Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial

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Summary

Background **The effect of the addition of adjuvant chemotherapy to concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma is unclear. We aimed to assess the contribution of adjuvant chemotherapy to concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone.**

Methods **We did an open-label phase 3 multicentre randomised controlled trial at seven institutions in China. Randomisation was by a computer-generated random number code. Patients were stratified by treatment centre and randomly assigned in blocks of four. Treatment allocation was not masked. We randomly assigned patients with non-metastatic stage III or IV (except T3–4N0) nasopharyngeal carcinoma to receive concurrent chemoradiotherapy plus adjuvant chemotherapy or concurrent chemoradiotherapy alone. Patients in both groups received 40 mg/m² cisplatin weekly up to 7 weeks, concurrently with radiotherapy. Radiotherapy was given as 2·0–2·27 Gy per fraction with five daily fractions per week for 6–7 weeks to a total dose of 66 Gy or greater to the primary tumour and 60–66 Gy to the involved neck area. The concurrent chemoradiotherapy plus adjuvant chemotherapy group subsequently received 80 mg/m² adjuvant cisplatin and 800 mg/m² per day fluorouracil for 120 h every 4 weeks for three cycles. Our primary endpoint was failure-free survival. We did efficacy analyses in our intention-to-treat population. Our trial is ongoing; in this report we present the 2 year survival results and acute toxic effects. This trial is registered with ClinicalTrials.gov, number NCT00677118.**

Findings **251 patients were assigned to the concurrent chemoradiotherapy plus adjuvant chemotherapy group and 257 to the concurrent chemoradiotherapy alone group. After a median follow-up of 37·8 months (range 1·3–61·0), the estimated 2 year failure-free survival rate was 86% (95% CI 81–90) in the concurrent chemoradiotherapy plus adjuvant chemotherapy group and 84% (78–88) in concurrent chemoradiotherapy only group (hazard ratio 0·74, 95% CI 0·49–1·10; p=0·13). Stomatitis was the most commonly reported grade 3 or 4 adverse event during both radiotherapy (76 of 249 patients in the concurrent chemoradiotherapy plus adjuvant chemotherapy group and 82 of 254 in the concurrent chemoradiotherapy alone group) and adjuvant chemotherapy (43 [21%] of 205 patients treated with adjuvant chemotherapy).**

Interpretation **Adjuvant cisplatin and fluorouracil chemotherapy did not significantly improve failure-free survival after concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma. Longer follow-up is needed to fully assess survival and late toxic effects, but such regimens should not, at present, be used outside well-designed clinical trials.**

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Introduction

According to the International Agency for Research on Cancer, there were 84 400 cases of nasopharyngeal carcinoma, and 51 600 deaths from it, in 2008.[1] The worldwide distribution of nasopharyngeal carcinoma is extremely unbalanced, with an age-standardised incidence rate of 20–50 per 100 000 males in south China to 0·5 per 100 000 in mainly white populations.[1] Radiotherapy is the primary treatment modality for non-disseminated nasopharyngeal carcinoma because of the anatomical location and radiosensitivity. Control of early-stage disease with radiotherapy alone is usually successful; however, the response of locoregionally advanced nasopharyngeal carcinoma is unsatisfactory, with 5 year overall survival of 87–96% in stage I–II and 67–77% in stage III–IVB.[2] According to the 6th American Joint Commission on Cancer (AJCC) staging system,[3] 60–70% of patients present with stage III–IVB disease.[4] The

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Intergroup 0099 study showed that concurrent chemoradiotherapy with adjuvant chemotherapy provided a 31% increase in 3 year overall survival,[5] and, since 1998, this regimen has been deemed the standard of care for advanced nasopharyngeal carcinoma.

In recent years, seven randomised phase 3 trials, which compared chemoradiation with radiotherapy alone, have confirmed the value of the addition of chemotherapy on survival for advanced nasopharyngeal carcinoma.[5–12] Three of these trials added concurrent chemotherapy to radiotherapy only;[9–12] whereas the other four trials adopted the regimen of concurrent chemoradiotherapy plus adjuvant chemotherapy, similar to the Intergroup 0099 study.[5–8] However, the latter four trials were unable to tease out the contribution of adjuvant chemotherapy because the control was radiotherapy alone. Furthermore, there were three phase 3 of pure adjuvant chemotherapy trials in nasopharyngeal carcinoma in which adjuvant chemotherapy was used alone, and these trials did not show a positive effect on survival.[13–15] Therefore, it is unclear whether adjuvant chemotherapy provides an additional survival benefit over concurrent chemoradiotherapy in advanced nasopharyngeal carcinoma.[16,17]

With the advent of intensity-modulated radiotherapy (IMRT), local control has been substantially improved and distant metastasis is now the main cause of treatment failure.[18] Further improvements in systemic control by the use of concurrent chemotherapy is unlikely because of drug-related toxic effects;[7] thus, it is important to address the issue of adjuvant chemotherapy. We therefore undertook a multicentre randomised controlled trial to compare concurrent chemoradiotherapy plus adjuvant chemotherapy with concurrent chemoradiotherapy alone, to appraise the contribution of adjuvant chemotherapy in locoregionally advanced nasopharyngeal carcinoma.

