Trial protocol

Two cycles of once-every-three-weeks versus once-a-week concurrent cisplatin chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma

FINAL PROTOCOL
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Principle Investigator: Dr. Yan-Qun Xiang
Sponsor: Sun Yat-sen University Cancer Center
Collaborators:
The Affiliated Hospital of Guilin Medical University
Study Coordinator: Dr. Si-Wei Li
The Fifth Affiliated Hospital, Sun Yat-Sen University
Study Coordinator: Dr. Qi Zeng

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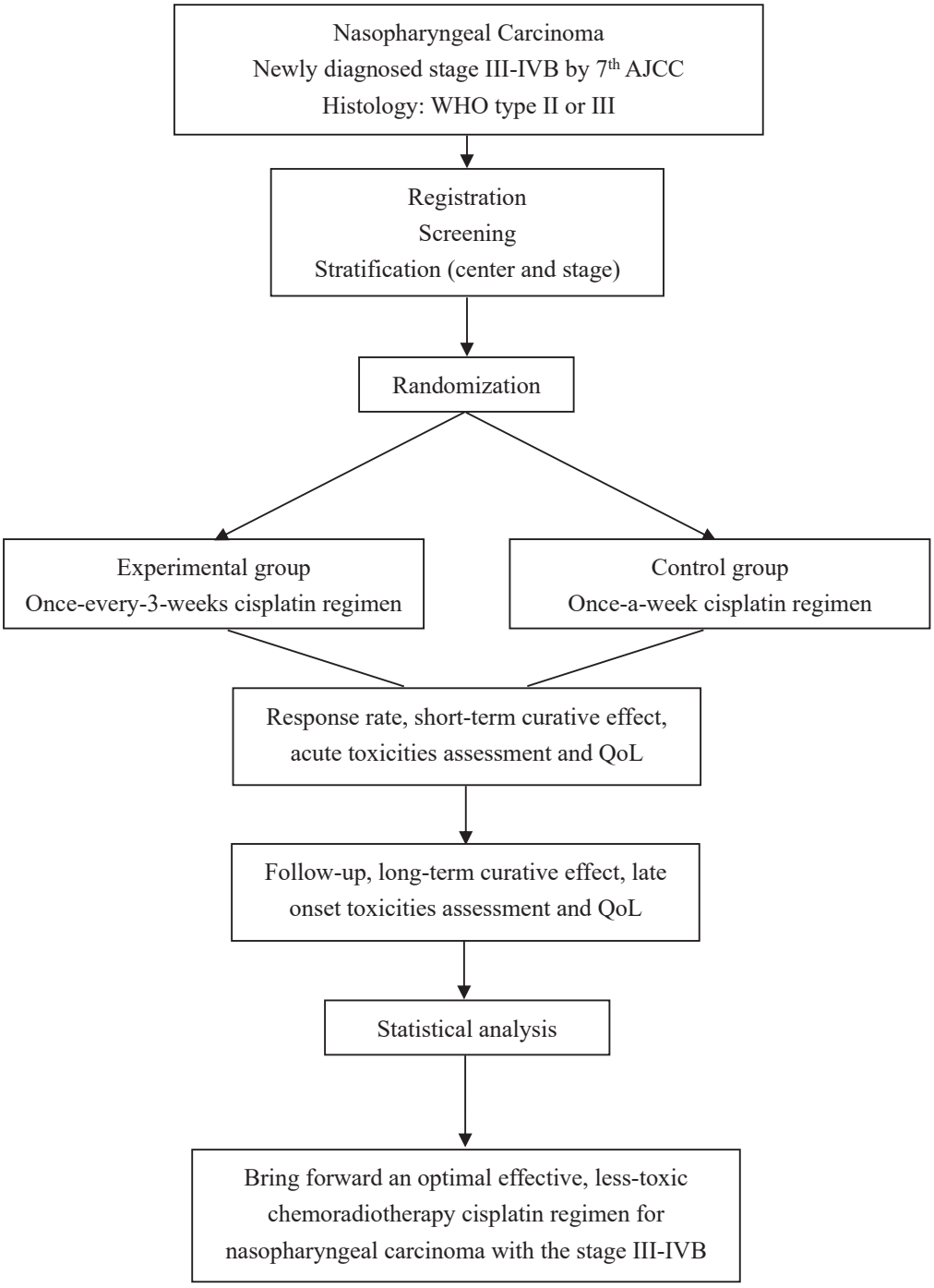
SCHEMA


