This supplement contains the following items:

1. Final protocol (Page 2–56).

2. Final statistical analysis plan (Page 57–60).

Trial protocol

Prospective non-inferior clinical trial comparing radiotherapy alone or concurrent chemoradiotherapy in patients with intermediate risk nasopharyngeal carcinoma

Final version: Aug, 2019

Trial Code: SYSUCC-2014-11

Principal Investigator Dr. Jun MA
Department of Radiation Oncology
Cancer Center, Sun Yat-sen University
651 Dongfeng Road East, Guangzhou, China
Tel: (020)-87343469; Fax: (020)-87343295;
e-mail: majun2@mail.sysu.edu.cn

Participating Centers

Sun Yat-sen University Cancer Center, Guangzhou, China
Lead Coordinator： Dr. Ying SUN
Dr. Fang Yun XIE
Dr. Wei Han HU
Dr. Ling-Long TANG
Department of Radiation Oncology

First People's Hospital of Foshan
Lead Coordinator： Dr. Ning ZHANG
Department of Radiation Oncology

The Wuzhou red cross hospital
Lead Coordinator: Dr. Bin DENG
Department of Radiation Oncology

The fifth Affiliated Hospital of Sun Yat-sen University

Lead Coordinator: Dr. Zhi Bin CHEN
Department of Radiation Oncology

Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
Lead Coordinator: Dr. Kun Yu YANG
Department of Oncology

Data Manager & Statistician Dr. Qing Liu
Department of Epidemiology, Cancer Center, Sun Yat-sen University

CONTENTS

List of abbreviations and definition of terms

Abbreviation or special term	Explanation
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
CI	Confidence interval
CT	Computed tomography
CCRT	Concurrent chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DMFS	Distant-failure free survival
EBV	Epstein-Barr virus
EBV DNA	Epstein Barr Virus deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FFS	Failure-free survival
GCP	Good Clinical Practice
GTV	Gross tumor volume
HR	Hazard ratio
IC	Induction chemotherapy
ICRU	International Commission on Radiation Units and Measurements
IMRT	Intensity-modulated radiotherapy
LRRFS	Locoregional relapse-free survival
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NPC	Nasopharyngeal carcinoma
OS	Overall survival
PET/CT	Positron emission tomography/computer tomography

PRV	Planning organs at risk volume
PTV	Planning target volume
q3wks	Every 3 weeks
QLQ-C30	Quality of Life Questionnaire–Core 30 module
QoL	Quality-of-life
RT	Radiotherapy
SAE	Serious adverse event
SYSUCC	Sun Yat-sen University Cancer Center
UICC	Union for International Cancer Control
ULN	Upper limit of normal
WHO	World Health Organization

SCHEMA

Nasopharyngeal Carcinoma

Histology: non-keratinizing

Staging: T1–2N1/T2–3N0 by the AJCC 2009 System*

↓

REGISTRATION

↓

STRATIFICATION

(by stage: T2N0, T1N1, T2N1, T3N0)

↓

RANDOMIZATION

ARM 1	ARM 2
Radiotherapy (RT) alone	Radiotherapy (RT) + Concurrent Cisplatin q3wk × 3
Intensity-modulated radiotherapy (IMRT) Total Dose: ≥ 66 Gy Dose / Fraction: 2–2.2 Gy daily Fractions / week: 5	Intensity-modulated radiotherapy (IMRT) Total Dose: ≥ 66 Gy Dose / Fraction: 2–2.2 Gy daily Fractions / week: 5

Concurrent Cisplatin 100 mg/m^2 IV
Days 1, 22 & 43

(Chemotherapy may be given within ± 1 day relative to the scheduled dates)

* The 7th edition of the American Joint Commission on Cancer staging system

1.0 BACKGROUND

Nasopharyngeal carcinoma (NPC) is a unique type of head and neck malignancy with an extremely unbalanced endemic distribution, and an age-standardized incidence rate of 20–50 per 100 000 males in south China to 0.5 per 100 000 in mainly white populations. According to the International Agency for Research on Cancer, there were 84,400 cases of NPC, and 51,600 deaths from it, in 2008 [1].

According to our previous study, about 30–40% of patients with NPC treated with intensity-modulated radiotherapy (IMRT) and comprehensive treatment between 2003 and 2006 presented with stage II disease (according to the 7th edition of the AJCC staging system[2]) and had relatively more unsatisfactory survival outcome than those with stage I disease when treated with two- dimensional conventional radiotherapy (2DCRT). Currently, concurrent chemoradiotherapy, with or without sequential chemotherapy (i.e., induction or adjuvant chemotherapy), is the standard treatment modality for stage II NPC, according to the National Comprehensive Cancer Network (NCCN) guidelines. There have been retrospective studies that demonstrated conflicting results: Some studies showed no benefit for all endpoints [3] or benefit for distant control and OS [4] from induction chemotherapy, or only improved locoregional control from concurrent chemotherapy [5]. Finally, Chen et al.[6] confirmed the improvement in 5 year overall survival (OS), progression-free survival (PFS) and distant metastasis-free survival (DMFS) after the addition of concurrent chemotherapy by performing a randomized trial; therefore, establishing the role of concurrent chemotherapy in stage II populations. Remarkably, all these studies were based on two-dimensional conventional radiotherapy (2DCRT).

As one of the key milestones in the management of NPC, IMRT offers improved tumor target conformity, higher dose to the target, superior radiobiological effect of accelerated fractionation, and better protection of normal organs at risk[7,8]; therefore, IMRT has gradually replaced 2DCRT and changed the treatment modality of NPC. With

better treatment outcomes from IMRT than 2DCRT[9-11], the differential gain in survival from additional chemotherapy was speculated to be smaller within the framework of IMRT[12,13]. A previous study showed inspiring long-term survival of patients with stage II disease treated with IMRT alone, exceeding 90% for all endpoints[14]. However, for the only two studies that investigated the efficacy of additional chemotherapy for this population treated with IMRT, the results were conflicting and the study samples were small [13,15]. Luo et al.[15] focused on 69 patients with stage I–II NPC and demonstrated an improvement in survival for all endpoints from additional concurrent chemotherapy. Notably, although patients with stage I disease were included, the locoregional and distant control rate for the patients treated with IMRT alone remained at 81.4–84.0%, which was far lower than that reported in a previous large-sample study[14] and in our study. The main reason for this difference may be that (1) Luo and colleagues' study was from a non-endemic area of China, (2) 71% of patients involved had World Health Organization (WHO) II histology, and (3) the study sample was small. Thus, we should be cautious when applying their findings to endemic areas with patients who have predominantly WHO III histology, which was found to confer better prognosis.[16] By contrast, Tham et al.[13] reported no significant improvement in all survival endpoints from chemotherapy of any schedule in 107 patients with stage II NPC. However, they did not focus on concurrent chemotherapy because most patients were treated with induction chemotherapy alone and only eight patients received concurrent chemotherapy,[13] which was proven to be the most effective chemotherapy regimen for NPC[17,18] and is most widely used in clinical practice to attempt better survival according to the influential NCCN guidelines. Therefore, their findings may not be representative evidence for the efficacy of chemoradiotherapy and provide limited persuasion for treatment reconsideration from oncologists.

Moreover, better local control exerted by IMRT has also changed the hazard distribution for the prognoses of NPC [19]. For example, the stage T3N0M0 subgroup has

been reported to have similar survival to those with stage II disease in the modern era [19,20]. With respect to N stage, research showed that neck lymph nodes with neoplastic spread[21], a maximal axial diameter of neck lymph node ≥ 30 mm[22], and a positive neck lymph node at level IV and/or Vb[23] were associated with poorer prognosis. Besides, Chan et al.[24] found that within a group of patients with stage I–II NPC, high (⩾ 4000 copy/ml) levels of pretherapy plasma Epstein-Barr virus (EBV) DNA identified a poor-risk group with a probability of distant failure similar to that of patients with advanced stage disease. Consequently, we included stage II and T3N0M0 disease and excluded neck lymph node with neoplastic spread, maximal axial diameter of neck lymph node ⩾ 30 mm, positive neck lymph node at level IV and/or Vb, and pretherapy plasma EBV DNA level ⩾4000 copy/ml as intermediate risk NPC in the era of IMRT in the present study.

