_a group achieved significantly higher FFR and a favourable trend in OS [67% versus 54%, $p = 0.074$; 0.69 (0.45–1.04)]; but for patients with $\geqslant$70 Gy, the improvement in both FFR and OS were statistically insignificant ($p \geqslant 0.11$).

4. Discussion

Since the publication of the landmark Intergroup-0099 Study[3] in the late nineties, combined therapy using cisplatin in concurrence with conventional–fractionated radiotherapy followed by adjuvant cisplatin plus fluorouracil became the standard treatment recommended for patients with locoregionally advanced NPC. This combined analysis of the NPC-9901 Trial[6] and the NPC-9902 Trial,[7] based on 441 patients with a median observation period of 6.1 years, provides more comprehensive data for studying the efficacy of the Intergroup-0099 regimen in patients with stage III-IVB non-keratinizing NPC. The only major limitation is that patients with keratinizing squamous cell carcinoma were not included; the current findings may not be extrapolated to these patients without further testing.

In line with the updated report of NPC-9901 Trial,[6] current comparisons based on intention-to-treat confirmed that the CRT_i group achieved significant improvement in overall FFR (9% increase at 5-year; $p = 0.019$), locoregional-FFR (7% increase, $p = .014$; Fig. 2A), and CSS (11% increase; $p = 0.008$; Fig. 3A) as compared to the RT_i group. Although the improvement in distant-FFR (5% increase, $p = 0.34$; Fig. 2B) was statistically insignificant, and the gain in OS was narrowed (6% increase, $p = 0.14$; Fig. 3B) because of increase in non-cancer deaths (treatment-related toxicities 1.8% and incidental causes 4%, $p = 0.012$), this study concurred with the previous trials[3,6,8,9] in supporting the current practice because reduction of tumour relapse and cancer-specific deaths is of top importance.

To provide additional data for assessing the factors contributing to the efficacy of the current chemotherapy regimen, we have conducted further exploratory studies based on ac-

Table 3 – Significant factors affecting outcome: hazard ratio (95% confidence interval) and *p* value.

Factor	Locoregional-failure	Distant-failure	All death
(I) Multivariate analysis with chemotherapy + other factors[a] as covariates			
Chemotherapy:	0.46 (0.28–0.75)	0.67 (0.47–0.95)	0.69 (0.51–0.94)
Yes versus No	$p = 0.002$	$p = 0.024$	$p = 0.019$
Stage group	1.64 (1.01–2.68)	2.20 (1.53–3.17)	1.84 (1.34–2.51)
IV versus III	$p = 0.046$	$p < 0.001$	$p < 0.001$
Lactate dehydrogenase		1.002 (1.001–1.004)	1.002 (1.001–1.003)
Per iu/L increase	$p = 0.28$	$p < 0.001$	$p < 0.001$
Age		1.022 (1.004–1.041)	1.037 (1.020–1.054)
Per year increase	$p = 0.26$	$p = 0.019$	$p < 0.001$
Sex	2.46 (1.20–5.05)		1.61 (1.06–2.45)
Male versus female	$p = 0.014$	$p = 0.094$	$p = 0.025$
Radiotherapy dose	0.92 (0.90–0.94)	0.96 (0.94–0.99)	0.96 (0.94–0.98)
Per Gy increase	$p < 0.001$	$p = 0.009$	$p < 0.001$
(II) Multivariate analysis with dose of each drug + other factors[a] as covariates			
Concurrent cisplatin	0.991 (0.985–0.997)		0.996 (0.992–0.999)
Per % dose increase	$p = 0.004$	$p = 0.89$	$p = 0.019$
Adjuvant cisplatin			
Per % dose increase	$p = 0.34$	$p = 0.95$	$p = 0.34$
Adjuvant fluorouracil		0.995 (0.991–0.999)	
Per % dose increase	$p = 0.62$	$p = 0.012$	$p = 0.39$
Other factors	Same conclusion about significance as above		

[a] Statistically significant factors on univariate analyses: including age, sex, stage group, lactate dehydrogenase, radiotherapy technique and total dose.