Nasopharyngeal Carcinoma
Newly diagnosed stage III-IVB by 7th AJCC
Histology: WHO type II or III
Registration
Screening
Stratification (center and stage)
Randomization
Experimental group
Once-every-3-weeks cisplatin regimen
Control group
Once-a-week cisplatin regimen
Response rate, short-term curative effect, acute toxicities assessment and QoL
Follow-up, long-term curative effect, late onset toxicities assessment and QoL
Statistical analysis
Bring forward an optimal effective, less-toxic chemoradiotherapy cisplatin regimen for nasopharyngeal carcinoma with the stage III-IVB

1 Background

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors in China, and is especially endemic in Southern China.[1] Radiotherapy is the primary treatment modality for non-disseminated NPC due to its deep-seated location and radiosensitivity. The 5-year survival rate in stage I NPC patients goes up to 90% when treated with radiotherapy alone. However, due to the covert location of the nasopharynx, many patients are asymptomatic and 70% of them have progressed to locoregionally advanced NPC at the time of diagnosis, which has a 5-year survival rate of only 30%-50% with radiotherapy alone.[2] Distant metastasis and local region relapse are the two main reasons of treatment failure. With the combined use of MRI, intensity-modulated radiotherapy (IMRT), and concurrent chemotherapy, locoregional control has substantially improved with rates of approximately 90% and failure-free survival was about 80% at 3 years.[3]

Concurrent chemoradiotherapy is now among the standard treatment for locoregionally advanced NPC, and cisplatin is the most commonly used drug.[4-10] In terms of dosing schedules, there are two conventional methods, including high-dose 100 mg/m^2 every three weeks[4,6] for three cycles and low-dose 40 mg/m^2 once a week[5,10] for seven cycles in clinical practice. In 1998, Al-Sarraf and colleagues first compared chemoradiotherapy versus radiotherapy alone in locoregionally advanced NPC and reported that concurrent chemoradiotherapy (100 mg/m^2 every three weeks for three cycles) with adjuvant chemotherapy (PF regimen for three cycles) is superior to radiotherapy alone with respect to progression-free survival (PFS) and overall survival (OS).[4] The 3-year follow-up results showed a statistically significant benefit for OS in the chemoradiotherapy group with 76% versus 46% in the radiotherapy alone group, respectively. Since then, the efficacy of this strategy was confirmed by subsequent randomized trials.[6,9] However, this regimen was associated with significant acute toxicity that limited dose delivery and only 63% patients completed three cycles of concurrent chemotherapy. Adjuvant chemotherapy has frequently been omitted due to cumulative toxicity with only 55% patients completed three cycles. Evidence suggests that lower-dose cisplatin (40 mg/m^2), administrated on a weekly basis concurrent with radiotherapy, offers a feasible alternative.[11,12] Nevertheless, Chan and colleagues conducted a randomized phase III trial that reported weekly cisplatin 40 mg/m^2 concurrent with radiotherapy obtained a significant survival benefit compared with radiotherapy alone.[5] However, patient compliance was still unsatisfactory with only 44% or 60% of patients actually completed six or five cycles of chemotherapy during radiotherapy.