Additionally, the addition of platinum-based chemotherapy obviously increased severe adverse-effects [5,6,12,25,26], the risk of treatment-related mortality [27], and the cost. Therefore, the possibility of omitting chemotherapy in this subgroup of patients was appealing in case of an absence of survival benefit.

Thus, we conducted the first non-inferior randomized trial to determine the value of concurrent chemotherapy with cisplatin for intermediate risk patients with NPC treated using IMRT. Given the results of the clinical studies mentioned above, we decide to adopt the concurrent regimen as cisplatin 100 mg/m^2 on day 1, 22, and 43.

2.0 OBJECTIVES

2.1 The primary objective

To study whether patients with intermediate risk NPC (T1–2N1/T2–3N0M0) treated with RT alone (RT group) have a 3-year FFS rate lower by 10% or more than those who treated with chemoradiotherapy (CRT group).

2.2 **Secondary objectives**

To assess overall survival, locoregional failure-free survival, distant failure-free survival, the response rate, the toxicity profile, and quality of life.

3.0 ELIGIBILITY CRITERIA

3.1 **Eligibility checklist (Form A)**

a. Patients with newly histologically confirmed non-keratinizing (according to WHO histologically type) NPC.
b. Age between 18 and 65 years old.
c. Tumor staged as T1–2N1/T2–3N0 (according to the 7th AJCC edition).
d. No evidence of distant metastasis (M0).
e. Satisfactory performance status: Karnofsky scale (KPS) $\geq$ 70 (Appendix I).
f. Adequate bone marrow: leucocyte count $\geq 4 \times 10^9$/L, neutrophil count $\geq 2 \times 10^9$/L, hemoglobin $\geq$ 120 g/L for males, $\geq$ 120 g/L for females, and platelet count $\geq 100 \times 10^9$/L.
g. Normal liver function tests: Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) < 1.5 × the upper limit of normal (ULN) concomitant with alkaline phosphatase (ALP) $\leq$ 2.5 × ULN, and bilirubin $\leq$ ULN.
h. Adequate renal function: creatinine clearance $\geq$ 60 ml/min.
i. Patients must be informed of the investigational nature of this study and give written informed consent (**Form B**).

3.2 Essential staging investigations:

a Magnetic resonance imaging (MRI) or enhanced computed tomography (CT) of the nasopharynx and the neck.

b Chest x-ray (or CT of the thorax).

c Liver scan.

d Bone scan.

3.3 Exclusion criteria

a. Neck lymph node with extracapsular spread. Maximal axial diameter of neck lymph nodes ⩾ 30 mm, positive neck lymph node at level IV or lower.

b. Pretherapy plasma EBV DNA level ⩾ 4000 copy/ml.

c. WHO type keratinizing squamous cell carcinoma or basaloid squamous cell carcinoma.

d. Age ≥ 65 or < 18.

e. Treatment with palliative intent.

f. Prior malignancy except adequately treated basal cell or squamous cell skin cancer, or *in situ* cervical cancer.

g. Pregnancy or lactation (consider a pregnancy test in women of child-bearing age and emphasize effective contraception during the treatment period).

h. History of previous RT (except for non-melanomatous skin cancers outside the intended RT treatment volume).

i. Prior chemotherapy or surgery (except diagnostic) for primary tumors or nodes.

j. Any severe intercurrent disease, which might bring unacceptable risk or affect the compliance of the trial, for example, unstable cardiac disease requiring treatment, renal disease, chronic hepatitis, diabetes with poor control (fasting plasma glucose > 1.5 × ULN), and emotional disturbance.

3.4 Criteria for removal from protocol treatment

a. Disease progression.

b. Unacceptable toxic effects. The reason(s) must be recorded in Form D.

c. Treatment delayed continuously more than 3 weeks, whatever the reason for

treatment delay.

d. Patients suffering from an intercurrent disease or having other conditions that significantly affect the assessment of clinical status or necessitate discontinuation of the drug, or both.
e. Poor compliance to drugs or clinical observation, or receipt other anti-tumor treatment.
f. A patient might withdraw from the study at any point for any reason.

4.0 STRATIFICATION / RANDOMIZATION SCHEME

4.1 **Stratification**:

Patients will be stratified according to the treatment centers and the stage.

4.2 **Registration and randomization**:

All the patients must be registered with the coordinator of the respective center prior to initiation of treatment. The allocation list was generated using a computer. Eligible patients will be randomized using a 1:1 allocation of patients to ARM1 and ARM2 with a block size of n = 4. Only the statistician and the study coordinator, who have no clinical involvement, are aware of the block structure, as recommended by Freedman et al. [29] After completion of all screening procedures, the investigators at each center will call the study coordinator and obtain the treatment assignments. Notably, the statistician and the study coordinator have no clinical involvement during the trial. Treatment group assignment is not masked.

Eligible patients will be randomized to either:

- ARM 1: Radiotherapy alone (see Section 6.1).
- ARM 2: Concurrent chemoradiotherapy (see Section 6.2)

5.0 END POINT EVALUATION CRITERIA AND THEIR DEFINITIONS

5.1 Primary endpoint

The primary end point is failure-free survival (FFS), which is defined as the interval between randomization and distant failure, locoregional failure, or death from any cause, whichever happened first.

5.2 Secondary endpoints

5.2.1 **Overall survival (OS):** OS is defined as the time from random assignment to death from any cause.

5.2.2 **Distant metastasis-free survival (DMFS):** DMFS is defined as the interval from randomization to the first distant metastasis or death from any cause.

5.2.3 **Locoregional relapse-free survival (LRRFS):** LRRFS is defined as the interval from randomization to the first local or regional recurrence, or death from any cause.

Note: Patients whose first event is a distant metastasis will be censored for locoregional recurrence and vice versa. If both distant metastasis and locoregional recurrence occur simultaneously, patients are considered as having an event for both DMFS and LRRFS.

5.2.4 Safety includes the incidence of acute toxicity (either hematological or non- hematological) during the treatment period. The Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, will be used for grading of toxic effects (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). Late radiation toxicities will be assessed according to the Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) late radiation

morbidity scoring scheme, including skin, neck tissue damage, hypothyroidism, dry mouth, dysphagia, trismus, and other adverse events.

5.2.5 Health-related quality of life is measured through paper-based questionnaires using the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3.0 (https://qol.eortc.org/questionnaire/eortc-qlq-c30/). Assessments will be considered complete only if all the questions were answered.

6. TREATMENT PLAN

6.1 **ARM 1 Treatment Schedule:** Radiotherapy alone

AGENT	DOSE	ROUTE	DAYS	INTERVAL	NOTES
RT	2–2.20 Gy/day	IMRT	Once daily, 5 fractions per week for ≥ 30 fractions		See following sections for directions

6.1.1 Equipment - Linear accelerators

6.1.2 Patients are recommended to be immobilized in the supine position and use a thermoplastic mask covering the head, neck, and shoulder. Both non-enhanced CT (for dose calculation) and contrast-enhanced CT (for target delineation) images will be obtained from the vertex to 2 cm below the sternoclavicular joint, with 3-mm slices.