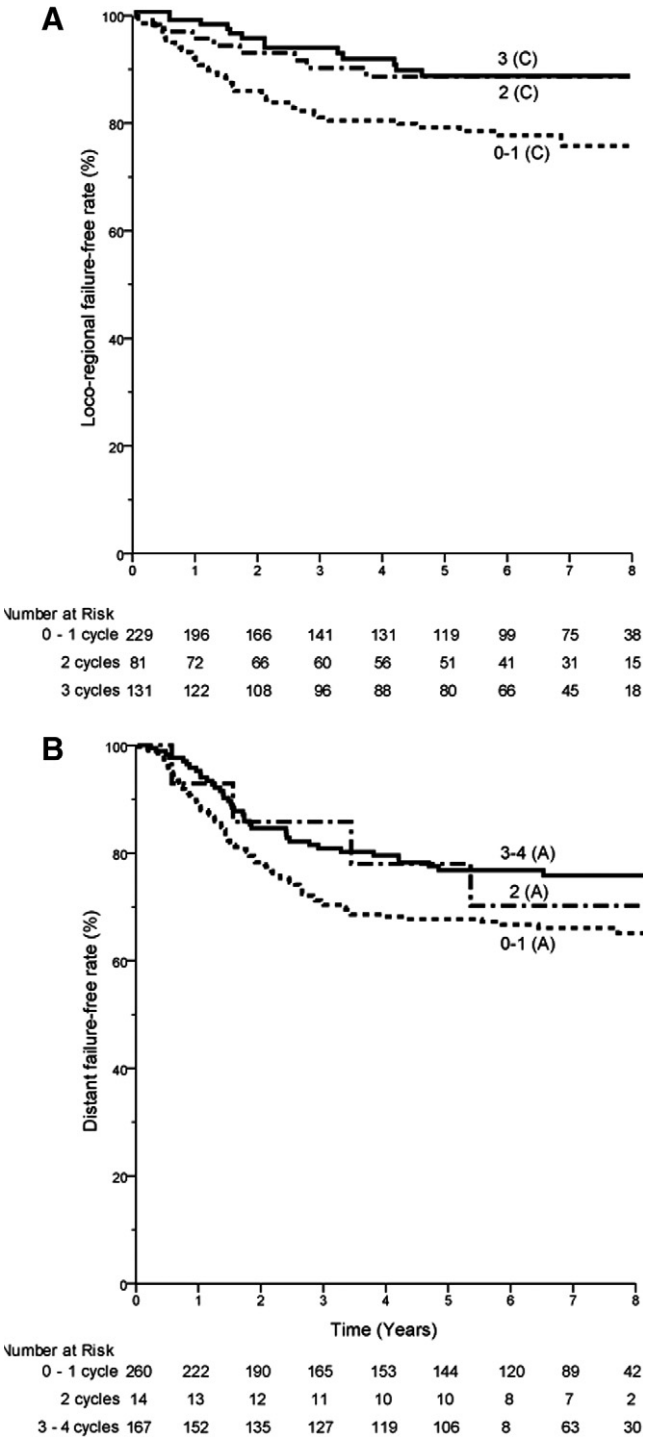

Fig. 5 – Kaplan–Meier estimates of (A) loco-regional failure-free rate and (B) distant failure-free rate. (C) = the number of cycles of concurrent chemotherapy received; (A) = the number of cycles of adjuvant chemotherapy received

tual treatment because three (1.4%) patients in the RT_i group received chemotherapy and conversely three (1.3%) in the CRT_i group did not receive chemotherapy. The comparisons were valid because the two treatment groups (CRT_a versus RT_a) were well balanced in all patient characteristics, tumour factors and radiotherapy parameters ($p \geqslant 0.12$). The findings are useful for generating hypotheses, but it should be cautioned that these are more subjected to selection biases than comparisons based on intention-to-treat.

The CRT_a group (patients who did receive addition of chemotherapy) achieved significant improvement not only in FFR and CSS, but also in OS (9% increase, $p = 0.037$; Fig. 4, Table 4) as compared with the RT_a group. When adjusted for other prognostic factors on multivariate analyses, the hazard of distant failure was also significantly reduced by 33% (5–53%) by the addition of chemotherapy (Table 3: $p = 0.024$). Both improvements give further support to the therapeutic value of the Intergroup-0099 regimen.

Three pressing questions remain: firstly, can we define the optimal dose so that we can reduce toxicity by avoiding unnecessary overdose or an ineffective phase of treatment? Secondly, how can we further enhance efficacy for distant control? Thirdly, can we provide more detailed information for clinicians and patients in their treatment decision? Better understanding of the parameters contributing to the efficacy of the current regimen is crucial for future design of chemotherapy regimen.

