Trial protocol

A Multicenter Randomized Controlled Trial Comparing Chemotherapy plus Locoregional Radiotherapy with Chemotherapy Alone for Primary Metastatic Nasopharyngeal Carcinoma

FINAL PROTOCOL

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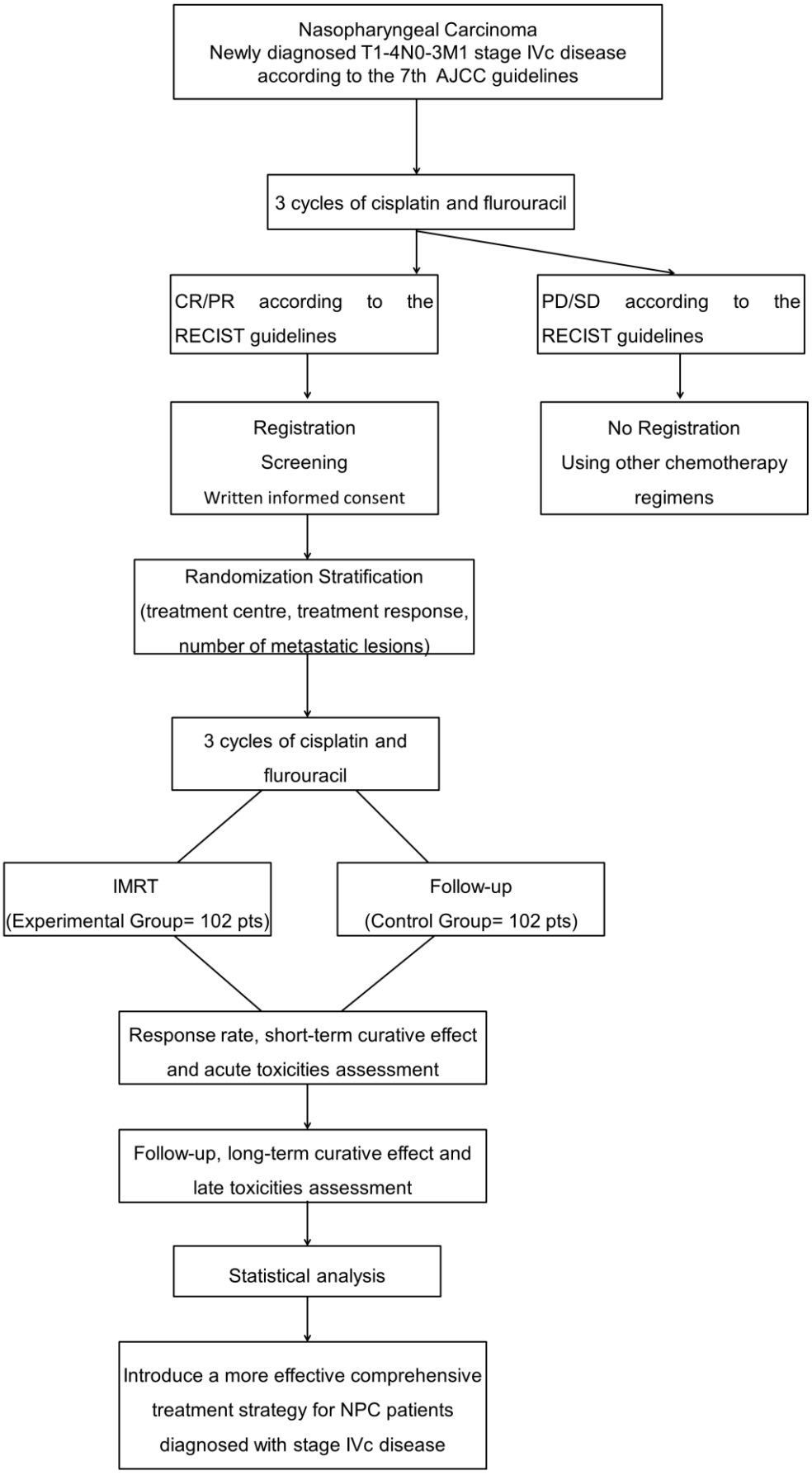
Nasopharyngeal Carcinoma
Newly diagnosed T1-4N0-3M1 stage IVc disease according to the 7th AJCC guidelines
3 cycles of cisplatin and flurouracil
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PD/SD according to the RECIST guidelines
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Introduce a more effective comprehensive treatment strategy for NPC patients diagnosed with stage IVc disease

1.0 Background

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors in China and has the highest incidence rate in South China and Hong Kong. The incidence exceeds 20/100,000 people worldwide. According to the GLOBOCAN 2008 data published by the International Cancer Institute, there were 33,101 newly diagnosed NPC patients and 20,899 deaths related to NPC in China in 2008, accounting for 40% of newly diagnosed NPC patients worldwide. Among other malignant tumors, NPC has an incidence rate that ranks 10th and a mortality rate that ranks 9th in China. The age of onset for NPC is approximately 40 to 50 years, and this disease has major impacts on society, the economy, and family members, and NPC also affects the ability to work. Radiation therapy is the main treatment for NPC. The 5-year overall survival (OS) rate of early-stage patients treated with intensity-modulated radiotherapy (IMRT) alone is over 90% (1). For advanced locoregional NPC patients without distant metastasis treated with radiotherapy (RT) and chemotherapy, the 5-year OS rate can reach 68-74.5% (2-3). Although NPC is a special type of head and neck squamous cell carcinoma (HNSCC), NPC differs from other HNSCCs in terms of epidemiology, pathology, clinical manifestations and treatment response, and NPC is the most invasive and most likely to metastasize of all HNSCCs. Approximately 6-10% of patients with NPC were diagnosed with distant metastases at the initial visit (4-6). Metastatic NPC (mNPC) is considered to be incurable, and palliative systemic chemotherapy is the primary treatment; these patients have a median OS of only 10-15 months (7). Therefore, exploring a comprehensive treatment model to improve the survival time of mNPC has become a hot topic for current research.