6.1.3 Target Volume Determination for IMRT:

Definition of target volumes is according to the International Commission on Radiation Units and Measurements reports 50 and 62. The principles of target volume determination for IMRT are as follows:

Principle of target volume determination for IMRT

Term	Definition	Note
Gross tumor volume (GTV)	Determined by physical examination, imaging (including MRI and PET/CT, if available) and endoscopic findings, including GTVnx and GTVnd.	
GTVnx	Includes the primary tumor volume and the enlarged retropharyngeal nodes	
GTVnd	The involved cervical LNs	
CTV1	GTVnx plus a 5–10-mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the high-risk sites of microscopic extension and the whole nasopharynx	The volume should also include the entire mucosal stratum and 5 mm of submucosal stratum of nasopharynx
CTV2	CTV1 plus a 5–10-mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the low-risk sites of microscopic extension, including the foramen lacerum, sphenoid sinus, clivus, oval foramen, parapharyngeal space, pterygoid fossae, the posterior parts of the nasal cavity, pterygopalatine fossae, retropharyngeal nodal regions, the cervical level where the involved LNs were located, and the elective neck area from level II to V (according to patient's treatment group)	Level Ib is irradiated electively if: (1) with involved level Ib LNs, (2) level IIa LNs has extracapsular extension or diameter ≥ 3 cm, (3) there exists extensive nodal disease in the ipsilateral neck, (4) the soft or hard palate, oral cavity, or ipsilateral nasal cavity is grossly involved

PTV	PTVnx, PTVnd, PTV1, PTV2 respectively refers to GTVnx, GTVnd, CTV1, and CTV2 plus an additional margin, with an anterior, superior, inferior, lateral extension of 5 mm, and a posterior extension of 3 mm in general, to compensate for the uncertainties in treatment set-up and internal organ motion.	
Organs at risk	Brainstem, temporal lobe, optic nerves, optic chiasm, lens, eyeballs, pituitary gland, parotid gland, salivary gland, mandible, larynx, oral cavity, inner and middle ear, the temporomandibular joint, thyroid gland, and pharyngeal constrictor muscle	Organs can be added or removed according to actual situations

6.1.4 The prescribed recommended dose is 68–70 Gy, with 2.0–2.2 Gy per fraction administered over 6–7 weeks (once per day, 5 fractions every week). The dose is 60–62 Gy and 54–56 Gy for the PTVs derived from CTV1 and CTV2, respectively. The radiation dose could be adjusted moderately according to the tumor volume.

6.1.5 Normal tissue dose constraints:

Normal tissue dose constraints by structure

Structure	Dose constraints
Spinal cord	Dmax* ≤ 45 Gy
Spinal cord_PRV	D1† ≤ 50 Gy
Brain stem	Dmax ≤ 54 Gy
Brain stem_PRV	D1 ≤ 60 Gy

Optic nerves	Dmax ≤ 54 Gy
Optic nerves_PRV	D1 ≤ 60 Gy
Optic chiasm	Dmax ≤ 54 Gy
Optic chiasm_PRV	D1 ≤ 60 Gy
Temporal lobe	Dmax ≤ 60 Gy
Temporal lobe_PRV	D1 ≤ 65 Gy
Lens	Dmean‡ < 8 Gy
Pituitary	Dmax < 60 Gy
Thyroid	Dmean < 35 Gy
Eyes	Dmean < 35 Gy
Mandible	Dmax < 70 Gy
Temporomandibular Joint	Dmax < 70 Gy
Parotid	Dmean < 26 Gy
Parotid	V30§ < 50%
Cochlea	Dmean < 50 Gy
Larynx	Dmean < 45 Gy
Trachea	Dmean < 45 Gy
Esophagus	V35 < 50%

PRV = planning organ at risk volume.

* Maximum point dose to the target volume.

† Dose received by 1% of the target volume.

‡ Mean dose to the target volume.

§ At least 50% of the gland will receive < 30 Gy (should be achieved in at least one gland).

6.16 Quality assurance of RT

Quality assurance of target delineation and dose coverage will be performed by the research team at Sun Yat-sen University Cancer Center. In addition, quality assurance of radiotherapy procedures will be performed by the research team at each participating center.

6.2 ARM 2 Treatment Schedule: Concurrent chemoradiotherapy

(Chemotherapy may be given within +/- 1 day relative to the scheduled dates)

6.2.1 Concurrent chemotherapy

AGENT	DOSE	ROUTE	DAYS	INTERVAL	NOTES
Cisplatin	100 mg/m^2	Infusion	Days 1, 22, and 43 (3 cycles)	21 days	See following sections for directions
RT	2–2.20 Gy/day	IMRT	Once daily, 5 fractions per week for ≥ 30 fractions		See 6.1

6.2.2 Administration:

6.2.2.1 During chemotherapy, patients are monitored using laboratory tests and monitored clinically during chemotherapy at least once per week and on the day before day 1 of each cycle.

6.2.2.2 Prehydration, posthydration. and the mannitol infusion scheme for Cisplatin will follow the individual institutional policy.

6.2.2.3 Before and after cisplatin, antiemetics, such as the 5-HT3-receptor antagonist, dexamethasone, and metoclopramide should be administered.

6.2.2.4 Measure fluid intake and output after Cisplatin, and give additional IV fluid to replace emesis or excess urinary output.

6.2.2.5 If only two cycles of concurrent chemotherapy are completed during the RT

phase, then the third cycle of concurrent chemotherapy should be given within a week after completion of RT.

6.2.2.6 Chemotherapy must not be administered until the absolute neutropenia count is >1,500 and the platelet count is > 100,000.

6.3 Salvage chemotherapy treatment

6.3.1 EBV evaluation at 1 week after completion of RT is required. If negative, follow up; If positive, patients should receive salvage chemotherapy of Cisplatin + Fluorouracil (5-Fu).

AGENT	DOSE	ROUTE	DAYS	INTERVAL	NOTES
Cisplatin	80 mg/m^2	Infusion	Days 29, 57, and 85 (3 cycles)	28 days	See following sections for directions
5-Fu	800 mg/m2/	Continuous intravenous infusion for 120 hours	Days 29–33, 57–61, and 85–89	28 days	See following sections for directions

7.0 DRUG INFORMATION

7.1 Cisplatin

7.11 Pharmacology and Pharmacokinetics: The dominant mode of action of Cisplatin appears to be inhibition of the incorporation of DNA precursors,

although protein and RNA synthesis are also inhibited. Plasma levels of Cisplatin decay in a biphasic mode, with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is caused by protein binding, which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete, with only 27 to 45% of the radioactivity excreted in the first 5 days. The initial fractions of radioactivity are largely unchanged drugs. Although this drug seems to act as an alkylating agent, data also indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

7.12 Toxicity: Human toxicity includes nausea, vomiting, anorexia, loss of taste, renal toxicity (with an elevation of BUN, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss, which initially is in the high-frequency range, as well as tinnitus), peripheral neuropathy, allergic reactions, and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about 2 weeks, with recovery generally at about 3 weeks after the initiation of therapy. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylate or combination chemotherapy.

7.13 Administration: Cisplatin should be given immediately after preparation as a rapid intravenous injection or slow intravenous infusion.

7.14 Storage & Stability: The intact vials should be stored under refrigeration. However, once reconstituted, the solution should be kept at room temperature to avoid precipitation. The solution should be used within 8 hours of reconstitution because of a lack of preservatives. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5 1/2 NS (precipitation occurs in D5W). Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

8.0 TOXICITY MONITORED AND DOSAGE MODIFICATIONS

8.1 Chemotherapy

Patients will be examined and graded for subjective/objective evidence of toxicities according to the CTCAE toxicity criteria (Appendix III).

8.1.1 There will not be any dose escalation of Cisplatin.

8.1.2 Chemotherapy dosage modifications are based on nadir counts and interim non-hematological toxicities of the preceding cycle.

8.1.3 A cycle can be delayed for up to 2 weeks to allow for a reduction in the severity of toxic events of grade 3/4 to a severity of grade 1 or less (with the exception of alopecia, fatigue, malaise, and nail changes). Delays beyond 2 weeks require discontinuation of chemotherapy.

8.1.4 Chemotherapy must be withheld until the neutrophil count is $\geq 1.5\times10^9$/L and the platelet count is $\geq 100\times10^9$/L.