Based on previous trials,[4-6,10,13] only 44% to 68% patients in the once-a-week arm received the seventh cycle and 52% to 88% patients in the once-every-3-weeks arm received the third cycle. The severe acute toxicities were the main reason for non-compliance in these trials. We noticed that, with the same cumulative dose intensity of cisplatin at 200 mg/m^2, compliance of five cycles in the once-a-week arm was significantly lower than that of two cycles in the once-every-3-weeks arm (60%-91% versus 86%-99%), implying the higher toxicity rates in the once-a-week arm.[4,5,10,13] Notably, Lee and colleagues recently conducted the combined analyses of the NPC-9901 and the NPC-9902 trials using once-every-3-weeks 100mg/m^2 cisplatin concurrently with 2DRT/3DRT to show that significant outcome improvement was achieved in patients with two and three cycles compared to patients receiving less than two cycles (5-year-

locoregional failure-free survival, 88%, 88%, and 79%, respectively).[14] However, no significantly different survival benefit was observed between patients who received two and three concurrent cycles of once-every-3-weeks 100 mg/m^2 cisplatin (p=0.83). This exploratory study emphasized that the concurrent phase is important for locoregional control and survival and the cumulative cisplatin dose of 200 mg/m^2 might be adequate.[14] Consequently, the low-dose and high-dose cisplatin schedules were never prospectively compared head-to-head with the high evidences. Thus, the optimal schedule and dose of cisplatin in concurrent chemoradiotherapy in intensity-modulated radiotherapy (IMRT) era remains unclear .

We therefore are going to conduct a non-inferiority multi-center randomized controlled clinical trial to assess the efficacy and toxicity profiles of once-every-3-weeks versus once-a-week schedule of cisplatin in locoregionally advanced NPC. The primary outcome measure is failure-free survival. The expected result is that the once-every-3-weeks regimen is noninferior to the once-a-week cisplatin regimen, and its side effects are fewer and milder. Therein, an improvement in patient compliance and quality of life could be obtained. If proved, high-grade evidence will be provided for the optimal cisplatin regimen to concurrent chemoradiotherapy of NPC.

2 Objectives

2.1 Primary Objectives

To determine whether concurrent chemoradiotherapy with two cycles of Once-every-3-weeks cisplatin regimen will result in noninferior failure-free survival as compared with those patients receiving once-a-week cisplatin regimen in staged III-IVB NPC patients.

2.2 Secondary Objectives

To compare overall survival, locoregional relapse-free survival, distant metastasis-free survival, response rate, toxicity profile, compliance of the treatment, quality of life and cost effectiveness between once-every-3-weeks and once-a-week groups.

3 Subject Enrollment

3.1 Eligibility Criteria

3.1.1 Patients with histologically confirmed non-keratinizing NPC (including differentiated type and undifferentiated type, WHO II or III).

3.1.2 Original clinical staged as T3-4N0-3M0 or T1-2N2-3M0 (AJCC 7th edition).

3.1.3 Age between 18-65 years.

3.1.4 WBC $\geq 4\times10^9$/L, PLT $\geq 100\times10^9$/L, HGB $\geq$ 90g/L.

3.1.5 With normal liver function test (TBil, ALT and AST $\leq$ 2.0*ULN).

3.1.6 With normal renal function test (Ccr $\geq$ 60 ml/min or Creatinine $\leq$ 1.5*ULN).

3.1.7 Satisfactory performance status: Karnofsky scale (KPS) $\geq$70.

3.1.8 Patients must be informed of the investigational nature of this study and give written informed consent.

3.2 Exclusion Criteria

3.2.1 Patients with histologically confirmed keratinizing squamous cell carcinoma (WHO I).

3.2.2 Age > 65 or < 18 years.

3.2.3 Treatment with palliative intent.

3.2.4 Prior malignancy except adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or superficial bladder tumors (Ta, Tis, and T1).

3.2.5 Prior chemotherapy or surgery (except diagnostic) to primary tumor or nodes.

3.2.6 History of previous radiotherapy (except for non-melanomatous skin cancers outside intended radiotherapy treatment volume).

