Concurrent chemoradiotherapy followed by adjuvant cisplatin–gemcitabine versus cisplatin–fluorouracil chemotherapy for N2–3 nasopharyngeal carcinoma: a multicentre, open-label, randomised, controlled, phase 3 trial

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Summary

Background Patients with N2–3 nasopharyngeal carcinoma have a high risk of treatment being unsuccessful despite the current practice of using a concurrent adjuvant cisplatin–fluorouracil regimen. We aimed to compare the efficacy and safety of concurrent adjuvant cisplatin–gemcitabine with cisplatin–fluorouracil in N2–3 nasopharyngeal carcinoma.

Methods We conducted an open-label, randomised, controlled, phase 3 trial at four cancer centres in China. Eligible patients were aged 18–65 years with untreated, non-keratinising, stage T1–4 N2–3 M0 nasopharyngeal carcinoma, an Eastern Cooperative Oncology Group performance status score of 0–1, and adequate bone marrow, liver, and renal function. Eligible patients were randomly assigned (1:1) to receive concurrent cisplatin (100 mg/m² intravenously) on days 1, 22, and 43 of intensity-modulated radiotherapy followed by either gemcitabine (1 g/m² intravenously on days 1 and 8) and cisplatin (80 mg/m² intravenously for 4 h on day 1) once every 3 weeks or fluorouracil (4 g/m² in continuous intravenous infusion for 96 h) and cisplatin (80 mg/m² intravenously for 4 h on day 1) once every 4 weeks, for three cycles. Randomisation was done using a computer-generated random number code with a block size of six, stratified by treatment centre and nodal category. The primary endpoint was 3-year progression-free survival in the intention-to-treat population (ie, all patients randomly assigned to treatment). Safety was assessed in all participants who received at least one dose of chemoradiotherapy. This study was registered at ClinicalTrials.gov, NCT03321539, and patients are currently under follow-up.

Findings From Oct 30, 2017, to July 9, 2020, 240 patients (median age 44 years [IQR 36–52]; 175 [73%] male and 65 [27%] female) were randomly assigned to the cisplatin–fluorouracil group (n=120) or cisplatin–gemcitabine group (n=120). As of data cutoff (Dec 25, 2022), median follow-up was 40 months (IQR 32–48). 3-year progression-free survival was 83·9% (95% CI 75·9–89·4; 19 disease progressions and 11 deaths) in the cisplatin–gemcitabine group and 71·5% (62·5–78·7; 34 disease progressions and seven deaths) in the cisplatin–fluorouracil group (stratified hazard ratio 0·54 [95% CI 0·32–0·93]; log rank p=0·023). The most common grade 3 or worse adverse events that occurred during treatment were leukopenia (61 [52%] of 117 in the cisplatin–gemcitabine group *vs* 34 [29%] of 116 in the cisplatin–fluorouracil group; p=0·00039), neutropenia (37 [32%] *vs* 19 [16%]; p=0·010), and mucositis (27 [23%] *vs* 32 [28%]; p=0·43). The most common grade 3 or worse late adverse event (occurring from 3 months after completion of radiotherapy) was auditory or hearing loss (six [5%] *vs* ten [9%]). One (1%) patient in the cisplatin–gemcitabine group died due to treatment-related complications (septic shock caused by neutropenic infection). No patients in the cisplatin–fluorouracil group had treatment-related deaths.

Interpretation Our findings suggest that concurrent adjuvant cisplatin–gemcitabine could be used as an adjuvant therapy in the treatment of patients with N2–3 nasopharyngeal carcinoma, although long-term follow-up is required to confirm the optimal therapeutic ratio.

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Introduction

Nasopharyngeal carcinoma, which is strongly associated with Epstein-Barr virus infection, is endemic in southeast Asia and southern China. Radiotherapy is the mainstay of treatment for nasopharyngeal carcinoma. Early-stage nasopharyngeal carcinoma is usually treated with radiotherapy alone; however, locoregionally advanced nasopharyngeal carcinoma requires more intensive treatment.[1] The concurrent adjuvant sequence was established when the US Intergroup 0099 trial[2] first reported a significant therapeutic benefit with cisplatin-based concurrent chemoradiotherapy followed by adjuvant cisplatin–fluorouracil chemotherapy versus radiotherapy alone. The efficacy of concurrent adjuvant cisplatin–fluorouracil chemotherapy has been indicated by multiple trials,[3–5] and so concurrent chemoradiotherapy plus adjuvant chemotherapy has become the standard of care for locoregionally advanced nasopharyngeal carcinoma.[6,7]

However, superiority of adjuvant chemotherapy compared with concurrent chemoradiotherapy alone was not found in two phase 3 trials.[8,9] The reasons for the negative results in previous trials might be related to the selection of patients and chemotherapy regimens. For instance, in the study by Chen and colleagues[8] 33% of patients in the concurrent chemoradiotherapy plus cisplatin–fluorouracil group presented with N1 disease, which might have adversely affected the study findings. In 2016, cisplatin–gemcitabine demonstrated superior activity compared with cisplatin–fluorouracil in treating recurrent and metastatic nasopharyngeal carcinoma.[10] However, in a study by Chan and colleagues,[9] the addition of adjuvant chemotherapy to a cisplatin–gemcitabine regimen for patients with detectable post-concurrent chemoradiotherapy plasma Epstein-Barr virus DNA, a potential marker of residual disease in nasopharyngeal carcinoma, did not to show significant survival benefit compared with observation. In Chan and colleagues' trial,[9] measuring plasma Epstein-Barr virus DNA at 6–8 weeks after concurrent chemoradiotherapy and then implementing a long interval of 12 weeks between completion of radiotherapy and start of adjuvant chemotherapy might be too late for adjuvant chemotherapy to be effective in eradicating subclinical micrometastases. Moreover, this regimen has not yet been compared with the standard cisplatin–fluorouracil regimen. The ongoing NRG-HN001 trial (NCT02135042) is investigating whether adjuvant gemcitabine and paclitaxel could substitute for cisplatin–fluorouracil in patients with nasopharyngeal carcinoma and detectable post-radiotherapy plasma Epstein-Barr virus DNA.

Patients with N2–3 disease are more likely to develop distant metastases and are expected to have increased

Research in context

Evidence before this study

The benefit of adjuvant chemotherapy for nasopharyngeal carcinoma remains controversial. Patients with regionally advanced nasopharyngeal carcinoma have a high risk of treatment failure despite the current practice of using a concurrent adjuvant cisplatin–fluorouracil regimen. Therefore, the value and optimal adjuvant chemotherapy regimen require further investigation. We searched PubMed for relevant articles and clinical trials published from database inception up to Dec 25, 2022, using the search terms "(nasopharyngeal carcinoma) OR (cancer) OR (neoplasm)", "chemoradiotherapy", AND "adjuvant chemotherapy", with no language restrictions. Only one phase 3 trial, published in 2018, comparing adjuvant cisplatin-gemcitabine versus observation did not show a significant survival benefit between the two treatment groups. However, the trial was performed over a long period of 12 weeks, from the end of radiotherapy to adjuvant chemotherapy, which might have been too late for adjuvant chemotherapy to eradicate subclinical micrometastases in patients with detectable post-treatment plasma Epstein-Barr virus DNA. In addition, two phase 3 trials assessing the efficacy of adjuvant capecitabine chemotherapy compared with observation alone showed significant survival improvements for adjuvant chemotherapy. However, this regimen has not yet been compared with the standard adjuvant cisplatin–fluorouracil regimen. The identification of optimal adjuvant regimens that effectively reduce disease progression remains a key clinical issue in the treatment of nasopharyngeal carcinoma.

Added value of this study

To the best of our knowledge, this is the first randomised, controlled, phase 3 trial to assess the efficacy and safety of concurrent chemoradiotherapy followed by adjuvant cisplatin–gemcitabine in patients with high-risk regionally advanced nasopharyngeal carcinoma compared with concurrent chemoradiotherapy followed by adjuvant cisplatin–fluorouracil. We found that the adjuvant cisplatin–gemcitabine regimen significantly improved progression-free survival compared with the traditional cisplatin–fluorouracil regimen in a selected cohort of patients with stage N2–3 nasopharyngeal carcinoma.