8.1.6 Dosage adjustments for the period of chemotherapy:

8.1.6.1 Concurrent chemotherapy

Cisplatin dose levels

–2	–1	Starting dose
60 mg/m^2	80 mg/m^2	100 mg/m^2

8.1.6.1 Salvage chemotherapy

Cisplatin dose levels

–1	Starting dose
60 mg/m^2	80 mg/m^2

8.1.7 Dosage adjustments for hematological toxicity:

8.1.7.1 Dose adjustment of Cisplatin is based on the nadir counts as follows:

Neutrophils		Platelets	Dose Adjustment
$\geq 1.0 \times 10^9$/L	and	$\geq 75 \times 10^9$/L	Full dose

0.5 to < 1.0 × 10^9/L	and/or	50 to < 75 × 10^9/L	Decrease 1 level
< 0.5 × 10^9/L or febrile neutropenia or neutropenic infection	and/or	25 to < 50 × 10^9/L	Decrease 2 levels

8.18 Dosage adjustments for non-hematological toxicity:

8.1.8.1 Hypersensitivity reactions: Severe hypersensitivity reactions (grade 3 or more) related to Cisplatin require immediate discontinuation of chemotherapy. Patients with a history of severe hypersensitivity reactions are withdrawn from the study.

8.1.8.2 Gastrointestinal toxicity (vomiting or diarrhea):

Toxicity		Dose Adjustment	
		Cisplatin	
Gastrointestinal toxicity			
II°			
III°			
IV°		Stop chemotherapy	

8.1.8.3 Renal toxicity

8.1.8.3.1 Chemotherapy must be withheld until creatinine clearance is ≥ 60 ml/min.

8.1.8.3.2 Chemotherapy must be stopped totally if creatinine clearance is

< 40 ml/min.

8.183.3 The dosage adjustments for creatinine clearance are as follows:

Creatinine clearance	Cisplatin
≥ 60 ml/min	Full dose
40–< 60 ml/min	Decrease 1 level
< 40 ml/min	Stop chemotherapy

8.1.8.4 Hepatic toxicity:

8.1.8.4.1 Chemotherapy must be withheld until bilirubin is ≤ 1.5 × ULN and AST and/or ALT are ≤ 2.5 × ULN, concomitant with alkaline phosphatase (ALP) ≤ 2.5 × ULN.

8.1.8.4.2 Chemotherapy must be stopped totally if bilirubin is > 2 × ULN, or AST/ALT are > 5 × ULN and/or ALP is > 5 × ULN.

8.1.8.4.3 The dosage adjustment of Cisplatin for aminotransferase is as follows:

Side Effect	Dose Adjustment
AST/ALT > 2.5 to ⩽ 5 × ULN and/or ALP > 2.5 to ⩽ 5 × ULN	Decrease 1 level
AST/ALT > 5 × ULN and/or ALP > 5 × ULN	Stop chemotherapy

8.1.8.4.4 Patients who are hepatitis B virus (HBV) carriers are monitored with serum HBV DNA assays before and during chemotherapy. They are suggested to see a specialist in hepatitis for antiviral therapy before chemotherapy.

8.1.8.5 Neurological toxicity: The dosage of Cisplatin decreases 1 level when patients suffer from neurotoxicity of grade 2. Patients with neurotoxicity of grade 3 or more are withdrawn from the study.

8.1.8.6 Ototoxicity: If patients develop clinical evidence of significant ototoxicity, audiometric evaluation is required. Patients with ototoxicity of grade 3 or more are withdrawn from the study.

8.1.8.7 Pulmonary toxicity: In cases of lung toxicity of grade 3 or more, Gemcitabine should be discontinued immediately and appropriate supportive care measures instituted.

8.1.9 Patients should be cautioned on the need for contraception during the treatment period.

8.1.10 Any death possibly attributed to drug therapy must be reported to the study coordinator and central office.

8.2 Radiotherapy

8.2.1 RT adjustments

Acute toxicities will be assessed and graded according to the CTCAE toxicity criteria (Appendix III). We allow no radiotherapy dose modifications.

8.2.2 RT adjustments for non-hematological toxicity:

The side effects of RT might include mucositis, anorexia, and skin reaction. The investigator will manage these conditions according to the clinical practice at the institution. Treatment interruptions are allowed if a grade 4 reaction or severely symptomatic reactions occur (in the judgment of the attending clinician).

8.2.3 RT adjustments for hematological toxicity:

RT will be withheld until the absolute neutrophil count is $\geq 0.5 \times 10^9$/L and the platelet count is $\geq 25 \times 10^9$/L.

9.0 ASSESSMENT AND FOLLOW-UP

9.1 Before treatment

All patients will receive standardized management for NPC, and they need to complete a series of examinations and provide relevant information for pathological diagnosis and clinical stage before admission into the trial:

a. Complete review of medical history
b. Collection of personal data
c. Present medications and treatment
d. Body examinations, including weight, height, and vital signs
e. Physical examination of the head and neck, including the nasopharynx and cervical LNs
f. Physical examination of the nervous system
g. Nasal endoscopy and lesion biopsy
h. Routine blood analyses
i. Blood biochemistry
j. Routine urine analyses

k. EBV serological tests (EBV antibodies)
l. EBV DNA is optional, depending on the laboratory availability of the participating centers
m. EKG
n. Imaging test of the tumor (enhanced MR of the head and neck, or CT if MRI was contraindicated)
o. Chest film or CT
p. Abdominal ultrasonography or CT
q. ECT bone scan
r. Positron emission tomography/computer tomography (PET/CT) is optimal and is performed at the discretion of the attending physician
s. EORTC QLQ-C30 and QLQ-H&N35 version 1.0 questionnaires are used to assess the patient's quality of life before the beginning of treatment.
t. Signed informed consent

9.2 During treatment

The following aspects need to be assessed from the start of treatment to the end.

a. MR of the head and neck should be performed before and after treatment. Chest film and abdominal ultrasonography are re-examined after treatment.
b. The use of concomitant drugs
c. General conditions
d. Acute toxicities assessment (NCI-CTC, version 4.0), including hypothyroidism, mucositis, and ototoxicity.
e. Routine blood analyses and blood biochemistry are required weekly during treatment.

f. Nasopharyngoscopy is performed before and after the treatment course, and is also required after each cycle of chemotherapy. The regression of enlarged lymph nodes is observed and measured.

9.2.1 Record of treatment details and acute reactions (Form D)

9.2.1.1 RT: RT technique, dose/fraction, total dose, and overall time should be recorded.

9.2.1.2 CRT: number of cycles, dose, delay of treatment time, and the cause of deviation from the scheduled treatment should be recorded.

9.2.1.3 The incidence of acute toxicity ≥ grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program of the National Cancer Institute should be recorded[30] (Appendix III).

9.3 Assessment during follow-up

9.31 The nasopharynx should be assessed using endoscopy approximately 4 weeks after completion of RT. Further investigations using MRI or CT should be arranged 16 weeks after the completion of RT. Treatment responses are also evaluated according to t the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)[31]. Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in their short axis to < 10 mm. Partial response (PR): At least a 30% decrease in the sum of diameters of

target lesions, taking as a reference the baseline sum diameters. Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as a reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study. If residual disease is found, whether to treat and which treatment modalities to be employed will be decided by individual clinicians. For statistical purposes, any residual disease found 16 weeks after the completion of RT will be regarded as local failure.

9.3.2 Participants will be followed-up at least every 3 months during the first 3 years, then every 6 months thereafter until death. Assessment of recurrence will include: Physical examination, hematology profiles, biochemistry profiles, nasopharyngeal fiber optic endoscopy, MRI or enhanced CT (if patients had contraindications for MRI) of nasopharynx and neck, CT examination of the chest and abdomen, and skeletal scintigraphy; plasma EBV DNA load tested in each institution if available; PET/CT in patients with detectable plasma EBV DNA, or those with a suspicion of locoregional disease or distant metastasis.

9.3.3 Local failure will be determined using histological pathology. Regional failure will be determined using fine-needle aspiration or surgical pathology of the cervical LNs. Distant metastasis will be determined using histological pathology if possible. Even in participants with long-term disease-free survival, MRI showing skull base bone destruction might persist. It is necessary to

combine clinical features and laboratory/imaging examinations to determine whether treatment failure has occurred, including symptoms, signs, EBV DNA level, PET/CT, and dynamic changes of MR images. If it is difficult to obtain histological evidence or if a patient refuses biopsy, but the imaging performance is typical of treatment failure (e.g., progression of skull base bone destruction, recurrent primary lesion, necrosis or progressive enlargement of LN), local or regional failure can be clinically diagnosed once approved by the investigators at each center. Records should be kept of the dates of diagnosis of locoregional and distant failures; the sites should also be recorded.