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

3.2.8 Any severe intercurrent disease, which may bring unacceptable risk or affect the compliance of the trial, for example, unstable cardiac disease requiring treatment, acute exacerbation of chronic obstructive pulmonary disease or other respiratory illness requiring admission to hospital, renal disease, chronic hepatitis, diabetes with poor control (fasting plasma glucose > 1.5×ULN), and mental disturbance.

3.3 Criteria for Removal from Protocol Treatment

3.3.1 Disease progression.

3.3.2 Unacceptable toxicity. The reason(s) must be recorded.

3.3.3 Intercurrent diseases which may affect assessments of clinical status to a significant degree and require discontinuation of drug, or both.

3.3.4 The patient may withdraw from the study at any time for any reason. The reason should be recorded.

4 Treatment Plan

4.1 Chemotherapy

4.1.1 Schedule and dose

4.1.1.1 Once-every-3-weeks Cisplatin Regimen (Experimental Group)

Cisplatin is infused with100mg/m^2 IV every 3 weeks (on the day 1 and 22) for two cycles during the radiotherapy phase.

4.1.1.2 Once-a-week Cisplatin Regimen (Control Group)

Cisplatin is infused with 40mg/m^2 IV once a week for six cycles during the radiotherapy phase.

4.1.2 Administration:

4.1.2.1 Once-every-3-weeks Cisplatin Regimen Administration Guidelines

Follow local hydration protocols to prevent/minimize nephrotoxicity. Pre-hydration (at least 12 hours prior to cisplatin administration, D0) and post-hydration (D1-3) with over 2,000ml of normal saline infused each time are both needed. The use of mannitol (D1) and furosemide (D1) is essential for it helps to reduce cisplatin-related nephrotoxicity by diuresis. Twenty-four hours urinary output should be recorded (D0-D3) and urinalysis will be performed (D2-D3). Electrolytes and serum creatinine are monitored during treatment, and a follow-up creatinine within 24-48 hours of the cisplatin dose is recommended.

One hour before concurrent chemotherapy, patients are given 5-hydroxytryptamine-3 receptor antagonists for anti-nausea and 10 mg dexamethasone for oral or intravenous 5-15 minutes (D1). Dexamethasone 10 mg and metoclopramide 20 mg quaque die were recommended in D1-D3.

4.1.2.2 Once-a-week Cisplatin Regimen Administration Guidelines

There are no need for hydration and diuresis. One hour before concurrent chemotherapy,

patients are given 5-hydroxytryptamine-3 receptor antagonists for anti-nausea.

4.1.3 Dosage Adjustments

4.1.3.1 General

4.1.3.1.1 Patients will be examined and graded for subjective/objective evidence of developing toxicity according to the CTCAE, v. 4.03 each day that chemotherapy is administered and weekly while receiving radiotherapy.

4.1.3.1.2 There will be no dose escalation for concurrent cisplatin.

4.1.3.1.3 Drug dose modifications for chemotherapy are intended to be permanent (i.e., if a patient's dose is reduced to 30 mg/m², it remains at the reduced dose for the duration of their treatment).

4.1.3.1.4 Prophylactic hematologic growth factors for neutropenia or anemia are not allowed during concurrent chemoradiotherapy.

4.1.3.1.5 Chemotherapy must not be administered until the absolute neutrophil count ≥ 1,500 and platelets count are ≥ 100,000.

4.1.3.2 Dose Adjustment for Hematologic Adverse Events

Cisplatin dose will be reduced by 25% full dose if the patients experience grade 3 neutropenia or grade 2 thrombocytopenia.

4.1.3.3 Dose Adjustment for Non-hematologic Adverse Events

4.1.3.3.1 Neutropenic fever

Temperature of 38.5° C with absolute neutrophil count (ANC) < 1000 is an expected potential complication of concurrent chemotherapy and radiotherapy. If neutropenic fever is noted, the chemotherapy dose reduction will be determined by the weekly blood counts.