Methods

Participants

For the **full protocol** see http://www.sysucc.org.cn/cn/department/gcp/upload/20111028725397349 9.pdf

Between June 1, 2006, and March 5, 2010, we did an open-label phase 3 multicentre randomised controlled trial at seven institutions in China. Eligible patients were aged 18–70 years with non-metastatic, histologically proven non-keratinising stage III or IV nasopharyngeal carcinoma, except T3–4N0 (6th AJCC). All participants had Karnofsky scores of at least 70, and adequate bone marrow, liver, and renal function. Our exclusion criteria included previous chemotherapy, radiotherapy, or definitive surgery of the primary tumour or lymph node. We also excluded patients with previous malignancy, with present other active cancer, who were pregnant or lactating, or who had unstable cardiac disease needing treatment. All participants provided written informed consent. Our protocol was approved by the ethics committee or institutional review board at each centre.

Randomisation and masking

Random assignment was done (via sealed envelopes) by the Clinical Trials Centre, Sun Yat-sen University Cancer Centre, with a computer-generated random number code. Participants were stratified according to treatment centre and randomly assigned in blocks of four based on a one-to-one treatment allocation (the block size was known only by the statistician). Treatment allocation was not masked. Investigators of each centre enrolled participants and assigned them to interventions.

Procedures

We compared concurrent chemoradiotherapy plus three cycles of cisplatin and fluorouracil adjuvant chemotherapy with concurrent chemoradiotherapy alone. The chemotherapy component of the concurrent chemoradiotherapy regimen consisted of 40 mg/m² cisplatin given as a 2 h intravenous infusion every week for a maximum of seven cycles, beginning on the first day of radiotherapy.[8,9] Dose modifications were not permitted during concurrent chemotherapy. All patients were treated with 2·0–2·27 Gy per fraction with five daily fractions per week for 6–7 weeks, administered as megavoltage photons using either two-dimensional radiotherapy (2DRT), IMRT, or three-dimensional conformal radiotherapy (3DCRT), in accordance with the treatment policy adopted by each centre. The cumulative radiation doses were 66 Gy or greater to the primary tumour and 60–66 Gy to the involved neck area. All potential sites of local infiltration and bilateral cervical lymphatics were irradiated to 50 Gy or greater.

Three cycles of adjuvant chemotherapy were given to patients in the concurrent chemoradiotherapy plus adjuvant chemotherapy group on days 29–33, 57–61, and 85–89 after radiotherapy,[8] by intravenous infusion of 80 mg/m² cisplatin on day 1 and 800 mg/m² per day fluorouracil on days 1–5 (120 h infusion). We made slight modifications to conventional schedules for fluorouracil (800 mg/m² per day by 120 h infusion to reach the total dose of 4000 mg/m² instead of 1000 mg/m² per day by 96 h infusion) because, in a previous study,[8] 61% of patients completed three cycles of adjuvant chemotherapy with 800 mg/m² per day fluorouracil, compared with 55% in the Intergroup 0099 study with 1000 mg/m² per day fluorouracil.[5] Furthermore, the chosen regimen has proven to be well tolerated and has resulted in superior complete response rates, as well as survival, in advanced head and neck cancer.[19]

Dose modifications during adjuvant chemotherapy were based on the preceding cycle nadir blood counts and interim toxic effects. Cisplatin was decreased to 60 mg/m² if the absolute neutrophil count was 1000–1500 cells per μL, platelet count was 50 000–75 000 per μL, or creatinine clearance was 40–60 mL/min. Cisplatin was decreased to 40 mg/m² if the absolute neutrophil count was less than 1000 cells per μL or the platelet count less than 50 000 per μL. Chemotherapy was stopped

completely if the creatinine clearance was less than 40 mL/min or if grade 3 or higher neurotoxicity or ototoxicity developed. Fluorouracil was decreased by 200 mg/m² in grade 2, and 400 mg/m² in cases of grade 3 mucositis or diarrhoea, and chemotherapy was stopped permanently if grade 4 toxic effects developed.

Participants were assessed every 3 months during the first 3 years, and every 6 months thereafter until death. All local recurrences were diagnosed with fibreoptic endoscopy and biopsy, MRI scan, or both, of the nasopharynx and the skull base showing progressive bone erosion and soft tissue swelling. Regional recurrences were diagnosed by clinical examination of the neck and, in doubtful cases, by fine needle aspiration or an MRI scan of the neck. Distant metastases were diagnosed by clinical symptoms, physical examinations, and imaging methods that included chest radiography, bone scan, MRI, CT, and abdominal sonography. Whenever possible, salvage treatments including re-irradiation, chemotherapy, and surgery, were given to participants after documented relapse or in persistent disease, in accordance with the standard practice of each centre.

Our primary endpoint was failure-free survival, and our secondary endpoints were overall survival, distant failure-free survival, locoregional failure-free survival, initial response rates after treatment, and toxic effects. We calculated failure-free survival from the date of randomisation to the date of treatment failure or death from any cause, whichever was first. We calculated overall survival from randomisation to death. For locoregional and distant failure-free survival analyses, we recorded the latencies (ie, time from randomisation) to the first locoregional or remote failure respectively.