9.3.4 All enrolled patients will be followed-up until death. The cause of death will be recorded. Death from an unknown cause will be counted as death caused by NPC if the disease is still present at the last follow-up assessment.

9.3.5 The earliest date of detecting symptomatic late toxicities ≥ grade 3 (exception: endocrine function and temporal lobe necrosis – the earliest date of grade 1-2 toxicity should be recorded as well), and the eventual maximum grade according to the Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) should be recorded[30] (Appendix II).

Schema of follow-up procedures

Time point	**Physical examinations**	**Nasophary ngoscopy**	**EBV DNA (if available)**	**MRI of nasopharynx and neck**	**CT of chest and abdomen**	**Bone scan**
3 months	√	√	√	√	√	√
6 months	√	√	√	opt	opt	
9 months	√	√	√	√	√	√

12 months	√	√	√	opt	opt	
15 months	√	√	√	√	√	√
18 months	√	√	√	opt	opt	
21 months	√	√	√	√	√	√
24 months	√	√	√	opt	opt	
27 months	√	√	√	√	√	√
30 months	√	√	√	opt	opt	
33 months	√	√	√	√	√	√
36 months	√	√	√	opt	opt	
42 months	√	√	√	√	√	√
48 months	√	√	√	√	√	
54 months	√	√	√	√	√	√
60 months	√	√	√	√	√	

Abbreviations: opt = optional; MRI = magnetic resonance imaging; EBV = Epstein-Barr virus.

10.0 SAFETY EVALUATIONS

10.1. Adverse events: Adverse events refer to any adverse medical events that occur in the patient. They do not necessarily have a causal relationship with treatment. Researchers should keep a detailed record of any adverse events that occur in the patients. The record of adverse events shall include a description of the adverse events, the time of occurrence, severity, duration, measures taken, and the final results and outcomes. Researchers should assess the possible association between the adverse events and the tested drugs according to the four-level classification of "positive relevance, possible irrelevance, positive irrelevance, and inability to determine."

10.2. Criteria for toxicity evaluation: Acute toxic effects will be graded using the CTCAE (version 4.0) (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-

06-14_QuickReference_5x7.pdf).

10.3. Serious adverse events (SAEs)

10.3.1 SAEs include: Death within 30 days after receiving the tested drug, or death caused by delayed toxicity of the test drug 30 days later; grade 3 or 4 toxicities that are considered life-threatening or require hospitalization for 7 days or more; those that cause permanent disability or dysfunction; that lead to secondary tumors; cause reactions to drug overdoses; or other unpredictable adverse drug reactions.

10.3.2 The following conditions do not need to be reported as SAEs: death caused by cancer progression; hospitalization for chemotherapy-related toxicity, such as bone marrow suppression, fever, nausea, vomiting, etc.; secondary hospitalization because of the tumor, such as weight loss, fatigue, electrolyte disturbance, pain treatment, anxiety, and palliative treatment; and planned hospitalization.

10.3.3 Reporting system for SAEs: This trial adopts a centralized safety collection with addresses for safety reporting by sites. Once an SAE is identified, it should be immediately reported to the principle investigator of the branch centers, the corresponding ethics committee, the trial leading center (SYSUCC), the sponsor investigator (Prof. Jun Ma; Tel: (020)-87343469; Fax: (020)-87343295), and the national health authorities within 24 hours, and recorded on the case report form. With the participation of key researchers, appropriate measures should be taken quickly. Toxic reactions and deaths that occur 30 days after the end of the trial do not need to be reported if it can be clearly determined that they have nothing to do with the treatment

11.0 STUDY CALENDAR AND DATA SUBMISSION SCHEDULE

According to protocol requirements for all eligible patients registered, data must be submitted to the central office according to protocol requirements for all eligible patient registered, whether or not the assigned treatment is administered.

11.1 Arm I: Radiotherapy alone

Time	Event	Laboratory#	Form
Pre-study	Registration Stratification Randomization	Physical examination, endoscopy, blood routine, liver function test, creatinine clearance, MRI/CT of the nasopharynx and neck region, chest x-ray, liver scan, electrocardiogram, bone scan, EBV evaluation	Form A. Eligibility checklist & registration Informed consent Form B. Imaging & clinical stage QoL
Week 1–6/7	Radiotherapy alone		Form C. Treatment & acute toxicity QoL
Post-RT 1 week	Assessment	EBV evaluation	Form C. Treatment & acute toxicity if salvage chemotherapy administered
Post-RT 4 and 16 weeks*	Assessment	Physical examination, endoscopy, MRI/CT of the nasopharynx and neck region, chest x-ray, liver scan, bone scan	Form D. Progress events
Every 3 months	Follow-up detection of failure	As indicated (biopsy is preferred)	Form D. Progress events

during the first 3 years	or late toxicity		
Every 6 months until death	Follow-up detection of failure or late toxicity	As indicated (biopsy is preferred)	Form D. Progress events

* Individual clinicians can choose the time for the first assessment after the completion of RT.

11.2 Arm II: Concurrent chemoradiotherapy

Time	Event	Laboratory#	Form
Pre-study	Registration Stratification Randomization	Physical examination, endoscopy, blood routine, liver function test, creatinine clearance, MRI/CT of the nasopharynx and neck region, chest x-ray, liver scan, electrocardiogram, bone scan	Form A. Eligibility checklist & registration Informed consent Form B: Imaging & clinical stage QoL
Week 1–6/7	Concurrent chemoradiotherapy		Form C. Treatment & acute toxicity QoL
Post-RT 1 week	Assessment	EBV evaluation	Form C. Treatment & acute toxicity if salvage chemotherapy administered
Post-RT 4 and 16 weeks*	Assessment	Physical examination, endoscopy, MRI/CT of nasopharynx and neck region, chest x-ray, liver scan, bone scan	Form D. Progress events

Every 3 months during the first 3 years	Follow-up detection of failure or late toxicity	As indicated (biopsy is preferred)	Form D. Progress events
Every 6 months until death	Follow-up detection of failure or late toxicity	As indicated (biopsy is preferred)	Form D. Progress events

* Individual clinicians can choose the time for the first assessment after completion of RT.

Form E, summarizing progress events, are to be completed every 3 months during the first three years, and then every 6 months until death, starting from 16 weeks after completion of RT until death, irrespective of the follow-up intervals.

12.0 SECURITY MEASURES AND QUALITY CONTROL

a. Train all the research staff before the study. Arrange one doctor in each participating center to take charge of tumor staging (according to the 7th AJCC edition), and make sure that every patient enrolled meets the criteria. Patients are given random numbers to determine which treatment group they are in.
b. Develop all kinds of Standard Operation Procedures associated with this study.
c. Develop a standardized evaluation system to unify the diagnostic criteria.
d. Make a monitoring plan of adverse effects and an emergency plan.
e. A research plan is made by all participating centers and approved by the Ethics Committee.
f. Establish a professional statistical plan.
g. Ensure that every participating center conducts the study at the same pace.
h. Arrange a quality controller, make a quality control plan, and check regularly.

i. Set up a coordination committee, a curative effect judging group, and a follow-up team.

13.0 DATA PROCESSING AND STATISTICAL ANALYSIS

13.1 Case report form (CRF)

A CRF is used to record clinical data in a clinical trial. All relevant information of the patient in the trial should be recorded in a timely and true manner. As original material, the CRF should not be changed at will. The researcher should sign and date when it is really necessary to correct the data. The CRF is triplicated and should be handed over to the statistical experts, researchers, and sponsors for storage after the trial.

13.2 Data management

After receiving the CRF, the data administrator will check the data and feedback possible questions. The investigators should verify the problem and respond as soon as possible. Then, the data administrator establishes a database in time and double-inputs the data. The principal investigator, data administrator, and statistician lock the database, which must be backed up. To ensure data security, non-permitted personnel cannot access and modify the trial data. Any data changes need to be approved by the principal investigator, statistician, and data administrator.