Implications of all the available evidence

This study suggests that the addition of adjuvant cisplatin–gemcitabine chemotherapy after concurrent chemoradiotherapy could improve survival in patients with stage N2–3 nasopharyngeal carcinoma, with an acceptable safety profile. These results support the potential role of adjuvant therapy with cisplatin–gemcitabine chemotherapy for the treatment of nasopharyngeal carcinoma.

benefit from adjuvant chemotherapy. To our knowledge, the NPC-9901 trial[3] is the only trial that has raised caution for the fact that the concurrent adjuvant cisplatin–fluorouracil regimen might not be adequate for distant control of N2–3 disease. Therefore, the optimal adjuvant chemotherapy regimen requires further investigation.

We aimed to explore the efficacy of a potentially more effective adjuvant chemotherapy regimen, cisplatin–gemcitabine, compared with the standard cisplatin–fluorouracil regimen in patients with high risk of distant metastasis (patients with stage N2–3 disease). We hypothesised that use of cisplatin–gemcitabine chemotherapy at 4 weeks after the end of radiotherapy, followed by administration every 3 weeks in the adjuvant setting, could provide an alternative to adjuvant cisplatin–fluorouracil in reducing distant metastasis and improving progression-free survival.

Methods

Study design and participants

This open-label, parallel-group, randomised, controlled, phase 3 trial was conducted at four cancer centres in China (appendix p 6). Patients were eligible if they were aged 18–65 years old with histologically confirmed, non-keratinising (WHO II or III type), nasopharyngeal carcinoma; stage T1–4 N2–3 M0 disease, as classified by the 7th edition of the American Joint Committee on Cancer TNM Staging System; Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1; adequate bone marrow (assessed by complete blood cell count) and liver and renal function (assessed by biochemical profile); and no previous treatment for cancer. The key exclusion criteria were receipt of treatment with palliative intent; previous malignancy, except adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer; lactation or pregnancy; or severe coexisting illness. Full inclusion and exclusion criteria are provided in the protocol (appendix).

See Online for appendix

The study was conducted in accordance with the principles of the Declaration of Helsinki and the results are reported according to CONSORT. The study protocol was approved by the Clinical Research Ethics Committee and Institutional Review Board of each participating institution. All patients provided written informed consent before participation.

Randomisation and masking

Patients who met the eligibility criteria were randomly assigned (1:1) to receive concurrent chemoradiotherapy followed by adjuvant chemotherapy with either cisplatin–gemcitabine (cisplatin–gemcitabine group) or cisplatin–fluorouracil (cisplatin–fluorouracil group). Randomisation was done at the Clinical Trials Centre of the Sun Yat-sen University Cancer Centre (Guangzhou, China) using a computerised random list generator and block randomisation, with a block size of six (known only to the statistician QL), and stratified by treatment centre and nodal category (N2 *vs* N3). To evaluate the efficacy of the concurrent adjuvant sequence, randomisation was done upfront before concurrent chemoradiotherapy. The standard operating procedure was formulated to guarantee the quality and implementation of concurrent chemoradiotherapy. After completing all screening procedures at each centre, the investigators contacted the study coordinator (PW) to obtain the treatment assignment. Patients and investigators were not masked to treatment group assignments; however, the central imaging group and statisticians were masked to patient assignment.

Procedures

Before randomisation, pretreatment evaluations were as follows: complete medical history; physical examinations; fibreoptic nasopharyngoscopy; histopathological diagnosis; MRI or CT (CT was indicated only in patients with contraindication to MRI) scan of the nasopharynx and neck, chest (radiograph or CT) and abdomen (abdominal sonography or CT) scan; a skeletal scintigraphy or whole body [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET/CT; electrocardiogram; complete blood count with differential count; biochemical profile; and plasma Epstein-Barr virus DNA load, tested by quantitative PCR (appendix p 4) before treatment, which was optional depending on the laboratory availability of the participating institution. Data on sex were collected from electronic medical records and race and ethnicity data were not collected. Baseline examinations were done within 14 days before randomisation.

Patients in both groups were irradiated with intensity-modulated radiotherapy.[11] The gross tumour volume (GTV) included the primary tumour and enlarged lymph nodes. Details of the radiotherapy plan are provided in the appendix (p 2). The prescribed doses of planning target volume for nasopharynx GTV, GTV of lymph nodes, high-risk clinical target volume, and low-risk clinical target volume were 70 Gy, 64–70 Gy, 60 Gy, and 54 Gy, respectively. We divided the accumulated dose into 33 fractions and administered five daily fractions per week for 7 weeks.[12]

Three patients in the profile receive induction chemotherapy. The three patients chose to change their supervising attending physician, who was not a investigator involved in this study, after randomisation. The new supervising physician chose induction chemotherapy for these patients at their own discretion. Cisplatin 100 mg/m^2 was intravenously administered every 3 weeks on days 1, 22, and 43 for three cycles concurrently with radiotherapy in both groups. For the cisplatin–gemcitabine group, adjuvant chemotherapy was given as a combination of gemcitabine (1 g/m^2) intravenously on days 1 and 8 and cisplatin 80 mg/m^2 intravenously for 4 h on day 1, repeated once every 3 weeks, starting on days 28, 49, and 70 after the end of radiotherapy

for up to three cycles. For the cisplatin–fluorouracil group, adjuvant chemotherapy was given as a combination of cisplatin 80 mg/m² intravenously for 4 h on day 1 and fluorouracil 4 g/m² by 96 h continuous intravenous infusion, once every 4 weeks, starting on days 28, 56, and 84 after the end of radiotherapy for up to three cycles. Chemotherapy dose adjustments were allowed for adverse events. Details of the allowed chemotherapy dose modifications and supportive measures are in the appendix (p 3). Patients were removed from the study if they had disease progression or severe comorbidities during treatment, or withdrew consent at any time during the study.

The first evaluation of tumour response was done 16 weeks after the completion of radiotherapy, per the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Patients were then assessed every 3 months during the first 3 years of follow up, and every 6 months thereafter (appendix p 9). Assessment of tumour relapse was done via MRI or CT of the nasopharynx and neck, nasopharyngoscopy, chest radiography or CT, abdominal sonography or CT, and skeletal scintigraphy; plasma Epstein-Barr virus DNA load (if available); and [¹⁸F]FDG PET/CT in patients with detectable plasma Epstein-Barr virus DNA, or those with a suspicion of locoregional disease or distant metastasis. When necessary, locoregional or distant relapse was confirmed by fine-needle aspiration or biopsy. All endpoints, including safety, were assessed locally and confirmed by the attending physician and further centrally reviewed (at Sun Yat-sen University Cancer Centre) for ratification. After completion of assigned treatment, further anticancer treatments (eg, chemotherapy, reirradiation, surgery, immunotherapy, and targeted therapy) were determined at the physician's discretion for patients with persistent disease or documented relapse whenever possible. Common Terminology Criteria for Adverse Events (version 4.0) was used to grade acute adverse events (ie, those that occurred during assigned treatment). Late adverse events, defined as radiation-related adverse events occurring from 3 months after completion of radiotherapy until the last follow-up visit and chemotherapy-induced haematological adverse events occurring from 3 months after completion of chemotherapy until the last follow-up visit, were graded according to both the Late Radiation Morbidity Scoring Scheme of the Radiation Therapy Oncology Group[13] and the Common Terminology Criteria for Adverse Events (version 4.0). Safety assessments (adverse events) and laboratory tests (blood routine and blood biochemistry profile) were done every week during treatment and then at every follow-up visit according to study calendar in the protocol (appendix).