We characterised tumour responses in accordance with the Response Evaluation Criteria in Solid Tumors[20] with the first assessment 16 weeks after radiotherapy. We assessed toxic effects weekly during concurrent chemoradiotherapy, during and on completion of adjuvant chemotherapy, and at subsequent predefined intervals. We graded chemotherapy-related toxic effects in accordance with Common Terminology Criteria for Adverse Events (version 3.0). We graded radiotherapy-related toxic effects in accordance with both the Acute and the Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group.[21]

Statistical analysis

Our study had an 80% power to detect a treatment failure hazard ratio (HR) of 0·56 (two-sided log-rank test p=0·05), assuming a 2 year failure-free survival rate of 85% in the concurrent chemoradiotherapy plus adjuvant chemotherapy group and 75% in the concurrent chemoradiotherapy only group.[8,9] We anticipated that 96 events were needed from 480 patients (240 per treatment group), therefore we needed to recruit a maximum of 253 patients per group (total 506), assuming 5% early dropout or loss to follow-up.[22]

Time-to-event data were described with the Kaplan-Meier curves, time-to-event intervals compared with the log-rank test (primary analysis). We treated missing time-to-event data due to loss of the patient to follow-up as censored data. We calculated HRs with the Cox proportional hazards model.[23] We did multivariable analyses with the Cox proportional hazards model to test the independent significance of different factors.[23] Covariates included host factors (ie, sex, age, performance status), tumour factors (ie, T and N classification), radiotherapy (ie, radiotherapy technique), and chemotherapeutic intervention (ie, treatment group). We compared initial response rates, toxicity rates, and other categorical variables with the χ^2 test (or Fisher's exact test, if indicated). All tests were two-sided, we deemed p values of less than 0·05 to be significant. We did a formal interim analysis on Dec 1, 2008. The significance threshold used for the interim analysis was defined by the O'Brien–Fleming type boundary (ie, p<0·003) for stopping the trial early

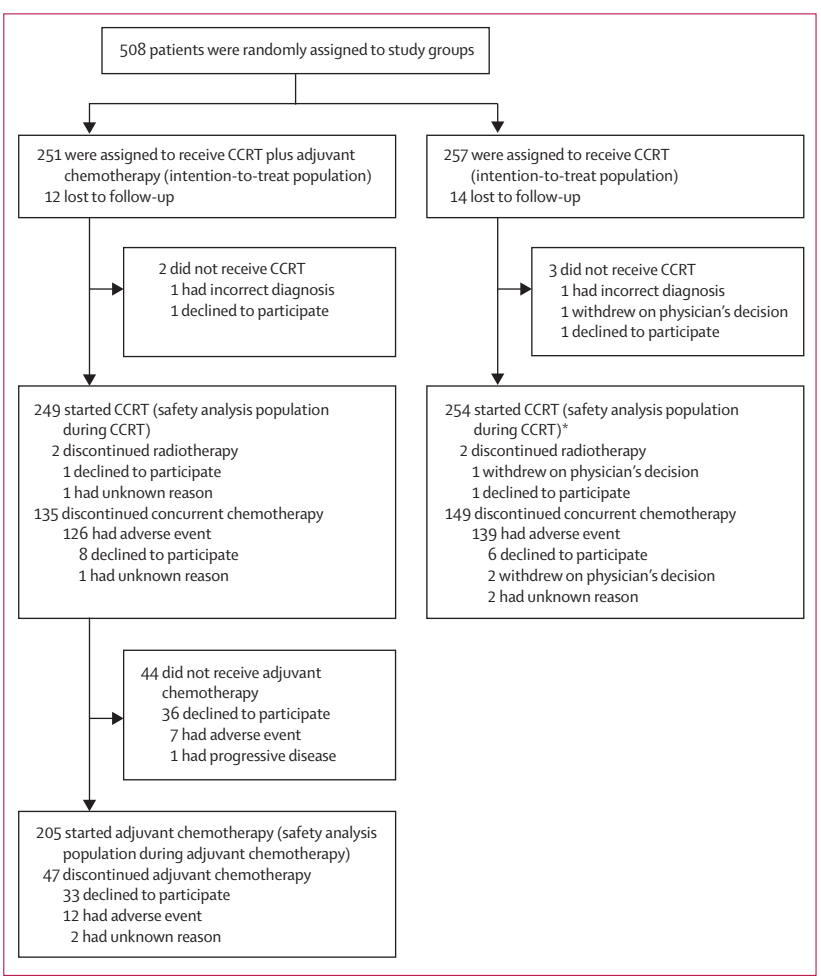

Figure 1: **Trial profile**
CCRT=concurrent chemoradiotherapy. *Three patients subsequently given adjuvant chemotherapy at their request.

and 0·049 for the final analysis, to preserve an overall 0·05 type I error rate. The cutoff date for the analysis presented here was July 4, 2011, after the prespecified number of events had occurred. We did all efficacy analyses in our intention-to-treat population, and only patients who received their randomly assigned treatments were included in adverse events analyses. All analyses were done with Stata (version 10). This trial is registered with ClinicalTrials.gov, number NCT00677118.

See Online for appendix

Role of the funding source

Our study is mainly funded by the Sun Yat-sen University Clinical Research 5010 Programme (No 2007037), and the sponsor of this study is Sun Yat-sen University, which is involved in trial management and audit. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Regular follow-up until death or the latest scheduled assessment was done for 482 (95%) of the 508 patients randomly assigned to study groups. The median follow-up was 37·8 months (range 1·3–61·0); 34 participants (7%) were followed up for less than 2 years. The two treatment groups were well balanced in terms of baseline demographic and clinical characteristics, and radiotherapy technique (table 1).