A major question regarding the design of the Intergroup-0099 regimen is the contribution of the adjuvant phase. To our knowledge, there is yet no randomized trial that compare concurrent–adjuvant versus concurrent-alone chemoradiotherapy. The only data available are a retrospective study by Cheng et al.[21] comparing concurrent–adjuvant chemotherapy versus radiotherapy or concurrent chemoradiotherapy alone, which showed that inclusion of the adjuvant phase was unnecessary for patients with low-risk (T1-2aN0-2M0), but beneficial for intermediate risk (T2b-3N0-2M0): the 5-year OS was 84% versus 63% ($p = 0.005$).

Review of randomized trials using concurrent chemotherapy alone[12,22–24] showed less consistent conclusions. Lin et al.[22] using concurrent cisplatin plus fluorouracil and Zhang et al.[23] using oxaliplatin reported significant benefit in both EFS and OS. However, subsequent re-analysis of the former trial[25] with retrospective re-staging of the accrued patients into different risk groups showed that the benefit was significant only for low-risk patients; and the trial by Zhang et al.[23] only had preliminary 2-year results. Kwong et al.[12] using uracil-tegafur with or without adjuvant cisplatin-based combination and Chan et al.[24] using weekly cisplatin only showed borderline improvement in OS ($p \geqslant 0.06$) and no significant improvement in FFR ($p \geqslant 0.14$). A subsequent randomized Phase II trial by Chan's group[26] showed that patients with addition of induction chemotherapy using docetaxel and cisplatin followed by concurrent weekly cisplatin achieved significantly higher OS than those treated by concurrent chemotherapy alone (94% versus 68% at 2-year; $p = 0.012$).

Multivariate analysis on the independent significance of each drug in this study showed that the phase and dose of drug used had significant impact on different aspects of tumour control (Table 3). The concurrent phase was indeed important for locoregional control and survival, but the impact on distant control was inadequate. Interestingly, it was the adjuvant phase, particularly fluorouracil in the drug combination, which had significant impact on distant control.

Further correlation with the number of cycles showed the locoregional-FFR for patients who received 0–1 concurrent

Table 4 – Comparison of outcome between patients with versus those without actual addition of chemotherapy: 5-year rates (p by log-rank), and hazard reduction (95% confidence interval).

	CRT_a group versus RT_a group	
	Failure-free rate (5-year)	Overall survival (5-year)
Whole series	68% versus 55% ($p = 0.002$) HR 0.63 (0.47–0.85)	72% versus 63% ($p = 0.037$) HR 0.73 (0.54–0.98)
Subset by stage group		
III ($n = 254$)	78% versus 64% ($p = 0.009$) HR 0.55 (0.35–0.87)	82% versus 70% ($p = 0.047$) HR 0.63 (0.40–1.00)
IVA-B ($n = 187$)	54% versus 43% ($p = 0.045$) HR 0.67 (0.45–0.99)	59% versus 52% ($p = 0.19$) HR 0.76 (0.51–1.14)
Subset by lactate dehydrogenase		
<200 iu/L ($n = 200$)	77% versus 65% ($p = 0.023$) 0.55 (0.33–0.93)	83% versus 73% ($p = 0.054$) 0.59 (0.34–1.02)
>200 iu/L ($n = 234$)	60% versus 47% ($p = 0.039$) 0.68 (0.47–0.98)	62% versus 55% ($p = 0.22$) 0.80 (0.55–1.15)
Subset by age		
<45 years ($n = 191$)	72% versus 62% ($p = 0.049$) 0.61 (0.37–1.00)	76% versus 69% ($p = 0.34$) 0.78 (0.47–1.30)
>45 years ($n = 250$)	64% versus 50% ($p = 0.020$) 0.64 (0.44–0.94)	68% versus 58% ($p = 0.059$) 0.70 (0.48–1.02)
Subset by sex		
Male ($n = 332$)	64% versus 50% ($p = 0.003$) 0.61 (0.44–0.85)	69% versus 59% ($p = 0.062$) 0.73 (0.52–1.02)
Female ($n = 109$)	77% versus 72% ($p = 0.52$) 0.79 (0.38–1.63)	81% versus 76% ($p = 0.45$) 0.76 (0.37–1.56)
Subset by radiotherapy total dose		
<70 Gy($n = 191$)	63% versus 45% ($p = 0.006$) 0.57 (0.37–0.86)	67% versus 54% ($p = 0.074$) 0.69 (0.45–1.04)
>70 Gy ($n = 250$)	71% versus 63% ($p = 0.11$) 0.70 (0.45–1.08)	75% versus 69% ($p = 0.21$) 0.76 (0.49–1.17)

cycles was significantly lower than those with more cycles (Fig. 5A; 79% versus 88%, $p \geqslant 0.04$), but there was little difference between those with two cycles versus those with three cycles ($p = 0.83$). The same pattern was observed when the comparison was based on the percent of dose of concurrent cisplatin. The distant-FFR for patients who received 0–1 adjuvant cycles was significantly lower than those with three or more cycles (Fig. 5B; 68% versus 77%, $p = 0.019$), but the adequacy of two cycles could not be interpreted because only 14 patients in this series had two adjuvant cycles. The same pattern was observed when the comparison was based on the percent of dose of adjuvant fluorouracil.