Outcomes

The primary endpoint was 3-year progression-free survival, assessed locally by the investigator at each centre and defined as the time from random assignment to documented local or regional relapse, distant metastasis, or death from any cause, whichever occurred first. Secondary endpoints were overall survival (defined as the time from random assignment to death from any cause), locoregional relapse-free survival (defined as time from random assignment to local or regional relapse or death from any cause), distant metastasis-free survival (defined as time from random assignment to distant metastasis or death from any cause), short-term response rate (assessed at 16 weeks with RECIST version 1.1), and safety (acute adverse events, occurring during study treatment, and radiation-related late adverse events, occurring from 3 months after completion of radiotherapy, and chemotherapy-induced adverse events, occurring from 3 months after completion of chemotherapy until end of follow up).

Statistical analysis

This trial was designed to evaluate whether concurrent adjuvant cisplatin–gemcitabine chemotherapy improved progression-free survival compared with concurrent adjuvant cisplatin–fluorouracil chemotherapy. The sample size calculation was performed with the Power Analysis and Sample Size software (version 15; NCSS, Kaysville, UT, USA). We estimated that the trial would have 80% power to detect a hazard ratio (HR) for disease recurrence or death of 0·48 using a log-rank test with a two-sided significance level of 0·05, assuming 3-year progression-free survival of 70% in the concurrent adjuvant cisplatin–fluorouracil group[3] and 84% in the concurrent adjuvant cisplatin–gemcitabine group. Considering a 3 year recruitment period and 3 years of follow-up, we anticipated that 62 events would be required in 196 patients (98 per treatment group). Furthermore, we assumed that 10% of patients would be lost to follow-up or would prematurely discontinue the trial; thus, 240 patients were required (120 patients in each group; appendix p 5).[14]

All efficacy analyses were performed in the intention-to-treat population, which included all patients randomly assigned to treatment. For the response rate evaluation, patients who did not undergo the baseline or post-baseline imaging measurements were defined as not assessable for short-term response and excluded from the analysis; however, the patients continue to be assessed in the subsequent follow-up timepoints for survival outcomes. In a prespecified analysis, progression-free survival was also analysed in the per-protocol population, which included patients who did not violate the eligibility criteria and who started randomly assigned treatments (ie, received at least two or three cycles of concurrent chemotherapy plus at least two or three cycles of adjuvant chemotherapy). For the safety analyses, patients who received at least one dose of chemoradiotherapy were included. Post-hoc assessment of acute adverse events was done by chemotherapy phase (ie, concurrent and adjuvant). Categorical were compared

using the χ^2 test or Fisher's exact test. Incidence of adverse events were compared using the χ^2 test. Continuous variables were compared using the Mann-Whitney *U* test.

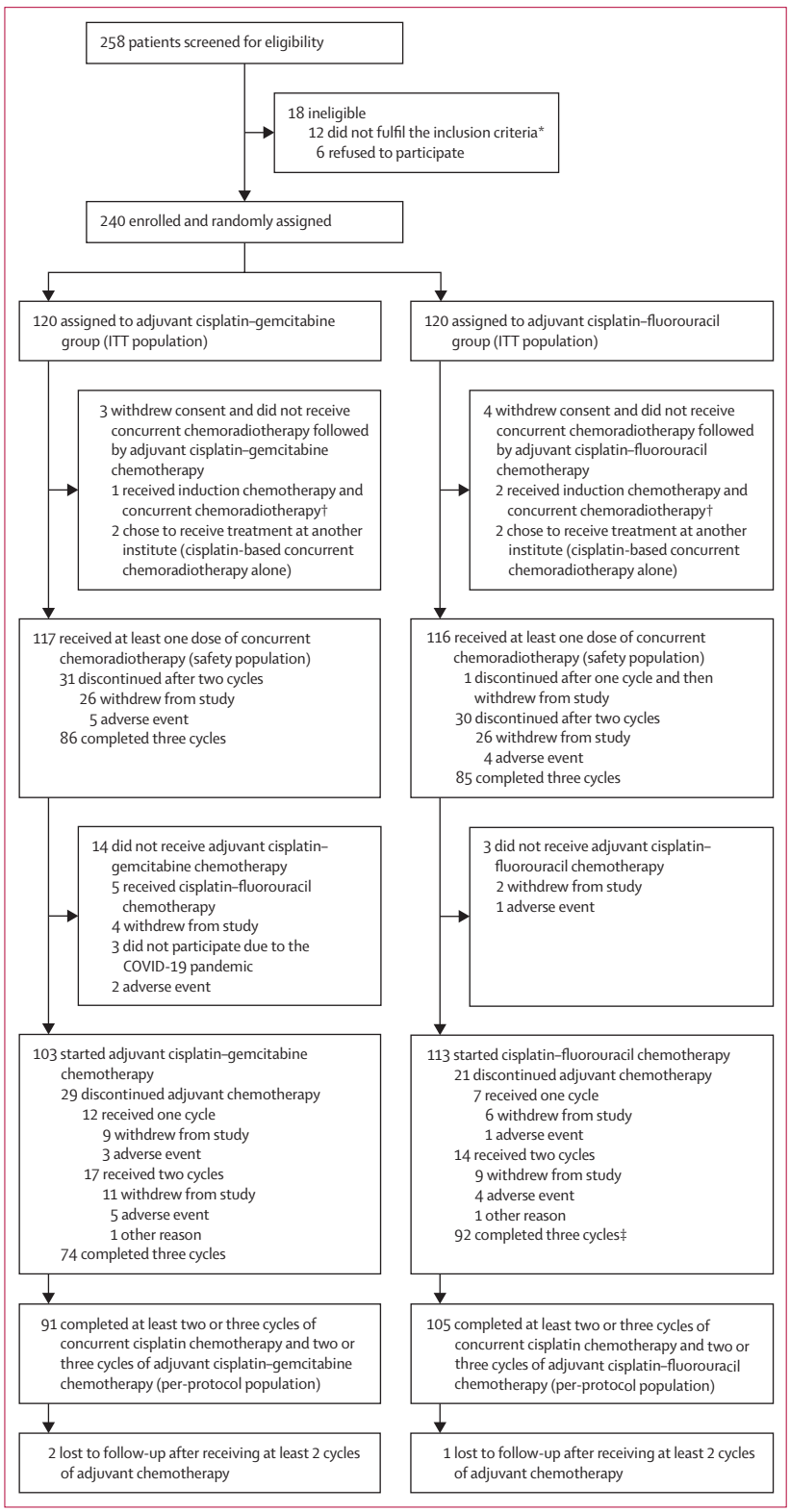


Figure 1: **Trial profile**
ITT=intention-to-treat. *Five patients had insufficient haematological function, three had insufficient renal function, two had inadequate hepatic function, one had severe cardiopathy, and one had synchronous lung cancer. †Received induction chemotherapy of cisplatin–fluorouracil followed by cisplatin-based concurrent chemoradiotherapy. ‡One patient only completed one cycle of concurrent chemotherapy.

Kaplan-Meier curves (with no informative censoring) were used to present progression-free survival and overall survival, and the two treatment groups were compared using log-rank tests stratified according to the treatment centre (any participating centres that enrolled fewer than five eligible patients was pooled into the stratum with another centre that had the same geographical, demographic, epidemiological characteristics, and hospital volume) and nodal category. HRs and 95% CIs were calculated using a stratified Cox proportional hazards model to estimate the effect of the experimental treatment, stratified by treatment centre and N stage (N2 *vs* N3), with assumptions of proportional hazards confirmed based on Schoenfeld residuals (appendix p 5).[15] The cumulative incidences of locoregional relapse and distant metastasis were presented by the Nelson-Aalen cumulative risk curves and estimated using the Fine-Gray subhazards model, with deaths regarded as competing events for locoregional and distant metastasis failure.[16] A post-hoc analysis of locoregional relapse patterns was performed. Missing time-to-event data due to loss to follow-up or no event observed at the time of the predefined primary analysis were censored. Right-censored data were used for survivorship estimates and the follow-up duration for patients lost to follow up was defined as the date from randomisation to the date of last follow-up visit.[17]

Multivariable analyses were performed using the Cox proportional hazards model to test the independent significance of different covariates with enter method for all survival outcomes.[18] With this method, all potentially important prognostic covariates, including age, sex, ECOG performance status, T stage, N stage, and treatment interventions, were entered in a single step to the model. Interaction analysis for the primary outcome was performed to explore whether the effect of experimental treatment varied in the subgroups defined according to age (<44 years *vs* ≥44 years), sex (male *vs* female), ECOG performance status (0 *vs* 1), overall stage (III *vs* IVA–B), T stage (T1–2 *vs* T3 *vs* T4; with post-hoc amendment to separate T3 and T4), and N stage (N2 *vs* N3). An interaction analysis was conducted using a treatment-by-covariate interaction test based on the Cox proportional hazards model,[19] each with one interaction term between one baseline covariate and treatment. We also assessed progression-free survival in subgroups (post hoc) stratified by overall disease stage, N stage, and T stage using the Kaplan-Meier method. A post-hoc analysis for treatment adherence and plasma Epstein-Barr virus

DNA within 14 days before adjuvant chemotherapy was also performed. A post-hoc analysis of the differences in non-cancer-related deaths between the groups was done. A prespecified analysis in each participating centre was not performed because of the small sample size (n<30) of recruited patients from some participating centres.