Four participants in the concurrent chemoradiotherapy plus adjuvant chemotherapy group and five in the concurrent chemoradiotherapy only group did not complete the scheduled total radiation dose. Treatment groups were similar with respect to the dose and duration of radiotherapy (appendix). 114 (45%) of 251 patients in the concurrent chemoradiotherapy plus adjuvant chemotherapy group and 105 (41%) of 257 of the concurrent chemoradiotherapy group completed all protocol-defined concurrent chemotherapy, with a median of six cycles (IQR 5–7) for both groups. The median total dose of cisplatin was 240 mg/m² (IQR 200–280) in both groups (90% of total scheduled dose in both groups; appendix). The reduction in chemotherapy cycles were mostly

	CCRT plus adjuvant chemotherapy group (N=251)	CCRT only group (N=257)
Sex (male)	192 (77%)	188 (73%)
Median age (years)	44 (19–68)	46 (18–68)
Karnofsky scale		
100	17 (7%)	21 (8%)
90	186 (74%)	168 (65%)
70–80	48 (19%)	68 (26%)
T classification[3]		
T1	15 (6%)	11 (4%)
T2	57 (23%)	57 (22%)
T3	111 (44%)	124 (48%)
T4	68 (27%)	65 (25%)
N classification[3]		
N1	82 (33%)	74 (29%)
N2	141 (56%)	156 (61%)
N3	28 (11%)	27 (11%)
Staging[3]		
III	162 (65%)	172 (67%)
IVA	63 (25%)	59 (23%)
IVB	26 (10%)	26 (10%)
Radiotherapy technique		
2DRT	131 (52%)	137 (53%)
IMRT	108 (43%)	107 (42%)
3DCRT	12 (5%)	13 (5%)

Data are n (%) or median (range). CCRT=concurrent chemoradiotherapy. 2DRT=two-dimensional radiotherapy. IMRT=intensity-modulated radiotherapy. 3DCRT=three-dimensional conformal radiotherapy.

Table 1: **Baseline characteristics**

	CCRT plus adjuvant chemotherapy group (N=251)	CCRT only group (N=257)	Hazard ratio* (95% CI)	p value
Failure-free survival				
Failures	41 (16%)	57 (22%)	..	
Rate at 1 year	95% (92–97)	89% (85–93)	0·74 (0·49–1·10)	0·13†
Rate at 2 years	86% (81–90)	84% (78–88)	..	
Overall survival				
Deaths	26 (10%)	34 (13%)	..	
Rate at 1 year	98% (95–99)	97% (93–98)	0·77 (0·46–1·29)	0·32†
Rate at 2 years	94% (90–96)	92% (88–95)	..	
Distant failure-free survival				
Distant failures	32 (13%)	45 (18%)	..	
Rate at 1 year	96% (92–97)	92% (88–95)	0·71 (0·46–1·10)	0·12†
Rate at 2 years	88% (83–92)	86% (81–89)	..	
Locoregional failure-free survival				
Locoregional failure	8 (3%)	15 (6%)	..	
Rate at 1 year	100% (97–100)	96% (93–98)	0·50 (0·21–1·16)	0·10†
Rate at 2 years	98% (95–99)	95% (91–97)	..	
Response to treatment				
Overall	249 (99%)	254 (99%)	..	
Complete	248 (99%)	250 (97%)	..	0·22‡
Partial	1 (0·4%)	4 (2%)	..	

Data are n (%) or rate (95% CI). CCRT=concurrent chemoradiotherapy. *Hazard ratios were calculated with the unadjusted Cox proportional hazards model. †p values were calculated with the unadjusted log-rank test. ‡Complete response rates were compared by use of an unadjusted χ^2 test.