13.3 Sample size determination:

The primary endpoint is FFS. Based on the study by Zhang et al. (Zhang F, Zhang Y, Li WF, et al. Efficacy of Concurrent Chemotherapy for Intermediate Risk NPC in the Intensity-Modulated Radiotherapy Era: a Propensity-Matched Analysis. Scientific reports 2015; 5: 17378.), we suppose that the 3-year FFS, about 90%, is

the same between RT alone and CCRT in the treatment of patients with NPC. We specify a non-inferiority margin of 10%, which is regarded as clinically acceptable in view of the expected reduced toxic effects and increased quality of life of patients receiving RT alone. Hence, to demonstrate non-inferiority, the upper limit of the 95% confidence interval (CI) for the difference in 3-year FFS between the two groups could not exceed 10%. With 80% power and a one-sided type I error of 5%, we needed at least 338 patients (169 in each group) to allow for a 5% dropout or loss to follow-up. We have the following set of hypotheses:

H_0: The RT group has a 3-year FFS rate not lower than the CRT group by 10% or more;

H_A: The RT group has a 3-year FFS rate lower than the CRT group by 10% or more.

Historical data suggest that a 3-year FFS rate of 90% can be expected for the CRT group.

13.4 Statistical analysis

Efficacy analyses are performed in the intention-to-treat population, which included all randomly assigned patients. Safety data and life quality data comprise all patients who had started the randomly assigned treatment. A comparison of the FFS, the primary end point, of ARM I with ARM II using the log-rank test will be used to evaluate efficacy. Similar comparisons will be made for OS, DMFS, and locoregional FFS. Cox regression analyses will be performed to quantify the effect of predictors on the survival outcomes. Analysis of FFS based on the per-protocol population will also be performed. The per-protocol population

comprises the eligible patients who started the randomly assigned treatment (received at least one dose of cisplatin) or observation. The statistical test for FFS is one-sided, and a p value < 0.05 is considered statistically significant. The left statistical tests were two-sided, and a p value < 0.05 is considered statistically significant.

Analysis includes:

a. General information:

   The distribution of clinical factors, including age, sex, and stages, are summarized using descriptive statistics.

b. Adverse effects:

   Acute and late radiation-related toxicities and sequelae in each group are summarized using descriptive statistics.

c. Long-term curative effect:

   3-year and 5-year FFS, OS, DMFS, and LRRFS rates are calculated according to follow-up visits.

d. Total data analysis:

   An overall analysis is conducted after data summarization.

e. Subgroup analysis: An interaction analysis for FFS based on the intention-to-treat population will be carried out to assess whether the treatment effect varies in subgroups defined using sex, age, KPS, T and N categories. A test of treatment-by-covariate interaction based on the Cox proportional-hazards model will be used.

f. Quality of life: EORTC QLQ-C30 questionnaires are used to assess the patients' quality of life. Patient responses to each of the EORTC QLQ-C30 questionnaire items are scored into scales representing functioning, symptoms, or health status; all items pointing to a domain will be averaged and the results

will be transformed into a 0–100 scale according to the EORTC scoring manual. Higher scores on the functioning scales and global health status suggest better function or health, whereas higher scores on the symptom scales indicate more severe symptoms. The difference in quality of life scores between groups will be compared using Mann–Whitney U tests.

14.0 ETHICAL CONSIDERATIONS

14.1 Ethical norms: This clinical trial must comply with the Helsinki Declaration, the Drug Clinical trial Management Code (GCP) issued by the SFDA, and related regulations. Before the commencement of this experiment, the approval of the ethics committee of each center must be obtained. During the clinical study, any changes made to this trial protocol should be reported to the Ethics Committee and placed on record.

14.2 Informed consent: Patients must provide informed consent to participate in the trial before receiving treatment to protect the legitimate rights and interests of the patients. It is the responsibility of the researcher to provide the subject, or his or her designated representative, with a complete and comprehensive description of the purpose of the study, the effects of the drug, the possible side effects, and possible risks, and to inform the subject of their rights. Conversation is a very important part of the informed consent process. If the subject and his or her legal representative are illiterate, the informed consent process shall be attended by a witness, who shall sign the informed consent form after oral consent by the subject or his or her legitimate representative. A copy of the informed consent form and the contact information for the researcher and the ethics committee must be provided to the patient on request.

14.3 Emergency measures: The test site must be equipped with the necessary medical rescue equipment, first aid drugs, and emergency measures.

14.4 Serious adverse event reporting: All serious and unexpected adverse experiences or death related to the drugs or radiotherapy must be reported to the study coordinator immediately (Form F). Serious adverse events (SAEs) to be reported include all deaths during or within 30 days of protocol treatment regardless of cause, grade 5 toxicity, life-threatening grade 4 toxicity, and/or unexpected toxicity. The Study Coordinator of the respective center should complete Part A of Form F and fax this within 24 hours to the Central Secretary (Dr. Jun Ma). Together with the Principal Investigator, appropriate and prompt action will be taken if warranted. Reactions and deaths beyond 30 days from protocol treatment that are judged definitely unrelated to treatment should not be reported.

15.0 QUALITY ASSURANCE

a. Train all the research staff before the study. Arrange one doctor in each participating centre to take charge of tumour staging (according to the 7th AJCC edition), and to make sure that every patient enrolled meets the criteria. Patients are given random numbers to determine which treatment group they are in.
b. Develop all kinds of Standard Operation Procedures associated with this study.
c. Develop a standardized evaluation system to unify diagnostic criteria.
d. Make a monitoring plan of adverse effects and an emergency plan.
e. A research plan is made by all participating centres and approved by the Ethics Committee.
f. Establish a professional statistical plan.
g. Ensure that every participating centre conducts the study at the same pace.

h. Arrange a quality controller, make a quality control plan, and check regularly.

i. Set up a coordination committee, a curative effect judging group, and a follow-up team.

16.0 MANAGEMENT OF TRIAL DRUGS

The management, distribution, and recovery of clinical drugs in this trial shall be the responsibility of the designated researcher. The researcher must ensure that all trial drugs are used only for subjects participating in the clinical trial, that their doses and usage are in accordance with the trial scheme, and that the remaining drugs are returned to the manufacturer. Experimental drugs should not be transferred to any non-clinical trial participant.

17.0 PROGRESS OF CLINICAL TRIALS

Expected trial start time: November 2015.

Expected completion time: November 2020.

Expected end of trial: December 2021

18.0 BIBLIOGRAPHY

[1] Jemal A, Bray F, Center MM, et al. Global cancer statistics [J]. CA Cancer J Clin, 2011,61(2):69-90.

[2] Edge SB, Byrd DR, Compton CC, et al. Ajcc cancer staging manual [M]. 7th. New York: Springer, 2010.

[3] Song CH, Wu HG, Heo DS, et al. Treatment outcomes for radiotherapy alone are comparable with neoadjuvant chemotherapy followed by radiotherapy in early-stage nasopharyngeal carcinoma [J]. Laryngoscope, 2008,118(4):663-670.

[4] Chua DT, Ma J, Sham JS, et al. Improvement of survival after addition of induction chemotherapy to radiotherapy in patients with early-stage nasopharyngeal carcinoma: Subgroup analysis of two phase iii trials [J]. Int J Radiat Oncol Biol Phys, 2006,65(5):1300-1306.

[5] Xu T, Hu C, Wang X, et al. Role of chemoradiotherapy in intermediate prognosis nasopharyngeal carcinoma [J]. Oral Oncol, 2011,47(5):408-413.

[6] Chen QY, Wen YF, Guo L, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage ii nasopharyngeal carcinoma: Phase iii randomized trial [J]. J Natl Cancer Inst, 2011,103(23):1761-1770.

[7] Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: An update of the ucsf experience [J]. Int J Radiat Oncol Biol Phys, 2002,53(1):12-22.