At the time of data cutoff (Dec 25, 2022), 58 events were observed, such that the prespecified number of events (62 events) for the primary endpoint had not been reached. The trial steering committee opted to report the results of the trial at this timepoint on the following grounds: the number of patients at risk at the 3-year timepoint in both groups reached the minimum number according to the method proposed by Gebski and colleagues,[20] thus, it was sufficient for the data to provide meaningful interpretation of Kaplan-Meier survival at 3 years; a lower-than-expected number of events occurred despite enriching for a high-risk study population; there was a substantial decrease in events beyond the third year of follow-up; and the study period had reached a median follow-up of 40 months.

Analyses were performed using SPSS (version 24.0) and Stata (version 15.1). All statistical tests were two-sided, and p<0·05 was considered statistically significant. This study is registered at ClinicalTrials.gov, NCT03321539.

Role of the funding source

Sun Yat-sen University was involved in trial management and auditing. All other funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Oct 30, 2017, to July 9, 2020, 258 patients were screened, of whom 240 were enrolled and randomly assigned to the adjuvant cisplatin–fluorouracil group (n=120) or cisplatin–gemcitabine group (n=120; intention-to-treat population; figure 1). Median age was 44 years (IQR 36–52), 175 (73%) of 240 of participants were male and 65 (27%) were female. 105 patients in the cisplatin–fluorouracil group and 91 patients in the cisplatin–gemcitabine group received two to three cycles of concurrent chemotherapy plus two to three cycles of adjuvant chemotherapy (per-protocol population; figure 1). Baseline characteristics were well balanced between the two groups (table 1). The pretreatment imaging methods for staging were similar between the two groups (appendix p 6). Because the criteria of test standard for plasma Epstein-Barr virus DNA varied at each centre, the plasma Epstein-Barr virus DNA data were only documented in Sun Yat-sen University Cancer Centre and 99 patients in each group had plasma Epstein-Barr virus DNA measurements. Seven patients withdrew from the trial before treatment initiation (figure 1). 230 (96%) of 240 patients had a tumour response assessment for distant metastasis between concurrent chemoradiotherapy and starting adjuvant chemotherapy and no distant metastases were reported.

As of data cutoff (Dec 25, 2022; median follow-up 40 months [IQR 32–48]), disease progression was reported in 37 (31%) of 120 patients in the cisplatin–fluorouracil group and 21 (18%) of 120 in the cisplatin–gemcitabine group. Given that only three enrolled eligible patients from the Affiliated Cancer Hospital and Institute of Guangzhou Medical University, data from this participating centre was pooled into the Sun Yat-sen University Cancer Centre. 3-year progression-free survival was 83·9% (95% CI 75·9–89·4; 19 disease progressions and 11 deaths) in the cisplatin–gemcitabine group and 71·5% (62·5–78·7; 34 disease progressions and seven deaths) in the cisplatin–fluorouracil group (stratified HR 0·54 [95% CI 0·32–0·93]; log-rank p=0·023; figure 2A). The prespecified statistical criteria for the superiority

	Cisplatin–gemcitabine group (n=120)	Cisplatin–fluorouracil group (n=120)
Age, years	45 (37–51)	44 (36–52)
Sex		
Male	84 (70%)	91 (76%)
Female	36 (30%)	29 (24%)
ECOG performance score		
0	68 (57%)	63 (53%)
1	52 (43%)	57 (48%)
Histology		
WHO II	2 (2%)	3 (3%)
WHO III	118 (98%)	117 (98%)
T stage*		
T1	3 (3%)	1 (<1%)
T2	16 (13%)	17 (14%)
T3	75 (63%)	78 (65%)
T4	26 (22%)	24 (20%)
N stage*		
N2	71 (59%)	72 (60%)
N3	49 (41%)	48 (40%)
Overall disease stage		
III	52 (43%)	54 (45%)
IVa	19 (16%)	18 (15%)
IVb	49 (41%)	48 (40%)
Pretreatment Epstein-Barr virus DNA†		
Median, copies per mL	1092 (216–5580)	1160 (286–5300)
DNA <2000 copies per mL	60/99 (61%)	61/99 (62%)
DNA ≥2000 copies per mL	39/99 (39%)	38/99 (38%)

Data are median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. *According to the American Joint Committee on Cancer staging system, 7th edition. †The plasma Epstein-Barr virus DNA test was optional in this trial and was not done for all enrolled patients, and data were only documented for patients enrolled at the Sun Yat-sen University Cancer Centre (n=99 in each group).

Table 1: **Baseline characteristics, intention-to-treat population**

of cisplatin–gemcitabine over cisplatin–fluorouracil were met. Consistent results were found in the per-protocol analysis (appendix p 16).

As of data cutoff, in the cisplatin–gemcitabine group, 12 (10%) of 120 patients died (nine died due to cancer, one due to septic shock, one due to stroke and one due to an unknown cause of death) and in the cisplatin–fluorouracil group 11 (9%) of 120 patients had died (all due to cancer). 3-year overall survival was 90·7% (95% CI 83·8–94·7) in the cisplatin–gemcitabine group versus 94·0% (87·8–97·1) in the cisplatin–fluorouracil group (figure 2B). As of data cutoff, in the cisplatin–fluorouracil group, 15 (13%) patients developed locoregional relapse and 25 (21%) patients developed distant metastasis, and in the cisplatin–gemcitabine group, five (4%) patients had locoregional relapse and 13 (11%) patients had distant metastasis. 3-year cumulative incidence of locoregional relapse was 2·6% (95% CI 0·8–8·1) in the cisplatin–gemcitabine group versus 13·2% (7·8–22·4) in the cisplatin–fluorouracil group (figure 2D) and 3-year cumulative incidence of distant metastasis was 10·9% (95% CI 6·2–19·2) versus 22·3% (14·9–33·2; figure 2C). In multivariable analyses, patients in the cisplatin–gemcitabine group also had reduced risk of disease progression or death, locoregional relapse, and distant metastasis than did patients in the cisplatin–fluorouracil group (appendix pp 12–14). Full survival outcome data, short-term response rate, the patterns of locoregional relapse (post hoc), and plasma Epstein-Barr Virus DNA