Table 2: **Survival and response to treatment**

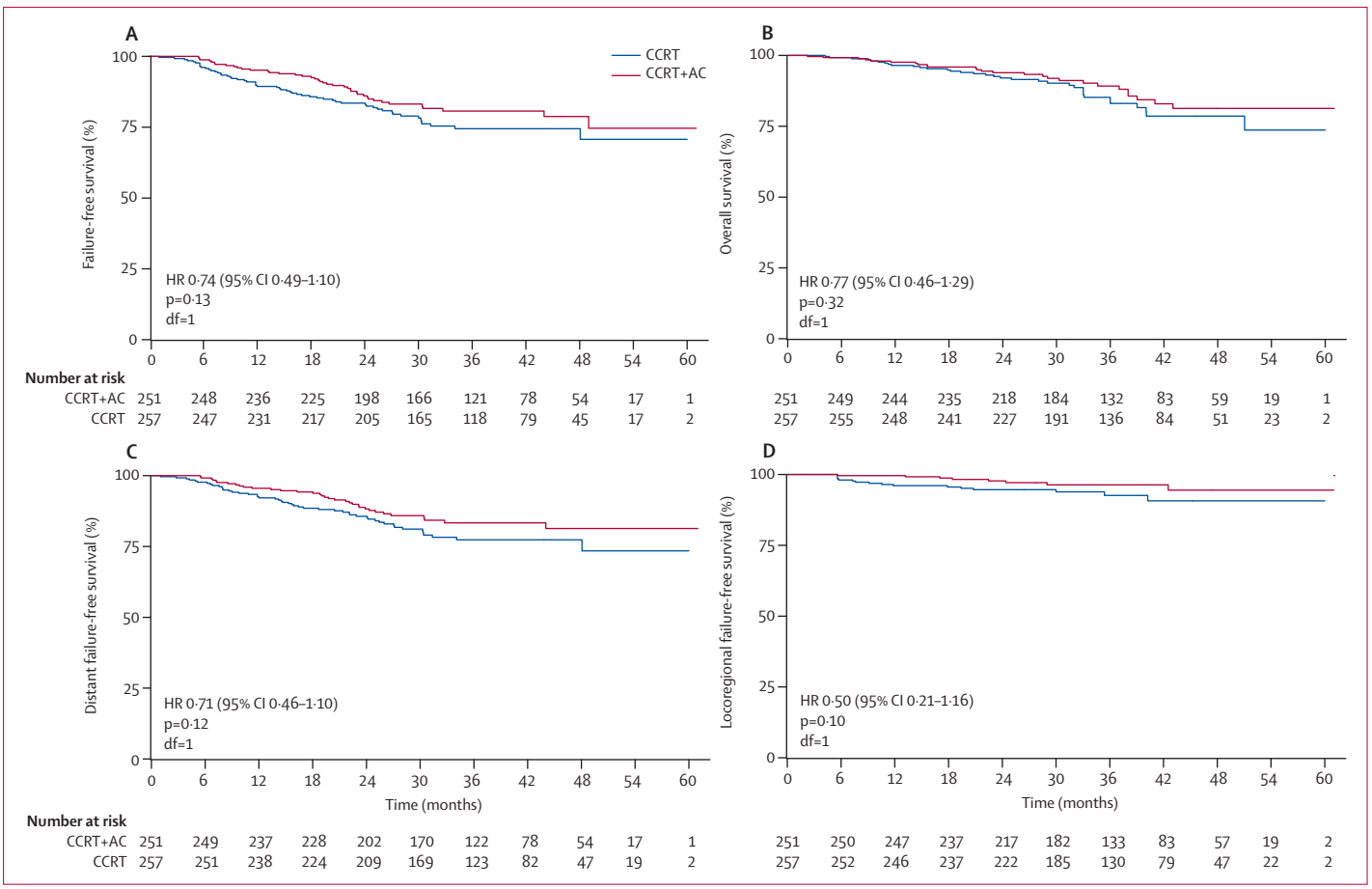

Figure 2: **Kaplan-Meier survival curves for the CCRT plus adjuvant chemotherapy group and the CCRT only group**
Failure-free survival (A), overall survival (B), distant failure-free survival (C), and locoregional failure-free survival (D). Hazard ratios (HRs) were calculated with the unadjusted Cox proportional hazards model; p values were calculated with the unadjusted log-rank test. CCRT=concurrent chemoradiotherapy. AC=adjuvant chemotherapy.

because of leucopenia, accounting for 98 (74%) of 133 reduced doses in the concurrent chemoradiotherapy plus adjuvant chemotherapy group and 112 (76%) of 148 in the concurrent chemoradiotherapy only group.

205 (82%) of 251 patients in the concurrent chemoradiotherapy plus adjuvant chemotherapy group commenced adjuvant chemotherapy (figure 1). All three cycles of adjuvant chemotherapy were completed by 158 (63%) of 251 participants in the concurrent chemotherapy plus adjuvant chemotherapy group, with a median three cycles (IQR 1–3). The median total cisplatin doses were 220 mg/m² (IQR 80–240; 92% of total scheduled doses) and fluorouracil doses were 8000 mg/m² (4000–12 000; 67% of total scheduled doses). Refusal by patients was the primary reason for uncompleted adjuvant chemotherapy (figure 1), and all dose reductions were because of haematological toxic effects or mucositis. There were treatment delays in 141 (69%) of 205 patients receiving adjuvant chemotherapy, as the result of adverse events and other reasons (appendix).

16 weeks after completion of radiotherapy the 248 patients (99%) in the concurrent chemoradiotherapy plus adjuvant chemotherapy group and 250 (97%) in the concurrent chemoradiotherapy only group had had a complete response, considering both the primary site and neck together (p=0·22; table 2). 98 patients experienced treatment failure (table 2). Estimated 2 year failure-free survival, overall survival, distant failure-free survival, or locoregional failure-free survival did not differ significantly between the study groups (figure 2, table 2). On multivariable analysis, treatment group was not a significant predictive factor for failure-free survival, overall survival, distant failure-free survival, or locoregional failure-free survival (table 3). We did exploratory subset analyses by radiotherapy techniques (IMRT *vs* 2DRT/3DCRT) and the results showed that the effect of adjuvant chemotherapy on failure-free survival, overall survival, distant failure-free survival, and locoregional failure-free survival was insignificant in both the IMRT and 2DRT/3DCRT subgroups (appendix).