4.1.3.3.2 Renal adverse events

Dose will be modified based on the creatinine clearance immediately prior to each cisplatin dose. The creatinine clearance is calculated with Cockcroft formulation. The dose modified as indicated below:

Creatinine Clearance	Cisplatin Dose Adjustment
≥ 60 ml/min	Full dose
40-60 ml/min	75% full dose
< 60 ml/min	Hold drug*

*Cisplatin must not be administered until creatinine clearance ≥ 60 ml/min. If creatinine clearance remains < 40 ml/min, the patient should not receive additional cisplatin.

4.1.3.3.3 Gastrointestinal Adverse Events

The dosage of cisplatin decreases 25% full dose when patients suffer from persistent grade 3 or more gastrointestinal adverse events.

4.1.3.3.4 Neurologic Adverse Events

The dosage of cisplatin decreases 25% full dose when patients suffer from neurotoxicity of grade 2. Patients with neurotoxicity of grade 3 or more are withdrawn from the study.

4.1.3.3.5 Ototoxicity

When patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. Patients with clinically significant hearing loss must not receive additional cisplatin. Cisplatin should be held for grade 3 hearing loss that has primarily a neurological basis; for grade 2 hearing loss with primarily a neurological basis, decrease 25% full dose.

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

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

4.2 Radiotherapy

Patients will be examined and graded for subjective/objective evidence of acute toxicities according to the Common Terminology Criteria for Adverse Events, version 4.03.

4.2.1 Radiotherapy Adjustments for Non-hematological Toxicity:

Side effects of radiotherapy may include mucositis and skin reaction. The investigator will manage these conditions according to clinical practice at the institution. No radiotherapy dose modifications are allowed. Treatment interruptions are allowed if symptomatic mucositis or skin reactions occur that, in the judgment of the attending clinician, warrants a break. The treatment is completed according to protocol for treatment breaks up to and including 14 days. If the break exceeded 14 days, the patient is removed from protocol treatment, completing treatment at the discretion of his or her physician but followed up and included in the analysis.

4.2.2 Radiotherapy Adjustments for Hematological Toxicity:

Radiotherapy will be withheld until ANC > 500 and platelet > 25,000.

4.2.3 Target Volume Determination for Intensity Modulated Radiotherapy

Radiotherapy treatment with intensity modulated radiotherapy (IMRT) techniques is mandatory. Target volumes are defined in accordance with the International Commission on Radiation Units and Measurements (ICRU) reports 50 and 62. The principle of target volume determination for IMRT and prescribed dose and fractionation are as the following descriptions.

4.2.4 Prescribed Dose and Fractionation:

All patients will be treated with IMRT using simultaneously integrated boost, 5 fractions per week. The prescribed dose is 66–70 Gy, 64–70 Gy, 60–64 Gy, and 54–58 Gy, in 30–33 fractions, for the PTVs derived from GTVnx, GTVnd, CTV1, and CTV2, respectively.

4.2.5 Normal tissue dose constraints

Structure	Dose constraints
Critical organ at risk	
Brain stem	Dmax ≤ 54 Gy
PRV-Brain stem	D1 ≤ 60 Gy
Spinal cord	Dmax* ≤ 45 Gy
PRV-Spinal cord	D1† ≤ 50 Gy
Optic nerve	Dmax ≤ 54 Gy
PRV-Optic nerve	D1 ≤ 60 Gy
Optic chiasm	Dmax ≤ 54 Gy
PRV-Optic chiasm	D1 ≤ 60 Gy
Temporal lobe	Dmax ≤ 60 Gy
PRV-Temporal lobe	D1 ≤ 65 Gy
Intermediate-risk organ at risk	
Pituitary	Dmax < 60 Gy
Mandibular	Dmax < 70 Gy
Temporomandibular Joint	Dmax < 70 Gy
Lens	Dmean‡ < 8 Gy
Eyes	Dmean < 35 Gy

Low-risk organ at risk	
Parotid	Dmean < 26 Gy
Parotid	V30¶< 50%
Cochlea	Dmean < 50 Gy
Tongue	Dmean < 45 Gy
Larynx	Dmean < 45 Gy

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)

4.3 Salvage Therapy

Nasopharyngeal surgery, neck dissections, secondary radiotherapy or chemotherapy may be given to patients with relapse or metastasis after treatment.