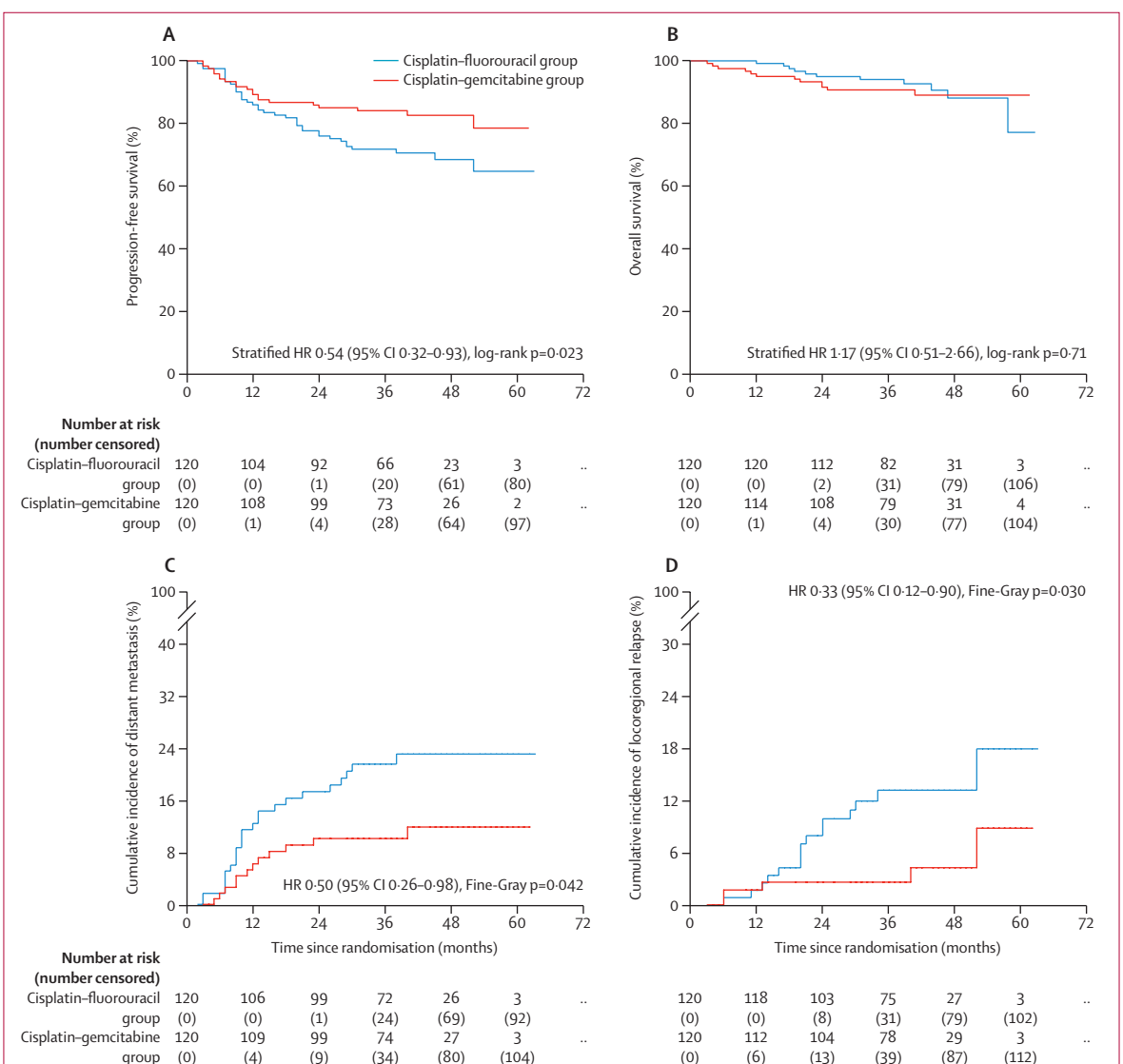
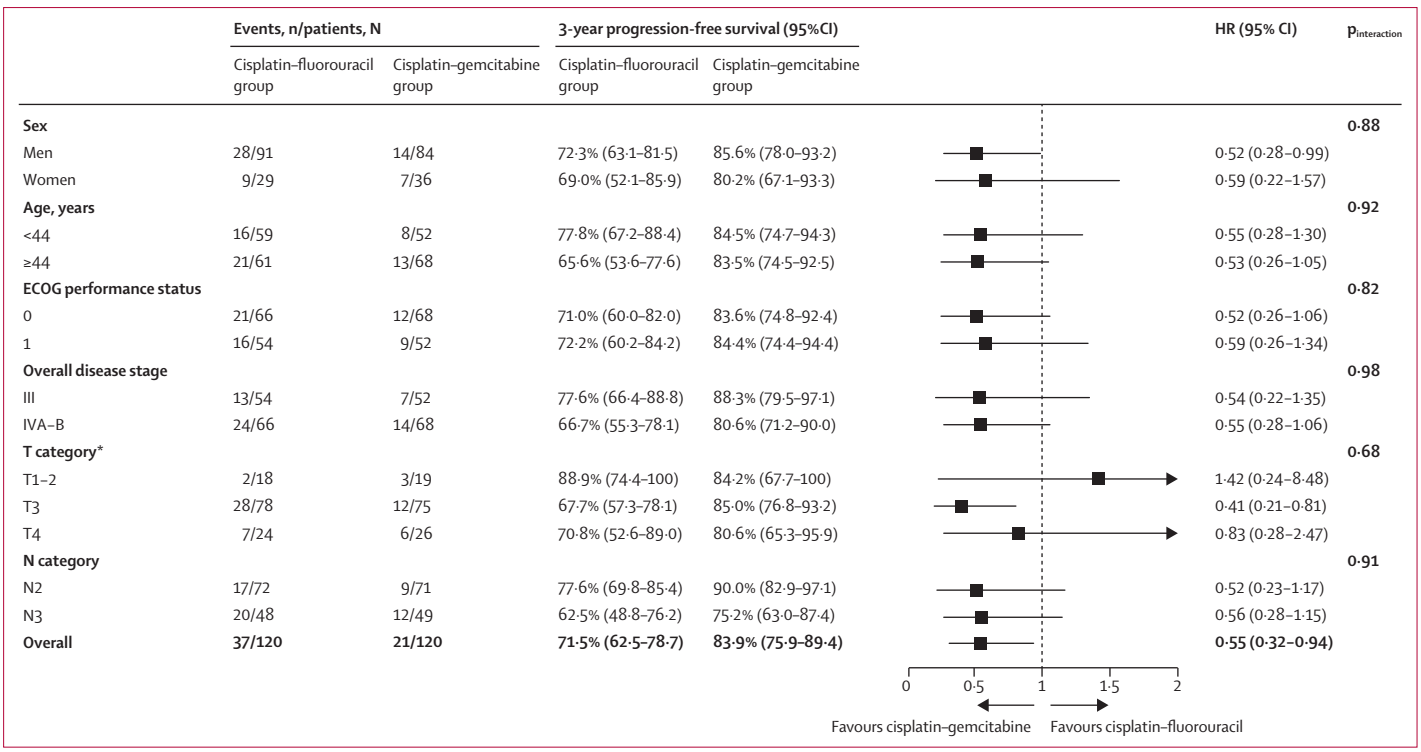


Figure 2: **Progression-free survival (A), overall survival (B), cumulative incidence of distant metastasis (C), and cumulative incidence of locoregional relapse (D), intention-to-treat population**

A stratified Cox proportional hazards model (A, B) and a Fine-Gray subhazards model (C, D) was used to calculate the HRs and their associated 95% CIs. HR=hazard ratio.



	Events, n/patients, N		3-year progression-free survival (95%CI)		HR (95% CI)	$p_{interaction}$
	Cisplatin–fluorouracil group	Cisplatin–gemcitabine group	Cisplatin–fluorouracil group	Cisplatin–gemcitabine group		
Sex						**0·88**
Men	28/91	14/84	72·3% (63·1–81·5)	85·6% (78·0–93·2)	0·52 (0·28–0·99)	
Women	9/29	7/36	69·0% (52·1–85·9)	80·2% (67·1–93·3)	0·59 (0·22–1·57)	
Age, years						**0·92**
<44	16/59	8/52	77·8% (67·2–88·4)	84·5% (74·7–94·3)	0·55 (0·28–1·30)	
≥44	21/61	13/68	65·6% (53·6–77·6)	83·5% (74·5–92·5)	0·53 (0·26–1·05)	
ECOG performance status						**0·82**
0	21/66	12/68	71·0% (60·0–82·0)	83·6% (74·8–92·4)	0·52 (0·26–1·06)	
1	16/54	9/52	72·2% (60·2–84·2)	84·4% (74·4–94·4)	0·59 (0·26–1·34)	
Overall disease stage						**0·98**
III	13/54	7/52	77·6% (66·4–88·8)	88·3% (79·5–97·1)	0·54 (0·22–1·35)	
IVA–B	24/66	14/68	66·7% (55·3–78·1)	80·6% (71·2–90·0)	0·55 (0·28–1·06)	
T category*						**0·68**
T1–2	2/18	3/19	88·9% (74·4–100)	84·2% (67·7–100)	1·42 (0·24–8·48)	
T3	28/78	12/75	67·7% (57·3–78·1)	85·0% (76·8–93·2)	0·41 (0·21–0·81)	
T4	7/24	6/26	70·8% (52·6–89·0)	80·6% (65·3–95·9)	0·83 (0·28–2·47)	
N category						**0·91**
N2	17/72	9/71	77·6% (69·8–85·4)	90·0% (82·9–97·1)	0·52 (0·23–1·17)	
N3	20/48	12/49	62·5% (48·8–76·2)	75·2% (63·0–87·4)	0·56 (0·28–1·15)	
Overall	**37/120**	**21/120**	**71·5% (62·5–78·7)**	**83·9% (75·9–89·4)**	**0·55 (0·32–0·94)**	