During CCRT, 156 (63%) of 249 patients in the concurrent chemoradiotherapy plus adjuvant chemotherapy group and 156 (61%) of 254 in the concurrent chemoradiotherapy only group experienced grade 3–4 toxic effects (p=0·78);

	Hazard ratio (95% CI)	p value*
Failure-free survival		
Sex, women *vs* men	0·64 (0·37–1·11)	0·11
Age, ≥45 years *vs* <45 years	1·11 (0·74–1·66)	0·62
Karnofsky scale, 100 *vs* 90 *vs* 70–80	1·02 (0·98–1·06)	0·38
T classification, T3–4 *vs* T1–2	1·33 (0·82–2·17)	0·25
N classification, N2 *vs* N1	1·75 (1·03–2·98)	0·04
N classification, N3 *vs* N1	2·15 (1·03–4·47)	0·04
Radiotherapy technique, IMRT *vs* 2DRT/3DCRT	1·26 (0·83–1·91)	0·28
Treatment group, CCRT plus adjuvant chemotherapy *vs* CCRT only	0·74 (0·49–1·10)	0·14
Overall survival		
Sex, women *vs* men	1·01 (0·53–1·91)	0·98
Age, ≥45 years *vs* <45 years	1·50 (0·88–2·54)	0·14
Karnofsky scale, 100 *vs* 90 *vs* 70–80	0·98 (0·93–1·03)	0·38
T classification, T3–4 *vs* T1–2	1·56 (0·82–2·97)	0·17
N classification, N2 *vs* N1	1·84 (0·93–3·63)	0·08
N classification, N3 *vs* N1	2·65 (1·10–6·39)	0·03
Radiotherapy technique, IMRT *vs* 2DRT/3DCRT	1·05 (0·60–1·83)	0·87
Treatment group, CCRT plus adjuvant chemotherapy *vs* CCRT only	0·79 (0·47–1·32)	0·37
Distant failure-free survival		
Sex, women *vs* men	0·78 (0·45–1·37)	0·39
Age, ≥45 years *vs* <45 years	1·19 (0·77–1·84)	0·43
Karnofsky scale, 100 *vs* 90 *vs* 70–80	1·01 (0·97–1·05)	0·69
T classification, T3–4 *vs* T1–2	1·36 (0·81–2·30)	0·25
N classification, N2 *vs* N1	1·90 (1·06–3·41)	0·03
N classification, N3 *vs* N1	2·44 (1·12–5·35)	0·03
Radiotherapy technique, IMRT *vs* 2DRT/3DCRT	1·10 (0·70–1·72)	0·68
Treatment group, CCRT plus adjuvant chemotherapy *vs* CCRT only	0·72 (0·46–1·11)	0·14
Locoregional failure-free survival		
Sex, women *vs* men	0·26 (0·06–1·14)	0·07
Age, ≥45 years *vs* <45 years	0·63 (0·28–1·46)	0·28
Karnofsky scale, 100 *vs* 90 *vs* 70–80	1·07 (0·99–1·17)	0·10
T classification, T3–4 *vs* T1–2	1·39 (0·47–4·09)	0·55
N classification, N2 *vs* N1	0·86 (0·32–2·32)	0·77
N classification, N3 *vs* N1	1·88 (0·46–7·65)	0·38
Radiotherapy technique, IMRT *vs* 2DRT/3DCRT	1·55 (0·65–3·72)	0·32
Treatment group, CCRT plus adjuvant chemotherapy *vs* CCRT only	0·44 (0·19–1·05)	0·06

Two patients (0·4%) declined to participate in the study after randomisation and they were excluded from the multivariable analyses. IMRT=intensity-modulated radiotherapy. 2DRT=two-dimensional radiotherapy. 3DCRT=three-dimensional conformal radiotherapy. CCRT=concurrent chemoradiotherapy. *p values were calculated with an adjusted Cox proportional-hazards model.

Table 3: **Summary of prognostic factors multivariable analyses**

there were no treatment-related deaths. Adverse events were similar in both groups (table 4). Of the 503 adverse events, the most commonly recorded grade 3–4 non-haematological adverse events were stomatitis (158; 31%),

	CCRT plus adjuvant chemotherapy group	CCRT only group	p value*
Grade 3–4 adverse events during CCRT			
Number treated with CCRT	249	254	..
Haematological			
Anaemia	3 (1%)	6 (2%)	0·33
Thrombocytopenia	14 (6%)	16 (6%)	0·75
Neutropenia	25 (10%)	29 (11%)	0·62
Leucopenia	59 (24%)	65 (26%)	0·62
Non-haematological			
Dermatitis	25 (10%)	29 (11%)	0·62
Stomatitis (mucositis)	76 (31%)	82 (32%)	0·67
Oesophagitis, dysphagia, or odynophagia	8 (3%)	13 (5%)	0·29
Nausea	32 (13%)	37 (15%)	0·75
Vomiting	29 (12%)	33 (13%)	0·63
Dry mouth	13 (5%)	21 (8%)	0·17
Ototoxicity	2 (1%)	1 (0·4%)	0·55
Nephrotoxicity	0	0	..
Neurotoxicity	1 (0·4%)	1 (0·4%)	0·99
Grade 3–4 adverse events during adjuvant chemotherapy			
Number treated with adjuvant chemotherapy	205	..	..
Haematological			
Anaemia	3 (2%)	..	..
Thrombocytopenia	8 (4%)	..	..
Neutropenia	21 (10%)	..	..
Leucopenia	29 (14%)	..	..
Non-haematological			
Stomatitis (mucositis)	43 (21%)	..	..
Oesophagitis, dysphagia, or odynophagia	9 (4%)	..	..
Nausea	23 (11%)	..	..
Vomiting	20 (10%)	..	..
Diarrhoea	6 (3%)	..	..
Ototoxicity	6 (3%)	..	..
Nephrotoxicity	1 (0·5%)	..	..
Neurotoxicity	2 (1%)	..	..