5 Data Collection

5.1 Before Treatment

All patients are under standardized management for NPC, and they need to perform a series of examinations as well as provide relevant information to confirm pathologic diagnosis and clinical stage before admitted into trial:

1. Medical history review
2. Personal data collection
3. Current medications and treatment
4. Body examinations, include height, weight and vital signs
5. Physical examination of head and neck region, include nasopharynx and cervical lymph nodes
6. Physical examination of the nervous system
7. Nasal endoscopy and lesion biopsy
8. CBC and differential, electrolytes and liver function test
9. Urinalysis.
10. EBV serologic tests (EBV antibodies, EBV DNA was optional, depending on the laboratory availability of the participating centers).
11. Electrocardiogram
12. Imaging, including enhanced MRI or enhanced CT of the head and neck (CT is indicated only in patients with contraindication to MRI)
13. Chest film or CT
14. ECT bone scan
15. Abdominal ultrasonography or CT
16. PET/CT is optional and is performed at the discretion of the attending physician
17. Signed informed consent

5.2 During Treatment

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

1. MRI of head/neck should be performed before and after treatment, and treatment responses is evaluated with the criteria of Response Evaluation Criteria in Solid Tumors

version 1.1. Chest film and abdominal ultrasonography are reexamined after treatment.

2. The use of concomitant drugs
3. General conditions
4. Acute and late onset toxicities assessment (Common Terminology Criteria for Adverse Events, version 4.03), include hematological toxicity, gastrointestinal reactions, hepatotoxicity and nephrotoxicity, mucositis, neurotoxicity and ototoxicity, etc.
5. Peripheral neuropathy
6. Laboratory tests: CBC and differential, blood biochemistry are required every week.
7. Indirect nasopharyngoscopy is performed to examine the tumor in nasopharynx every week, and the regression of enlarged lymph nodes is observed and measured. Nasal endoscopy is performed before and after treatment course, and is also required every two weeks.
8. EORTC QLQ-C30 and QLQ-H&N35 (V1.0) is used to assess patient's quality of life, and the change of their quality of life is recorded at the time points of every week during treatment, three months, six months, and one year after radiotherapy.

6 Follow Up

After completion of treatment, patients are followed up every 3 months during the first 3 years and every 6 months thereafter until death. The nasopharynx will be assessed by endoscopy approximately 4 weeks after completion of radiotherapy. Further investigations with MRI or CT will be arranged 3 months after completion of radiotherapy. Treatment responses are also evaluated according to the RECIST, version 1.1. If residual disease is found, whether to treat and which treatment modalities to be employed will be decided by individual clinician. For statistical purpose, any residual disease found 16 weeks after completion of RT will be considered as local failure. Similarly, any residual nodal disease at 16 weeks after RT is considered as regional failure. Follow-up procedure includes physical examination of nasopharynx and head-neck region, and plasma EBV DNA (EBV DNA was optional, depending on the laboratory availability of the participating centers) for every 3 months; abdominal sonography, chest film are routinely performed annually; enhanced MRI or CT of head and neck for 3 months after radiotherapy and annually thereafter.

Failure should preferably be confirmed by fine needle aspiration (FNA) or biopsy. In case of equivocal finding of the origin of metastases, plasma EBV DNA and/or in situ hybridization for Epstein-Barr virus-encoded RNA (EBERs) expression in biopsy tissue should be considered for confirming nasopharynx origin. Clinical diagnosis is accepted for sites not easily accessible if classical changes are shown on imaging. The dates of diagnosis of local, nodal, and distant failure will be recorded. The earliest date of detecting symptomatic late onset toxicities and the eventual maximum grade by 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.