Figure 3: **Subgroup analysis of progression-free survival, intention-to-treat population**
An unstratified Cox proportional hazards model was used to calculate the HRs and their associated 95% CIs. HR=hazard ratio. *Post-hoc analyses for stage T3 and T4 disease.

(post-hoc), non-cancer-related deaths, and anticancer treatments after relapse are in the appendix (pp 10, 11, 15).

Prespecified and post-hoc subgroup analyses of progression-free survival are shown in figure 3 and the appendix (pp 17–19).

Treatment adherence and number of cycles of each treatment received by group are shown in figure 1 and appendix (p 7). Median interval from the day of randomisation to the first day of adjuvant chemotherapy was 94 days (IQR 86–101) in the cisplatin–gemcitabine group and 95 days (87–101) in the cisplatin–fluorouracil group. Median interval from the last day of radiotherapy to the first dose of adjuvant chemotherapy was 35 days (IQR 27–43) in the cisplatin–gemcitabine group and 34 days (29–44) in the cisplatin–fluorouracil group.

Dose reductions were reported in 20 (17%) of 120 in the cisplatin–gemcitabine group and 25 (21%) of 120 patients in the cisplatin–fluorouracil group during the concurrent phase and in 63 (53%) and 48 (40%) during the adjuvant phase (some patients had dose reductions in both phases). 54 (45%) of 120 in the cisplatin–gemcitabine group and 48 (40%) of 120 patients in the cisplatin–fluorouracil group discontinued treatment, and the most frequent reasons were patient withdrawal (concurrent phase: 26 [22%] in the cisplatin–gemcitabine group *vs* 27 [23%] in the cisplatin–fluorouracil group; adjuvant phase: 20 [17%] *vs* 15 [13%]) and adverse events (concurrent phase: five [4%] *vs* four [3%]; adjuvant phase: eight [7%] *vs* five [4%]). The most frequent adverse events leading to discontinuation in the cisplatin–gemcitabine group were leukopenia (eight [7%] of 120) and thrombocytopenia (four [3%] of 120). In the cisplatin–fluorouracil group, the most frequent adverse event leading to discontinuation was leucopenia (four [3%]) and anaemia (two [2%]) The cumulative dose and dose intensity of chemotherapy drugs, and chemotherapy and radiotherapy compliance are in the appendix (p 7).

Safety was assessed in 116 patients in the cisplatin–fluorouracil group and 117 patients cisplatin–gemcitabine group who initiated randomly assigned chemoradiotherapy. The most common acute adverse events of grade 3 or worse were leukopenia (61 [52%] of 117 in the cisplatin–gemcitabine group *vs* 34 [29%] of 116 patients in the cisplatin–fluorouracil group), neutropenia (37 [32%] *vs* 19 [16%]), and mucositis (27 [23%] *vs* 32 [28%]; table 2). A significantly higher incidence of grade 3 or worse leukopenia and neutropenia were seen in the cisplatin–gemcitabine group than in the cisplatin–fluorouracil group, whereas the frequency of diarrhoea was higher in the cisplatin–fluorouracil group than the cisplatin–gemcitabine group, although these analyses were underpowered due to small patient numbers (table 2). Post-hoc exploratory analyses of acute adverse events during the concurrent and adjuvant phases are shown in the appendix (p 8). One (1%) patient in the cisplatin–gemcitabine group had a treatment-related death (septic shock due to neutropenic infection) which occurred after one cycle of adjuvant chemotherapy. No treatment-related deaths occurred in the cisplatin–fluorouracil group. The

	Cisplatin–gemcitabine group* (n=117)				Cisplatin–fluorouracil group (n=116)				p value for events grade ≥1†	p value for events grade ≥3†
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5		
Any adverse event	20 (17%)	81 (69%)	16 (14%)	1 (<1%)	37 (32%)	65 (56%)	14 (12%)	0	0·054	0·0086
Haematological events										
Leukopenia	54 (46%)	54 (46%)	7 (6%)	0	77 (66%)	29 (25%)	5 (4%)	0	0·44	0·00039
Neutropenia	59 (50%)	28 (24%)	8 (7%)	1 (<1%)	79 (68%)	15 (13%)	4 (3%)	0	0·51	0·010
Anaemia	88 (75%)	23 (20%)	0	0	87 (75%)	16 (14%)	0	0	0·090	0·23
Thrombocytopenia	25 (21%)	7 (6%)	4 (3%)	0	15 (13%)	5 (4%)	1 (<1%)	0	0·025	0·22
Non-haematological events										
Vomiting	44 (38%)	17 (15%)	0	0	47 (41%)	18 (16%)	1 (<1%)	0	0·47	0·70
Nausea	75 (64%)	23 (20%)	0	0	84 (72%)	15 (13%)	0	0	0·74	0·17
Constipation	58 (50%)	0	0	0	57 (49%)	0	0	0	0·95	..
Diarrhoea	19 (16%)	0	0	0	23 (20%)	6 (5%)	0	0	0·098	0·014
Hiccups	11 (9%)	3 (3%)	0	0	14 (12%)	0	0	0	0·98	0·25
Weight loss	92 (79%)	4 (3%)	0	0	90 (78%)	5 (4%)	0	0	0·98	0·99
Mucositis	74 (63%)	24 (21%)	3 (3%)	0	72 (62%)	29 (25%)	3 (3%)	0	0·43	0·43
Dermatitis	76 (65%)	7 (6%)	1 (<1%)	0	79 (68%)	9 (8%)	2 (2%)	0	0·31	0·46
Fever	6 (5%)	3 (2·6%)	0	0	6 (5%)	1 (1%)	0	0	0·62	0·62
Sensory neuropathy	28 (24%)	0	0	0	28 (24%)	0	0	0	0·97	..
Auditory or hearing	20 (17%)	4 (3%)	0	0	19 (16%)	4 (3%)	0	0	0·90	1·00
Dry mouth	71 (61%)	12 (10%)	0	0	76 (66%)	8 (7%)	0	0	0·80	0·36
Hypokalaemia	56 (48%)	4 (3%)	0	0	49 (42%)	8 (7%)	2 (2%)	0	0·95	0·16
Hyponatraemia	65 (56%)	13 (11%)	0	0	54 (47%)	18 (16%)	1 (<1%)	0	0·55	0·24
Hypocalcaemia	41 (35%)	0	1 (<1%)	0	38 (33%)	4 (3%)	0	0	0·96	0·36
Total bilirubin	20 (17%)	0	0	0	19 (16%)	1 (<1%)	0	0	0·98	0·50
Increased alanine aminotransferase	52 (44%)	3 (3%)	0	0	60 (52%)	1 (<1%)	0	0	0·40	0·62
Increased aspartate aminotransferase	36 (31%)	2 (2%)	0	0	29 (25%)	0	0	0	0·21	0·50
Increased creatinine	94 (80%)	2 (2%)	0	0	100 (86%)	0	0	0	0·39	0·50

Data are n (%). Data are for grade 1–2 adverse events reported in 10% or more patients and all grade 3, 4, and 5 adverse events. Safety analyses were done in the safety population, comprising all patients who commenced the randomly assigned treatment. *One cisplatin–gemcitabine-related death (septic shock due to neutropenic infection) occurred after one cycle of adjuvant chemotherapy. †These analyses were not adequately powered and should be interpreted with caution.