Data are n or n (%). CCRT=concurrent chemoradiotherapy. *p values were calculated with the χ^2 test.

Table 4: **Adverse events**

nausea (69; 14%), and vomiting (62; 12%). The most common grade 3–4 haematological adverse events were leucopenia (124; 25%), neutropenia (54; 11%), thrombocytopenia (30; 6%), and anaemia (nine; 2%).

During adjuvant chemotherapy, 87 (42%) of 205 patients experienced grade 3–4 toxic effects; there were no treatment-related deaths. The most commonly recorded grade 3–4 non-haematological adverse events were stomatitis, nausea, and vomiting (table 4). Grade 3–4 leucopenia or neutropenia were recorded in 35 (17%) of 205 patients, with the next most common events being thrombocytopenia and anaemia (table 4).

Discussion

In our trial, adjuvant cisplatin and fluorouracil chemotherapy did not improve outcome, with no significant effect on the risk of treatment failure, or estimated 2 year failure-free survival, overall survival, distant failure-free survival, or locoregional failure-free survival (panel).

Adjuvant cisplatin and fluorouracil chemotherapy is the recommended regimen for advanced nasopharyngeal carcinoma.[5] A recent study on recurrent or metastatic head and neck cancer[24] showed that, although the response rate to the combination of cisplatin and fluorouracil was superior to that achieved with single drugs, survival did not improve. Therefore, it is possible that adjuvant cisplatin and fluorouracil is not an effective combination for the eradication of micrometastases in head and neck cancers and nasopharyngeal carcinoma. Intriguingly, newer drugs, such as taxanes and gemcitabine, have shown promising results in the settings of neoadjuvant and palliative chemotherapy in nasopharyngeal carcinoma.[25,26] A meta-analysis by Blanchard and colleagues[27] showed a significant improvement of overall survival and progression-free survival with the addition of docetaxel to cisplatin and fluorouracil induction chemotherapy in patients with squamous-cell carcinoma of the head and neck. Therefore, new combinations of more tolerable drugs that might improve the efficacy of chemotherapy as an adjunct in advanced nasopharyngeal chemotherapy should be investigated.

Compliance to three cycles of adjuvant chemotherapy in our trial (158 [63%] of 251) was similar to other studies (52–61%);[5–8] however, 46 (18%) of 251 patients did not receive any adjuvant chemotherapy, 100 (49%) of 205 receiving adjuvant chemotherapy had dose reductions, and 141 (69%) of 205 had delays in treatment. Further improvement in survival benefit was inevitably hampered by the suboptimum dose intensity. The incidence of grade 3–4 oropharyngeal mucositis and nausea during concurrent chemoradiotherapy were similar to other trials,[8,9] which led to hypoalimentation and were significant problems. It was obvious that acute toxic effects during concurrent chemoradiotherapy decreased patient tolerance to adjuvant chemotherapy. Therefore, it is possible that giving combinations of newer drugs before, rather than after, concurrent chemoradiotherapy to improve compliance might result in further improvements in systemic control. In a phase 2 study in stage III–IVB nasopharyngeal carcinoma, Hui and colleagues[25] compared the benefit of sequential neoadjuvant cisplatin with docetaxel in addition to concurrent cisplatin radiotherapy. All patients in the neoadjuvant group received the allocated treatment, and had a significantly reduced risk of death (HR 0·24, 95% CI 0·08–0·73; p=0·01). This encouraging result is currently being confirmed in at least four randomised trials assessing new combinations of induction chemotherapy with subsequent concurrent chemoradiotherapy (NCT00828386, NCT00201396, NCT00997906, and NCT01245959).

Another possible reason for the lack of benefit is that cisplatin and fluorouracil perhaps benefits only those with a lower distant tumour burden. From the seven trials that compared chemoradiation with radiotherapy alone,[5–12] two trials that included only patients with N2–N3 disease did not show any improvement in distant metastases;[7,9,10] whereas the trials that took all patients in stage III–IVB showed the benefit on distant control.[5,6,8,11,12] Moreover, in two subset re-analyses of previous phase 3 trials on nasopharyngeal

Panel: Research in context

Systematic review

We searched PubMed with the terms "nasopharyngeal carcinoma", "concurrent chemoradiotherapy", "adjuvant chemotherapy", and "randomised clinical trial", and WHO's International Clinical Trial Registry Platform and www.clinicaltrials.gov with the term "nasopharyngeal carcinoma", to establish that no other trials had compared concurrent chemoradiotherapy plus adjuvant chemotherapy with concurrent chemoradiotherapy alone. Seven randomised phase 3 trials that compared chemoradiation with radiotherapy alone have confirmed the value of the addition of chemotherapy for advanced nasopharyngeal carcinoma.[5–12] Three of these trials added concurrent chemotherapy to radiotherapy only;[9–12] whereas the other four used concurrent chemotherapy plus adjuvant chemotherapy.[5–8] However, the latter four trials were unable to tease out the contribution of adjuvant chemotherapy, because the control group was radiotherapy alone. Furthermore, the overall survival results from the concurrent chemoradiotherapy alone[10,11] and concurrent chemoradiotherapy plus adjuvant chemotherapy trials[5,6] seemed much the same. Further, three phase 3 trials for nasopharyngeal carcinoma in which adjuvant chemotherapy was used alone indicated that adjuvant chemotherapy did not have a positive effect on survival.[13–15] Moreover, two meta-analyses involving over ten randomised trials of more than 2500 patients with advanced nasopharyngeal carcinoma reported an absolute benefit on overall survival of 4–6% at 5 years with the use of chemotherapy.[16,17] However, the survival benefit of the addition of chemotherapy was essentially noted when chemotherapy was given concomitantly with radiotherapy. At the time this trial was designed, it was thus unclear whether adjuvant chemotherapy provides an additional survival benefit over concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma.