All patients will be followed-up until death and cause of death recorded. Deaths due to unknown cause are counted as death due to NPC if disease is still present at last assessment.

7 Safety Measures and Quality Control

1. Provide systematic learning program for every member in the research group. Arrange

one doctor in each center to be in charge of tumor staging, which must be in accordance with the 7th AJCC edition, and to make sure that every patient enrolled is eligible. Patients are given randomization numbers to determine which group they are in.

2. Make monitoring plan of adverse effects and emergency plan.
3. Research plan is made by all participating centers and approved by Ethics Committee.
4. Develop all kinds of standard operation procedures related to this study.
5. Establish standardized evaluation system to unify diagnostic criteria, curative effect judging criteria, etc.
6. Establish professional statistical plan.
7. Research staffs are trained before the study.
8. Ensure that every participating center conducts the study at the same pace.
9. Arrange quality controller, make quality control plan and check regularly.
10. Set up coordination committee, curative effect judging group and follow-up team.

8 Statistical Analysis

8.1 Endpoint Definitions

8.1.1 Primary Endpoint

Failure-free survival: The failure-free survival is defined as the time from randomized assignment to documented local or regional relapse, distant metastasis, or death from any cause, whichever occurs first.

8.1.2 Secondary Endpoints

8.1.2.1 Overall Survival

The overall survival is defined as the time from randomized assignment to the date of death from any cause or censored at the date of last follow-up.

8.1.2.2 Locoregional Relapse-Free Survival

The locoregional relapse-free survival is defined as the time from randomized assignment to the date of local or/and regional relapse.

8.1.2.3 Distant Metastasis-Free Survival

The distant metastasis-free survival ss defined as the time from randomized assignment to the the time of distant metastasis.

8.1.2.4 Short-term Response

The change of nasopharyngeal tumor and cervical lymph nodes will be evaluated by physical examination, nasopharyngoscopy, and MRI/CT imaging 3 months later after treatment. Tumor response is classified according to RECIST, version 1.1. Complete response is defined as no unequivocal soft tissue mass in the local region and all cervical lymph nodes are less than 10 mm in the short axis. Partial response is defined as at least a 30% decrease in the sum of diameters of target lesions, compared to baseline sum diameters. Progressive disease is defined as at least a 20% increase in the sum of diameters of target lesions (an absolute increase of at least 5 mm), or the appearance of one or more new lesions. Stable disease is defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

8.1.2.5 Adverse events

Acute toxicities are assessed according to Common Terminology Criteria for Adverse Events (version 4.03).

Acute toxicities include hematological toxicity, mucositis, allergic reactions and other adverse events and serious adverse events. Late onset radiation toxicities are assessed using the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Late onset toxicities include neurotoxicity, ototoxicity and other complications and sequelae.

8.1.2.6 Quality of Life

EORTC QLQ-C30 and QLQ-H&N35 (V1.0) are used to assess life quality of patients, and the change of their life quality is recorded and evaluated weekly (Week 1-6) from before the beginning of treatment to end, three months, six months, and one year after radiotherapy.

8.1.2.7 Cost-effectiveness analysis

Cost is estimated giving consideration of direct cost such as drug fees, examination fees, ward fees and nursing fees, etc. Make cost-effectiveness analysis by calculating cost-effectiveness ratio (ratio between the direct cost and short- or long-term curative effect) and incremental cost-effectiveness ratio (ratio between increased cost and increased short- or long-term curative effect).

8.2 Sample Size Estimate

The primary endpoint is 3-year progression-free survival. Based on the literatures at the time of study design,[13,15-17] we hypothesized that failure-free survivals was 80% at 3 years for the concurrent chemoradiotherapy group. Clinical noninferiority was defined as not more than the allowable 10% difference in survival rates between once-every-3-week and once-a-week treatment groups. If the 95% CI lower boundary of the difference between the failure-free survival of the two groups did not cross -10% then this trial would be positive in proving noninferiority. Because previous data reported that cisplatin-based concurrent chemoradiotherapy resulted in a benefit in failure-free survival of approximately 19-45% at 3 years compared with radiotherapy alone, the non-inferiority margin of 10% was specified.[4,9] With an 80% power and a one-sided type I error 0.025, we calculated an enrollment of 246 patients per arm (total 492), assuming 5% early dropout rates or lost to follow-up.