Table 2: **Acute adverse events, safety population**

most common grade 3 or worse late adverse event was auditory or hearing loss (six [5%] of 117 in the cisplatin–gemcitabine group *vs* ten [9%] in the cisplatin–fluorouracil group. There were no significant differences in late adverse events or non-cancer-related deaths (post hoc) between the groups (table 3; appendix p 10).

Discussion

To our knowledge, this is the first report of a concurrent adjuvant cisplatin–gemcitabine regimen to show significant improvement in 3-year progression-free survival compared with the traditional cisplatin–fluorouracil regimen in patients with N2–3 nasopharyngeal carcinoma.

Since the Intergroup 0099 study,[2] concurrent adjuvant cisplatin–fluorouracil chemotherapy has become the standard treatment for locoregionally advanced nasopharyngeal carcinoma. An individual patient network meta-analysis[6] also showed that a concurrent adjuvant sequence was the most efficacious regimen with the highest survival benefit across all survival outcomes. Exploratory combined analyses of the NPC-9901 and NPC-9902 trials further suggested that both concurrent and adjuvant phases contributed to tumour control.[21] However, a phase 3 trial[8] that compared concurrent chemoradiotherapy plus adjuvant cisplatin–fluorouracil chemotherapy with concurrent chemoradiotherapy did not show survival benefits. Notably, the phase 3 trial

	Cisplatin–gemcitabine group (n=117)				Cisplatin–fluorouracil group (n=116)				p value for events grade ≥1*	p value for events grade ≥3*
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5		
Any adverse event	94 (80%)	14 (12%)	0	0	86 (74%)	16 (14%)	0	0	0·26	0·68
Haematological events										
Leukopenia	20 (17%)	1 (<1%)	0	0	20 (17%)	1 (<1%)	0	0	0·87	>0·99
Neutropenia	13 (11%)	1 (<1%)	0	0	9 (8%)	2 (2%)	0	0	0·59	>0·99
Anaemia	60 (51%)	0	0	0	52 (45%)	0	0	0	0·17	..
Thrombocytopenia	1 (<1%)	0	0	0	1 (<1%)	0	0	0	>0·99	..
Non-haematological events										
Auditory or hearing loss	25 (21%)	6 (5%)	0	0	26 (22%)	10 (9%)	0	0	0·44	0·29
Trismus	3 (3%)	0	0	0	4 (3%)	0	0	0	0·99	..
Dysphagia	3 (3%)	0	0	0	3 (3%)	0	0	0	>0·99	..
Skin	25 (21%)	1 (<1%)	0	0	25 (22%)	0	0	0	0·90	>0·99
Subcutaneous soft tissue	25 (21%)	2 (2%)	0	0	27 (23%)	2 (2%)	0	0	0·73	>0·99
Dry mouth	69 (59%)	4 (3%)	0	0	73 (63%)	3 (3%)	0	0	0·62	>0·99
Cranial neuropathy	3 (3%)	0	0	0	3 (3%)	1 (<1%)	0	0	0·99	0·50

Data are n (%). Late adverse events analyses were done in the safety population, comprising all patients who commenced randomly assigned treatment. *These analyses were not adequately powered and should be interpreted with caution.

***Table 3*: Late adverse events, safety population**

did not have a non-inferiority design.[8] Therefore, it cannot be concluded that concurrent chemoradiotherapy was non-inferior to concurrent chemoradiotherapy plus adjuvant cisplatin–fluorouracil. The debate as to whether concurrent chemoradiotherapy plus adjuvant cisplatin–fluorouracil is the most efficacious treatment strategy remains controversial. Studies of the addition of adjuvant chemotherapy in patients at high risk of disease progression have tested single or novel combination drugs.[10,26]

Cisplatin–gemcitabine is found to be an efficacious chemotherapeutic regimen for nasopharyngeal carcinoma in trial settings. In recurrent or metastatic nasopharyngeal carcinoma, the cisplatin–gemcitabine regimen showed superior efficacy compared with cisplatin–fluorouracil.[10] Notably, the addition of induction cisplatin–gemcitabine to concurrent chemoradiotherapy has been shown to significantly improve survival compared with chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma.[22] However, the NPC-0502 trial[9] did not show superiority of cisplatin–gemcitabine in the adjuvant chemotherapy setting compared with observation alone in patients with post-concurrent chemoradiotherapy detectable Epstein-Barr virus DNA. The possible reasons for these results are as follows: first, the optimal time interval between concurrent chemoradiotherapy and adjuvant chemotherapy for nasopharyngeal carcinoma has not yet been defined. On the basis of several phase 3 studies,[2,3,8] the adjuvant chemotherapy regimens recommended by National Comprehensive Cancer Network guidelines (version 2.2023) were with an interval of 4 weeks between concurrent chemoradiotherapy and adjuvant chemotherapy. A systematic review and meta-analysis of adjuvant chemotherapy and survival in resected colorectal cancer found that initiation of adjuvant chemotherapy within 3 weeks after surgery significantly reduced the recurrence rate compared with initiation after 3 weeks and that overall survival decreased by 14% for every 4-week delay in the initiation of adjuvant chemotherapy.[23] Second, measuring Epstein-Barr virus DNA at 6–8 weeks after treatment might not be timely for distinguishing patients who are at high risk of disease progression. A previous study has shown that patients with detectable post-radiotherapy Epstein-Barr virus DNA have a poor prognosis and detectable Epstein-Barr virus DNA preceded radiological and clinical evidence of recurrence by a median of 2·3 months.[24] In an observational study investigating the surveillance value of a PET/CT scan at 12 weeks after concurrent chemoradiotherapy (unpublished; NCT03601390), we found that 58 (11%) of 506 with locoregionally advanced nasopharyngeal carcinoma had residual or new metastatic disease at this timepoint, and adjuvant chemotherapy could become a form of palliative chemotherapy. In the NPC-0502 trial,[9] among 216 patients with detectable post-radiotherapy Epstein-Barr virus DNA at 6–8 weeks, PET/CT scan indicated that 36 patients had residual disease and 25 patients had developed distant metastasis. The actual proportions of patients with recurrence before adjuvant chemotherapy might be higher than those found at

radiological examinations. Consequently, the interval of 12 weeks to start adjuvant chemotherapy might be too late for cisplatin–gemcitabine to be effective in treating patients with such a high distant tumour burden.

In the current study, adjuvant cisplatin–gemcitabine was administered 4 weeks after the end of radiotherapy and was repeated every 3 weeks for three cycles. The interval of 4 weeks between chemoradiotherapy and adjuvant chemotherapy might be more appropriate than the interval of 12 weeks for minimising potential residual and occult metastatic disease.[9] Furthermore, the intensity of the once every 3 weeks schedules of cisplatin–gemcitabine regimen might be more effective than a traditional once every 4 weeks cisplatin–fluorouracil regimen. Interestingly, we found that patient benefit from adjuvant cisplatin–gemcitabine seems to be mainly attributed to the improvement of locoregional control. Our study population was enriched with patients who had stage N2–3 tumours and a high risk of distant metastases, hence, adjuvant chemotherapy was administrated to eradicate both residual disease in locoregional sites and subclinical micrometastases. In post-hoc analyses, we found that the majority of recurrences were in-field recurrences for both local and nodal recurrences. Our findings concur with the 2021 meta-analysis of chemotherapy in nasopharyngeal carcinoma,[7] which reported that patients treated with concurrent chemoradiotherapy plus adjuvant chemotherapy had reduced risk of locoregional failure. A more effective and intense chemotherapy regimen with cisplatin–gemcitabine than cisplatin–fluorouracil and no delay in concurrent chemoradiotherapy administration might have contributed to favourable locoregional control in our study. Moreover, these results were consistent with those of the NPC-9901 trial,[3] which focused on N2–3 disease and showed significantly favourable disease-free survival of patients who had concurrent chemoradiotherapy plus adjuvant chemotherapy, compared with radiotherapy, and the authors suggested this adjuvant chemotherapy was a key contributor to the improved locoregional control rate. A 2022 phase 3 trial[25] showed that concurrent adjuvant capecitabine achieved higher failure-free survival and locoregional-relapse free survival than concurrent chemoradiotherapy alone. Another trial[26] concerning metronomic capecitabine as adjuvant chemotherapy followed by concurrent chemoradiotherapy with or without induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma also reported improved survival for failure-free survival, overall survival, distant failure-free survival, and locoregional failure-free survival compared with observation alone. However, 19% of patients in the aforementioned study who were treated with adjuvant capecitabine had N1 disease, and so had a better prognosis than patients with N2–3 disease.[26] Additionally, this adjuvant capecitabine regimen has not yet been compared with the standard cisplatin–fluorouracil regimen. Owing to the advent of new multidisciplinary synthetic therapies for salvage treatment, the overall survival time of recurrent and metastatic nasopharyngeal carcinoma has been shown to be prolonged (median progression-free survival 10–35·9 months);[27,28] however, the efficacy of adjuvant cisplatin–gemcitabine in our study we found no difference in 3-year overall survival.