Hence, our data suggest that besides giving cisplatin during the concurrent phase, additional chemotherapy in a sequential phase using fluorouracil-containing combination is needed for improving distant control. The Intergroup-0099 regimen could be refined by reducing from three to two concurrent cycles (that is, reducing the dose of concurrent cisplatin to 200 mg/m^2) without affecting the efficacy. The patients should be informed of the importance of compliance, and vigorous efforts should be made to support them to receive adequate doses.

This study also provides more data for different subsets so that clinicians and patients could have more specific information for treatment decision (Table 4). The CRT_a group achieved significantly higher FFR than the RT_a group in all subsets except female patients and those with radiotherapy total dose $\geqslant$70 Gy. As the radiotherapy in this series (with only half of patients treated by conformal technique to $\geqslant$70 Gy) is suboptimal by modern standard, the magnitude of benefit by chemotherapy is likely to be more difficult to demonstrate for patients irradiated with intensity-modulated technique.

The magnitude of improvement in OS was greatest for patients with stage III disease (12% increase at 5-year, $p = 0.047$) and then those with LDH <200 iu/L (10% increase, $p = 0.054$), but the improvement for patients with stage IVA-B disease and those with LDH $\geqslant$200 iu/L was statistically insignificant (7% increase, $p \geqslant 0.19$). Hence our data suggest that while the Intergroup-0099 regimen could achieve significant therapeutic benefit for patients with moderate risk (stage III, low LDH), more potent therapy is needed for patients with higher risk.

One logical strategy for future improvement is to change the sequence from concurrent–adjuvant to induction–concurrent chemotherapy because meta-analyses showed that induction chemotherapy *per se* could significantly reduce both locoregional and distant failures.[13] Studies by Lee et al.[27,28] on induction chemotherapy with cisplatin-fluorouracil followed by concurrent cisplatin showed that 98% of patients could complete three cycles of induction chemotherapy without substantial jeopardy of tolerance in the concurrent phase. Furthermore, this could significantly reduce the primary

tumour volume by 61% (mean), leading to better radiation dose coverage by subsequent intensity-modulated radiotherapy ($p < 0.02$).

Another strategy is to enhance the efficacy of radiotherapy by changing from conventional to accelerated fractionation. Preliminary results from the NPC-9902 Trial[7] showed that the accelerated-fractionation chemoradiotherapy group achieved significantly better FFS than the conventional–fractionation chemoradiotherapy group (94% versus 74% at 3-year, $p = 0.004$). The Hong Kong Nasopharyngeal Cancer Study Group is currently conducting a randomized trial (NPC-0501 Trial) to evaluate the therapeutic benefits by changing the chemotherapy sequence from concurrent–adjuvant to induction–concurrent and/or changing the radiotherapy schedule from conventional to accelerated fractionation. In addition, this trial attempts to study the possibility of replacing fluorouracil with the oral pro-drug capecitabine.

In conclusion, our results support the current practice of adding concurrent cisplatin plus adjuvant cisplatin-fluorouracil to radiotherapy for treating patients with locoregionally advanced NPC. Our exploratory studies suggest that the concurrent phase is important for locoregional control and survival, cisplatin 200 mg/m^2 in two concurrent cycles might be adequate; additional treatment using fluorouracil-containing combination could contribute to improving distant control. Vigorous efforts should be made to encourage and support patients to receive adequate dose of both radiotherapy and chemotherapy. Continual search for more potent therapy for patients with highest risk (stage IV, high LDH) is needed.

Contributors

AWML, SYT, RC, WHL were responsible for the conception and design of the study; AWML, SYT, RKCN, DTTC, ATCC, TXL, LS, TT, WTN, TWL, YTF, GKHA, SFL, CZ, BOS, EHT were responsible for contribution of patients; AWML, LKC, RC were responsible for data analyses and interpretation; AWML was responsible for writing the manuscript.

Funding

This study is funded by three charitable organisations including the Hong Kong Cancer Fund, Ho Hung Chiu Medical Foundation Limited and the Hong Kong Anti-Cancer Society.

Conflict of interest statement

None declared.