8.3 Stratification /Randomization Scheme

8.3.1 Stratification

Patients will be stratified according to the treatment centers and stage (T1-4N2, T1-4N3, T3N0-1, and T4N0-1).

8.3.2 Randomization

Eligible patients are randomized using a 1:1 allocation of patients to two groups. Stratified randomization is performed within each stratum based on treatment center and clinical stages and is also blocked. The randomized block design is conducted by Good Clinical Practice Center in Sun Yat-Sen University Cancer Center and block size will be chosen by the statistician (Prof. Qing Liu) so that each block contains the patients in equal proportion. This procedure helps to ensure both randomness and investigator blinding (the block sizes are known only to the statistician), as recommended by Friedman et al (Friedman J, Furberg, C, DeMets D. Fundamentals of clinical trials. New York: Springer-Verlag; 1998). Randomization will be generated by the statistician in opaque, sealed envelopes, labeled by stratum, which will only be unsealed after patient registration. Patients will be identified by a unique subject number that will remain constant for the duration of the study.

8.4 Data Management

All information about enrolled patients after registration will be sent to Sun Yat-Sen University Cancer Center for management. We have stewards taking charge of database management, and our data platform allows simultaneous input and double check.

8.5 Case Report Form (CRF)

The case report form is designed before the study. The CRF is required to record detailed medical history, treatment and follow-up information, and it should be easy to fill in as well as save in database.

8.6 Analytical Approach

The results of this study are analyzed by the intention-to-treat approach, and all eligible patients are analyzed according to the randomization scheme. Per-protocol analysis is used to include all patients who received at least two cycle of concurrent cisplatin in the once-every-3-week group and at least five cycles of concurrent cisplatin the once-a-week group. The Kaplan–Meier estimator is used to estimate the survival function from lifetime data, and log-rank test to compare the difference of survivals between two groups. Response rates, incidence of toxicities are compared by the chi-square test. Quality of life was analyzed using a mixed effect model. Multiple prognostic factors are analyzed by Cox regression. The statistical test for failure-free survival was one sided, and the non-inferiority p value of less than 0.025 was considered statistically significant; the left statistical tests were two-sided, and a p value of less than 0.05 was considered statistically significant.

9 Ethical Considerations

1. This study must be approved by an appropriate institutional ethic committee.

2. An informed consent must be obtained from individual patients. Copy of the Consent Form, contact number of investigator and ethics committee will be available to patient on request.

3. All serious and unexpected adverse events or death related to the drugs or radiotherapy must be reported to the study coordinator immediately. Serious adverse events (SAE) 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 respective center should complete form and fax this within 24 hours to the Principal Investigator (Dr. Yan-Qun Xiang, Tel: 020-87343359, Fax: 020-87343392), the center of clinical trials, the institutional ethic committee and Sun Yat-sen University Cancer Center. 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.

10 Timeline

Time	Events
Jan, 2011-Apr, 2011	Trial protocol development Data platform construction and systematic training in research team Trial initial meeting
May, 2011-May, 2015	Recruitment, Assessment Follow-up and detection of failure or late toxicity

	Database completed
June, 2015-June, 2020	Follow-up Write research paper and get published on the international journals.

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Appendix I

STAGING CRITERIA – the 7th AJCC edition

Nasopharynx (T)

T1	Nasopharynx, soft tissue of oropharynx and/or 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, orbit

Regional Lymph Node (N)

N1	Unilateral lymph node(s) < 6 cm, above supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph node(s) < 6 cm
N2	Bilateral lymph node(s) < 6 cm, above 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	T2	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 considerablel 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