In our study, with regard to adverse events that were significantly different, leukopenia, neutropenia, and thrombocytopenia were the most common acute adverse events in the cisplatin–gemcitabine group, whereas diarrhoea and mucositis were the most common acute adverse events in the cisplatin–fluorouracil group. However, the results of the aforementioned analyses were underpowered. The incidence of grade 3–4 haematological adverse events in the cisplatin–gemcitabine group was higher than that reported in a study conducted in recurrent and metastatic nasopharyngeal carcinoma.[10] The residual toxicities of the concurrent chemoradiotherapy phase and the relatively short interval to start adjuvant chemotherapy might result in a relatively high frequency of haematological adverse events and lead to the discontinuation of cisplatin–gemcitabine chemotherapy. In general, adjuvant chemotherapy in this trial was relatively well tolerated, with acceptable dose intensities. Hence, the results of the present study suggest that patients might benefit from additional adjuvant cisplatin–gemcitabine regimens.

Nevertheless, the latest version (version 2.2023) of the National Comprehensive Cancer Network guidelines recommends induction chemotherapy plus chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma, with level 1 evidence. Although, compliance to induction chemotherapy is better than that usually seen for adjuvant chemotherapy, use of induction chemotherapy before concurrent chemoradiotherapy would compromise the compliance of concurrent chemoradiotherapy. Based on the results of several meta-analyses,[6,7] concurrent chemoradiotherapy is the basis of treatment of locoregionally advanced nasopharyngeal carcinoma and greatly improves survival outcome. The proportion of patients who completed three cycles of concurrent chemotherapy in the induction cisplatin–gemcitabine study was only 39%.[22] A previous study reported that prolonged time from induction chemotherapy to radiotherapy might contribute to greater disease progression, which has raised concerns regarding the increased risk of locoregional relapse.[29] Early introduction of radiotherapy might help to prevent locoregional relapse. Therefore, ongoing trials (NCT03306121 and NCT01797900) comparing induction chemotherapy (cisplatin–paclitaxel liposome–fluorouracil or cisplatin–paclitaxel) plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy plus adjuvant chemotherapy (cisplatin–fluorouracil or cisplatin–paclitaxel and future trials comparing induction

chemotherapy (cisplatin–paclitaxel liposome–fluorouracil or cisplatin–gemcitabine) plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy plus adjuvant chemotherapy (cisplatin–gemcitabine or oral metronomic chemotherapy [capecitabine with or without immunotherapy]) would either reaffirm the efficacy of adjuvant chemotherapy or validate the use of induction chemotherapy in high-risk nasopharyngeal carcinoma.

In our study, we staged patients based on the 7th edition of the American Joint Committee on Cancer staging system. The 8th edition of this system was published in 2016, but was not adopted in clinical practice for cancer diagnosis until 2018. Hence, because some of our patient population was enrolled in 2017—before this clinical practice roll-out—we chose to continue to stage all patients in our cohort using the 7th edition for consistency of staging throughout the cohort. According to the 8th edition, N3 disease includes all patients with metastatic lymph nodes below the caudal border of the cricoid cartilage (regardless of laterality), such that some patients with N2 disease classified with the 7th edition might be upstaged to N3 disease when classified with the 8th edition, and the proportion of patients with N3 disease would increase with the newer staging system.

Our study has several limitations. First, the study was conducted in an endemic area; thus, whether the findings can be applied to non-endemic regions remains to be determined in future studies. Second, early randomisation (before concurrent chemoradiotherapy) has limitations in fully evaluating the efficacy of adjuvant chemotherapy. A randomisation allocation scheduled after concurrent chemoradiotherapy completion might be more appropriate. Third, various Epstein-Barr virus DNA measurements performed at different institutions could yield large variability in the viral DNA copy number detected without harmonisation. Fourth, the majority of patients were recruited from a single centre, which might limit the generalisability of the treatment results. Fifth, the upper limit of age was set to 65 years, and so whether the concurrent adjuvant cisplatin–gemcitabine regimen can be applied to older patients (aged >65 years) remains to be investigated. Sixth, baseline PET/CT was not mandatory, which might result in misdiagnosis of occult distant metastases. Seventh, our study cohort might still represent a low-risk group of patients given that two-thirds of patients had Epstein-Barr virus DNA levels of less than 2000 copies per mL. Eighth, because the sample size of patients who received the full dose regimen was not equal between the treatment groups, the per-protocol analyses were underpowered. Ninth, the number of events in our study was immature according to our initial sample size calculations. Finally, although progression-free survival is a robust surrogate endpoint for overall survival in nasopharyngeal carcinoma,[30] the effect of the concurrent adjuvant cisplatin–gemcitabine regimen on early overall survival was not significant. A longer follow-up period is required to establish whether there is a benefit for overall survival.

In conclusion, our study showed improved progression-free survival and predictable tolerability of concurrent adjuvant cisplatin–gemcitabine chemotherapy compared with adjuvant cisplatin–fluorouracil chemotherapy after concurrent chemoradiotherapy. These findings support the potential role of adjuvant cisplatin–gemcitabine therapy as a treatment option for patients with locoregionally advanced nasopharyngeal carcinoma, however, further studies are needed in more globally diverse populations to confirm these findings and to determine the optimal therapeutic dose, and haematological toxicity of the cisplatin–gemcitabine regimen should be carefully managed during treatment.

Contributors

H-QM, L-QT, RS, and Q-YC were responsible for study conception and design, supervision of the project, quality assessment, review, and approval of the manuscript. L-TL, HL, YH, J-HY, S-YX, Y-YL, S-SG, and BQ contributed to the design of the clinical trial, writing of the protocol, recruitment and treatment of patients, data and trial management, data analysis and interpretation, and writing and final approval of the report. X-YL, D-PC, FJ, X-SS, Z-CY, S-LL, and D-HL were involved in the design of the clinical trial, recruitment and treatment of patients, data and trial management, and review of the report. J-BL, QL, PW, LG, H-YM, and FQ participated in the recruitment and treatment of patients, data and trial management, and the report preparation. QY and Y-JL contributed to the statistical analysis and interpretation, and the toxicity and data review. G-DJ and D-XW contributed to patient accrual and writing or review of the completed report. J-JY and CZ were involved in trial management and toxicity review. L-TL, J-HY, S-YX, L-QT, and H-QM accessed and verified the data. All authors accessed the data reported in the study and approved the final draft of the report.

Declaration of interests

We declare no competing interests.

Data sharing

Data that support the findings of this study are available on reasonable request to the corresponding author. De-identified participant data will be made available after approval by the corresponding author and Sun Yat-sen University Cancer Center. A detailed research protocol will be required for evaluation of the reasonability of the data request. The corresponding author and Sun Yat-sen University Cancer Center reserve the right to decide whether or not to share the data based on the materials provided by researchers.

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