[8] Kwong DL, Sham JS, Leung LH, et al. Preliminary results of radiation dose escalation for locally advanced nasopharyngeal carcinoma [J]. Int J Radiat Oncol Biol Phys, 2006,64(2):374-381.

[9] Lai SZ, Li WF, Chen L, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? [J]. Int J Radiat Oncol Biol Phys, 2011,80(3):661-668.

[10] Peng G, Wang T, Yang KY, et al. A prospective, randomized study comparing

outcomes and toxicities of intensity-modulated radiotherapy vs. Conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma [J]. Radiother Oncol, 2012,104(3):286-293.

[11] Lee AW, Ng WT, Chan LL, et al. Evolution of treatment for nasopharyngeal cancer - success and setback in the intensity-modulated radiotherapy era [J]. Radiother Oncol, 2014.

[12] Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: Npc-9901 trial by the hong kong nasopharyngeal cancer study group [J]. J Clin Oncol, 2005,23(28):6966-6975.

[13] Tham IW, Lin S, Pan J, et al. Intensity-modulated radiation therapy without concurrent chemotherapy for stage iib nasopharyngeal cancer [J]. Am J Clin Oncol, 2010,33(3):294-299.

[14] Su SF, Han F, Zhao C, et al. Long-term outcomes of early-stage nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy alone [J]. Int J Radiat Oncol Biol Phys, 2012,82(1):327-333.

[15] Luo S, Zhao L, Wang J, et al. Clinical outcomes for early-stage nasopharyngeal carcinoma with predominantly who ii histology treated by intensity-modulated radiation therapy with or without chemotherapy in nonendemic region of china [J]. Head Neck, 2013.

[16] Cheung F, Chan O, Ng WT, et al. The prognostic value of histological typing in nasopharyngeal carcinoma [J]. Oral Oncol, 2012,48(5):429-433.

[17] Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: An individual patient data meta-analysis of eight randomized trials and 1753 patients [J]. Int J Radiat Oncol Biol Phys, 2006,64(1):47-56.

[18] Langendijk JA, Leemans CR, Buter J, et al. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: A meta-analysis of the published literature [J]. J Clin Oncol, 2004,22(22):4604-4612.

[19] Chen L, Mao YP, Xie FY, et al. The seventh edition of the uicc/ajcc staging system

for nasopharyngeal carcinoma is prognostically useful for patients treated with intensity-modulated radiotherapy from an endemic area in china [J]. Radiother Oncol, 2012,104(3):331-337.

[20] Sun Y, Tang LL, Chen L, et al. Promising treatment outcomes of intensity-modulated radiation therapy for nasopharyngeal carcinoma patients with n0 disease according to the seventh edition of the ajcc staging system [J]. BMC Cancer, 2012,12(68.

[21] Mao YP, Liang SB, Liu LZ, et al. The n staging system in nasopharyngeal carcinoma with radiation therapy oncology group guidelines for lymph node levels based on magnetic resonance imaging [J]. Clin Cancer Res, 2008,14(22):7497-7503.

[22] Li W-F, Sun Y, Mao Y-P, et al. Proposed lymph node staging system using the international consensus guidelines for lymph node levels is predictive for nasopharyngeal carcinoma patients from endemic areas treated with intensity modulated radiation therapy [J]. International Journal of Radiation Oncology*Biology*Physics, 2013,86(2):249-256.

[23] Yue D, Xu Y-F, Zhang F, et al. Is replacement of the supraclavicular fossa with the lower level classification based on magnetic resonance imaging beneficial in nasopharyngeal carcinoma? [J]. Radiotherapy and Oncology, 2014,113(1):108-114.

[24] Leung SF, Chan AT, Zee B, et al. Pretherapy quantitative measurement of circulating epstein-barr virus DNA is predictive of posttherapy distant failure in patients with early-stage nasopharyngeal carcinoma of undifferentiated type [J]. Cancer, 2003,98(2):288-291.

[25] Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase iii randomized intergroup study 0099 [J]. J Clin Oncol, 1998,16(4):1310-1317.

[26] Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: Progression-free survival analysis of a phase iii randomized trial [J]. J Clin Oncol, 2002,20(8):2038-2044.

[27] Zhang AM, Fan Y, Wang XX, et al. Increased treatment-related mortality with additional cisplatin-based chemotherapy in patients with nasopharyngeal carcinoma treated

with standard radiotherapy [J]. Radiother Oncol, 2012,104(3):279-285.

[28] Edge SB BD, Compton CC, Fritz AG, Greene FL, Trotti A. (ed). American joint committee on cancer staging manual [M]. 7th. New York: Springer, 2010.

[29] Freedman J, Furberg C, DeMets D. Fundamentals of clinical trials [M]. New York: Springer-Verlag, 1998.

[30] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (rtog) and the european organization for research and treatment of cancer (eortc) [J]. Int J Radiat Oncol Biol Phys, 1995,31(5):1341-1346.

[31] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised recist guideline (version 1.1) [J]. Eur J Cancer, 2009,45(2):228-247.

[32] Chow SC, Shao J, Wang H. Sample size calculations in clinical research [M]. New York: Marcel Dekker, 2003.

19.0 Appendix I

STAGING CRITERIA – the 7th AJCC edition[28]

Nasopharynx (T)

T1	Nasopharynx, soft tissue of the oropharynx, and/or the nasal fossa without parapharyngeal extension
T2	Parapharyngeal extension
T3	Invades bony structures and/or paranasal sinuses
T4	Intracranial extension, involvement of cranial nerves, infratemporal fossa, hypopharynx, and orbit

Regional Lymph Node (N)

N1	Unilateral lymph node(s) < 6 cm, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph node(s) < 6 cm
N2	Bilateral lymph node(s) < 6 cm, above the supraclavicular fossa
N3	(a) > 6 cm or (b) in the supraclavicular fossa

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
Stage III	T3	N0, N1	M0
	T1, T2, T3	N2	M0
Stage IVA	T4	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Appendix II

Performance Status (Karnofsky scale)

100	No complaints; No evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Able to carry on normal activity with effort; Some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated, although death not imminent
20	Very sick; hospitalization necessary; requires active supportive treatment
10	Moribund; fatal processes progressing rapidly
0	Dead

Appendix III

Toxicity Criteria

INSTRUCTIONS

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for a similar toxicity, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused the death of the patient.
4. Refer to the detailed toxicity guidelines in the CTCAE system for acute induction chemotherapy and chemoradiotherapy toxicity not covered on this table.
5. Refer to the detailed toxicity guidelines in the RTOG system for late radiation toxicity not covered in this table.
6. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
7. An accurate baseline prior to the start of therapy is necessary.

Acute induction chemotherapy and chemoradiotherapy toxicity (CTCAE System)

Toxicity	Grade 3	Grade 4	Grade 5
Rash: dermatitis associated with radiation	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Mucositis/stomatitis (clinical	Confluent ulcerations or pseudomembranes;	Tissue necrosis; significant spontaneous	Death

examination)	bleeding with minor trauma	bleeding; life-threatening consequences	
Anorexia	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
Nausea	Inadequate oral caloric or fluid intake; IV fluids, tube feeding, or TPN indicated ⩾ 24 h	Life-threatening consequences	Death
Vomiting	⩾ 6 episodes in 24 h; IV fluids or TPN indicated ≥ 24 h	Life-threatening consequences	Death
Dry mouth	Symptoms leading to inability to adequately aliment orally, IV fluids, tube feedings, or TPN indicated unstimulated saliva < 0.1 ml/min	-	-
Dysphagia	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥ 24 h	Life-threatening consequences (e.g., obstruction, perforation)	Death
Diarrhea	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids	Life-threatening consequences (e.g., hemodynamic collapse)	Death

	indicated ⩾ 24 h; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL		
ALT	> 5.0–20.0 × ULN	> 20.0 × ULN	-
AST	> 5.0–20.0 × ULN	> 20.0 × ULN	-
CRE	> 3.0–6.0 × ULN	> 6.0 × ULN	Death
Hearing (without a monitoring program)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (> 90 dB)	-
Neuropathy: sensory	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
Neuropathy: motor	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
Leukocytes	1.0 to < 2.0 × 10^9/L	< 1.0 × 10^9/L	Death
Neutrophils	0.5 to < 1.0 × 10^9/L	< 0.5 × 10^9/L	Death
Hemoglobin	65 to < 80 g/L	< 65 g/L	Death
Platelets	25.0 to < 50.0 × 10^9/L	< 25.0 × 10^9/L	Death
Weight loss	⩾ 20% of baseline; tube feeding or TPN indicated	-	-
lethargy	Severe fatigue interfering with ADL	Disabling	-
Hair loss /alopecia (scalp or body)	-	-	-