Interpretation

The results of our study offer direct evidence that three cycles of adjuvant cisplatin and fluorouracil chemotherapy add little survival benefit to concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma.

carcinoma,[28,29] concurrent chemotherapy or induction chemotherapy only resulted in significant improvement for groups with earlier stage disease (ie, lower tumour burden). Our trial included only patients with higher distant tumour burden (excluding T3–4N0 patients), which might have overwhelmed any potential beneficial effects of adjuvant cisplatin and fluorouracil chemotherapy on distant control.

A greater improvement of treatment results with IMRT than with 2DCRT was shown primarily by achieving a higher local tumour control rate in patients with nasopharyngeal carcinoma.[18] In our trial, 215 (42%) of 508 patients were treated with IMRT, which we postulate improved 2 year locoregional failure-free survival of both the concurrent chemoradiotherapy plus adjuvant chemotherapy and concurrent chemoradiotherapy only groups. The favourable results of locoregional failure-free survival in both groups might have narrowed any potential gain in local control offered by adjuvant chemotherapy. We did not treat all our participants with IMRT, so our findings cannot be directly extrapolated to patients treated with IMRT; however, our findings suggest that increasing the availability of IMRT might further reduce the potential therapeutic gain of adjuvant chemotherapy. Estimation of sample size for future trials should be based on higher baseline results by IMRT and more realistic magnitude of benefit to avoid being underpowered.

For our study we focused on stage III–IVB patients and excluded T3–4N0 patients. Our main reason was that patients with T3–4N0 disease had a relatively lower risk of distant metastasis, compared with T3–4N1/N2–3 patients.[4] We wanted to include only the patients who were most likely to benefit from adjuvant chemotherapy, because a more homogeneous cohort of patients would have enhanced the power of our trial with the same sample size. However, the present nasopharyngeal carcinoma AJCC staging system[3] is restricted in its diagnostic reach to the anatomical extent of the tumours, and does not accurately categorise patients at high risk of disease recurrence. An increasing number of biological, genetic, molecular, and other non-anatomical factors might affect the prognosis of patients. For example, patients with nasopharyngeal carcinoma and persistently detectable plasma Epstein-Barr virus (EBV) DNA after chemoradiation were more likely to experience disease recurrence than those without.[30] The NPC-0502 study (NCT00370890) is designed to assess the benefit of adjuvant chemotherapy in patients at high risk of disease recurrence, identified with detectable plasma EBV DNA 6 weeks after chemoradiation. Hence, it is inadequate to apply only the TNM staging system for participant selection in a clinical trial, and use of biomarkers will probably enhance the power of future clinical trials to obtain positive results.

It should be noted that the different radiotherapy techniques used in this trial might have confounded the findings. However, the two treatment groups were well balanced according to radiotherapy technique (table 1), and subgroup analyses by radiotherapy technique (IMRT *vs* 2DRT/3DCRT) showed no differences in the effect of adjuvant chemotherapy (appendix). Therefore, different radiotherapy techniques had a restricted effect in our results. Although we reported the 2 year survival results that corresponded to the required number of events defined by our protocol (n=96), we still need to follow up the patients closely and report 5 year follow-up results when more events become available to fully assess the survival and late toxic effects.

In conclusion, addition of three cycles of adjuvant cisplatin and fluorouracil chemotherapy to concurrent chemoradiotherapy did not significantly improve survival compared with concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. The potential therapeutic gain of adjuvant chemotherapy in patients treated with IMRT should be explored in the future, but a reasonable recommendation would be that such a regimen should not be used outside well-designed clinical trials.

Contributors

JM was the principal investigator and participated in the trial design, study management, data and toxicity review, review of the report, and final approval. LC, C-SH, X-ZC, G-QH, Z-BC, YaS, and W-XL contributed to the trial design, writing of the protocol, recruitment and treatment of the patients, data and trial management, data analysis and interpretation, writing, and final approval of the report. Y-YC, F-YX, S-BL, and YC were involved in trial design, recruitment and treatment of the patients, data and trial management, and review of the report. T-TX, BL, G-XL, S-YW, B-MZ participated in recruitment and treatment of the patients, data and trial management, and report preparation. YG and Y-MC were responsible for statistical analysis and interpretation, and toxicity and data review. YiS, Y-PM, and L-LT contributed to patient accrual and writing of the report or reviewing the completed report. M-ZL was involved in trial management and toxicity review. All authors have seen and approved the final draft.

Conflicts of interest

We declare that we have no conflicts of interest.

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