Acknowledgements

We are grateful to the Hong Kong Cancer Fund, Ho Hung Chiu Medical Foundation Limited, and the Hong Kong Anti-Cancer Society for their financial support. We thank co-investigators, Data Monitoring Committee, data managers, internal monitors, all colleagues and patients involved in this trial.

REFERENCES

1. Yeh SA, Tang Y, Lui CC, et al. Treatment outcomes and late complications of 849 patients with nasopharyngeal carcinoma treated with radiotherapy alone. *Int J Radiat Oncol Biol Phys* 2005;**62**:672–9.
2. Yi JL, Gao L, Huang XD, et al. Nasopharyngeal carcinoma treated by radical radiotherapy alone: ten-year experience of a single institution. *Int J Radiat Oncol Biol Phys* 2006;**65**: 161–8.
3. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup Study 0099. *J Clin Oncol* 1998;**16**:1310–7.
4. Chow E, Payne D, O'Sullivan B, et al. Radiotherapy alone in patients with advanced nasopharyngeal cancer: comparison with an Intergroup study – is combined modality treatment really necessary? *Radiother Oncol* 2002;**63**:269–74.
5. Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol* 2005;**23**:6966–75.
6. Lee AW, Tung SY, Chua DT, et al. Randomized trial of radiotherapy plus concurrent–adjuvant chemotherapy vs radiotherapy alone for regionally-advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* 2010;**102**:1188–98.
7. Lee AW, Tung SY, Chan AT, et al. Preliminary results of a randomized study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation for locally-advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2006;**66**:142–51.
8. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against Cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol* 2005;**23**:6730–8.
9. Chen Y, Liu MZ, Liang SB, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of China. *Int J Radiat Oncol Biol Phys* 2008;**71**:1356–64.
10. Rossi A, Molinari R, Boracchi P, et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. *J Clin Oncol* 1988;**6**:1401–10.
11. Chi KH, Chang YC, Guo WY, et al. A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. *Int J Radiat Oncol Biol Phys* 2002;**52**:1238–44.
12. Kwong DL, Sham JS, Au GK, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol* 2004;**22**:2643–53.
13. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: An individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys* 2006;**64**:47–56.
14. Shanmugarantnam K, Sobin LH. *Histological typing of tumors of the upper respiratory tract and ear*. 2nd ed. New York: Springer-Verlag; 1991.
15. Fleming ID, Cooper JS, Henson DE, et al. *American joint committee on cancer: AJCC cancer staging manual*. 5th ed. Philadelphia: Lippincott-Raven; 1997.

16. Sobin LH, Wittekind Ch. *International union against cancer (UICC): TNM classification of malignant tumors*. 5th ed. New York: Wiley-Liss; 1997.
17. Freedman J, Furberg C, DeMets D. *Fundamentals of clinical trials*. New York: Springer-Verlag; 1998.
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958;**53**:457–81.
19. Peto R, Pike MC, Groupitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977;**35**:1–39.
20. Cox DR. Regression models and life tables. *J Roy Statist Soc B* 1972;**34**:187–220.
21. Cheng SH, Tsai YC, Yen KL, et al. Prognostic significance of parapharyngeal space venous plexus and marrow involvement: Potential landmarks of dissemination for stage I-III nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2005;**61**:456–65.
22. Lin JC, Jan JS, Hsu CY, et al. Concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol* 2003;**21**:631–7.
23. Zhang L, Zhao C, Peng PJ, et al. Phase III study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma: preliminary results. *J Clin Oncol* 2005;**23**:8461–8.
24. Chan ATC, Teo PML, Ngan RK, et al. Concurrent chemotherapy–radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol* 2002;**20**:2038–44.
25. Lin JC, Liang WM, Jan JS, Jiang RS, Lin AC. Another way to estimate outcome of advanced nasopharyngeal carcinoma –i s concurrent chemoradiotherapy adequate. *Int J Radiat Oncol Biol Phys* 2004;**60**:156–64.
26. Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of cisplatin-radiotherapy with and without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol* 2009;**27**:242–9.
27. Lee AW, Yau TK, Wong HM, et al. Treatment of stage IV(A-B) nasopharyngeal carcinoma by induction–concurrent chemoradiotherapy and accelerated fractionation. *Int J Radiat Oncol Biol Phys* 2005;**63**:1331–8.
28. Lee AW, Lau KY, Hung WM, et al. Potential improvement of tumor control probability by induction chemotherapy for advanced nasopharyngeal carcinoma. *Radiother Oncol* 2008;**87**:204–10.