Allergic reaction	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
Fever (in the absence of neutropenia, where neutropenia is defined as ANC < 1.0×10^9/L)	> 40 °C, for ≤ 24 h	> 40 °C, for > 24 h	Death
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0×10^9/L)	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
Teeth	Full mouth extractions indicated	-	-

Late RT toxicity (RTOG/EORTC System)

Toxicity	Grade 3	Grade 4
Temporal lobe necrosis	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia) (major intellectual impairment; persistent & minor mood/	Seizures; paralysis; Coma; Required surgical treatment (complete loss of memory; complete

	personality change; cannot perform a simple task)	disorientation; total disintegration; incapable of self-care)
Spinal cord/Brainstem	Objective neurological findings (partial sensory loss; persistent motor weakness; incomplete sphincter control)	Mono, para quadriplegia (total sensory loss; complete motor power loss; complete incontinence)
Peripheral nerves	Persistent paresthesia; 50% decrease in power	Total sensory loss; complete motor power loss
Hypothalamic-pituitary: male gonad	Persistent loss in libido	Impotent
Female gonad	Persistent loss in libido; amenorrhoea; anovulation; osteoporosis	Infertile (involuntary); osteoporotic fracture
Thyroid	Persistent fatigue; needs supplemental heat; obvious puffiness; obvious hoarseness/slow speech; > 50% decrease in T4	-
Adrenal	Drowsiness & weakness darkened skin; > 50% decrease in cortisol	Paralysis; Coma
Ear	Persistent pain/otitis; persistent (daily) tinnitus; severe hearing loss, frequent difficulties with loud speech	Refractory pain/otitis; Refractory (constant) tinnitus; Complete deafness
Eyeball	Severe keratitis; severe retinopathy or detachment; severe glaucoma (severe loss of vision but able to	Panopthalmitis blindness (unable to perform daily activity)

	perform daily activity)	
Bone	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis (regular narcotic)	Necrosis; spontaneous fracture (surgical intervention)
Trismus	Severe joint stiffness; severe pain; severe limitation of movement (dental gap 0.5–1 cm)	Necrosis; complete fixation (dental gap < 0.5 cm)
Dry mouth	Complete dry mouth, no response to any stimulus	Fibrosis
Subcutaneous tissue soft tissue/ muscle	Severe induration; severe loss of subcutaneous tissue; contracture > 10% linear reduction (secondary dysfunction)	Necrosis (total dysfunction)
Soft tissue skin/ mucosa	Marked atrophy; gross telangiectasia (≥ 50%)	Ulceration

Final statistical analysis plan

1.0 Endpoint definitions

1.1 Primary endpoint: Failure-free survival (FFS), which is defined as the interval between randomization and distant failure, locoregional failure, or death from any cause, whichever happened first.

1.2 Secondary endpoints

1.2.1 Overall survival (OS): OS is defined as the time from random assignment to death from any cause.

1.2.2 Distant metastasis-free survival (DMFS): DMFS is defined as the interval from randomization to the first distant metastasis or death from any cause.

1.2.3 Locoregional relapse-free survival (LRRFS): LRRFS is defined as the interval from randomization to the first local or regional recurrence, or death from any cause.

1.2.4 Safety indicators: Acute radiation-related toxicities are assessed using the National Cancer Institute Common Toxicity Criteria version 4.0 scale. Acute radiation-related toxicities include dermatitis, mucositis, dry mouth, dysphagia, trismus, and subcutaneous soft tissue. Late radiation toxicities are assessed according to the Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme, including skin, neck tissue damage, hypothyroidism, dry mouth, dysphagia, trismus, and other adverse events.

1.2.5 Quality of Life: EORTC QLQ-C30 questionnaires are used to assess the quality of life of patients, before RT, during treatment, and during survival follow-up.

2.0 Data processing and statistical analysis

2.1 Case report form (CRF)

A CRF is used to record clinical data in a clinical trial. All relevant information of the patient in the trial should be recorded in a timely and true manner. As original material, the CRF should not be changed at will. The researcher should sign and date when it is really necessary to correct the data. The CRF is triplicated and should be handed over to the statistical experts, researchers, and sponsors for storage after trial.

2.2 Data management

After receiving the CRF, the data administrator will check the data and feedback possible questions. The investigators should verify the problem and respond as soon as possible. Then, the data administrator establishes a database in time and double-inputs the data. The principal investigator, data administrator, and statistician lock the database, which must be backed up. To ensure data security, non-permitted personnel cannot access and modify the trial data. Any data changes need to be approved by the principal investigator, statistician, and data administrator.

2.3 Sample Size Estimate

The primary endpoint is FFS. Based on a study by Zhang et al. (Zhang F, Zhang Y, Li WF, et al. Efficacy of Concurrent Chemotherapy for Intermediate Risk NPC in the Intensity-Modulated Radiotherapy Era: a Propensity-Matched Analysis. Scientific reports 2015; 5: 17378.), we suppose that the 3-year FFS, about 90%, is the same between RT alone and CCRT in the treatment of patients with NPC. We specify a non-inferiority margin of 10%, which is regarded as clinically acceptable in view of the expected reduced toxic effects and increased quality of life of patients receiving RT alone. Hence, to demonstrate non-inferiority, the upper limit of the 95% CI for the difference in 3-year FFS between the two groups could not exceed 10%. With 80% power and a one-sided type I error of 5%, we needed at least 338 patients (169 in each group) to allow for a 5% dropout or loss to follow-up.

2.4 Analytical approach

Efficacy analyses are performed in the intention-to-treat population, which included all the randomly assigned patients. Safety data and life quality data comprise all patients who had started the randomly assigned treatment. A comparison of the FFS, the primary end point, of ARM I with ARM II using the log-rank test will be used to evaluate efficacy. Similar comparisons will be made for OS, DMFS, and LRRFS. Cox regression analyses will be performed to quantify the effect of predictors on the survival outcomes. Analysis of FFS based on the per-protocol population will also be performed. The per-protocol population comprised the eligible patients who started the randomly assigned treatment (received at least one dose of cisplatin) or IMRT alone. The statistical test for FFS is one- sided, and a p value <0.05 is considered statistically significant. The left statistical tests were two-sided, and a p value < 0.05 is considered statistically significant.

Analysis includes:

a. General information:

   The distribution of clinical factors, including age, sex, and stages, are summarized using descriptive statistics.

b. Adverse effects:

   Acute and late radiation-related toxicities and sequelae in each group are summarized using descriptive statistics.

c. Long-term curative effect:

   3-year and 5-year FFS, OS, DMFS, and LRRFS rates are calculated according to follow-up visits.

d. Total data analysis:

   An overall analysis is conducted after data summarization.

e. Subgroup analysis: An interaction analysis for FFS based on the intention-to-treat population will be carried out to assess whether the treatment effect varies in subgroups defined using sex, age, T and N categories. A test of treatment-by-covariate interaction based on the Cox proportional-hazards model will be used.

f. Quality of life: EORTC QLQ-C30 questionnaires are used to assess the quality of life of the patients. Patient responses to each of the EORTC QLQ-C30 questionnaire items are scored into scales representing functioning, symptoms, or health status; all items pointing to a domain will be averaged and the results will be transformed into a 0–100 scale according to the EORTC scoring manual. Higher scores on the functioning scales and global health status suggest better function or health, whereas higher scores on the symptom scales indicate more severe symptoms. The difference in quality of life scores between groups will be compared using mixed effect model.