In the past, active primary tumor treatment for epithelial cancer with distant

dissemination was not considered beneficial for patient survival and was not routinely used. Furthermore, studies have shown that surgically excising primary tumors may interrupt the dormancy of micrometastases, thereby accelerating the progression of metastases (8). However, there is increasing evidence that radical surgical resection or RT for primary tumors can significantly improve OS in patients with distant metastases. In 2001, the New England Journal of Medicine and The Lancet published two prospective studies that evaluated the value of nephrectomy in distant metastatic renal-cell carcinoma. Both studies found that radical nephrectomy combined with postoperative interferon alpha-2b systemic drug therapy could significantly prolong the median survival time of patients compared with interferon alpha-2b therapy alone. The median survival time increased from 8.1 to 11.1 months and from 7 months to 17 months, with P values of 0.05 and 0.03, respectively (9-10). In addition, the combination treatment regimen was associated with a longer disease-free survival time than with interferon alpha-2b therapy alone (from 3 months to 5 months, P = 0.04) (10). To date, only two prospective studies have evaluated the role of locoregional treatment in patients with distant metastatic cancer. Elisabetta Rapiti and colleagues evaluated 300 patients with newly diagnosed metastatic breast cancer and found that patients who underwent radical mastectomy with negative margins had a 40% reduction in the risk of death compared with those who did not undergo surgery (P=0.049). Interestingly, the study also found that patients who underwent radical mastectomy but had positive margins did not experience this survival benefit (11), suggesting that completely removing the primary lesion is beneficial for the survival outcomes of newly diagnosed patients with metastatic breast cancer. Ruiterkamp conducted a meta-analysis of 10 retrospective studies that investigated local surgical treatment for metastatic breast cancer and found a combined-effects hazard ratio (HR)

of 0.65 (95% CI, 0.59-0.72) (12). Similarly, studies have shown that RT for primary lesions is also beneficial for the survival outcomes of metastatic breast cancer patients. Several retrospective studies have also found that radical prostatectomy or local RT to prostate lesions is also beneficial in prolonging the survival time of patients with distant metastases (14-18).

As early as January 1889, Stephen Paget first proposed and interpreted the "seed and soil" hypothesis of tumor metastasis. He believed that the distant organs are either not completely passive or that they have no choice but to develop metastatic lesions. Now, 120 years later, Paget's theory has been extended to the fact that radical treatment for primary tumors can interfere with the "soil" in addition to killing the "seeds", thus improving the survival outcomes of patients with distant metastases. In August 2011, Nature Review Clinical Oncology published a review article by Scott C. Morgan and Chris C. Parker, which systematically reviewed the role of local treatment on primary tumors and boldly speculated that local radical treatment can block the progression of distant metastatic lesions and prolong the OS time of patients with distant metastases. The article also advocates for a prospective study similar to the aforementioned clinical trials for kidney cancer, with OS as the primary end point (19).

According to the NCCN guidelines (version 2.2011), platinum-based systemic chemotherapy is the main treatment for mNPC. RT is only suitable for nasopharyngeal tumors and regional metastatic lymph nodes to control local symptoms, such as headaches or nosebleeds, or for a small number of patients with isolated metastatic lesions or small lesions (20-21). However, a recent case report indicated that a small number of patients who received systemic cisplatin-based chemotherapy and local high-dose RT could achieve tumor-free survival between 29 and 91 months (22). Another report retrospectively analyzed 105 mNPC patients who

received more than 30 Gy of locoregional RT. Of these patients, 96 patients (91%) received systemic chemotherapy, and 71 patients (68%) received more than 65 Gy of primary RT. The median OS time was 25 months, and the 2- and 5-year OS rates were 50% and 17%, respectively (23), which were significantly higher than the previously reported 2- and 3-year OS rates of 35% and 18% (24). Further univariable analysis also showed that patients who received more than 65 Gy during primary RT had a median OS time of 27 months, which was significantly longer than that of patients who received less than 65 Gy of locoregional RT (median survival: 12 months, P =0.05) (23). However, these results were based on retrospective studies, and the evidence was still not convincing. For example, the finding that patients who received comprehensive therapy had better prognoses than those who did not receive comprehensive therapy might be attributed to the patient selection bias. Therefore, the value of locoregional RT for mNPC need to be further validated in rigorous prospective clinical trials.

Previous studies have shown that the number of chemotherapy cycles is also an independent prognostic factor. The 3-year OS rate of patients who received more than 6 cycles of chemotherapy is significantly higher than those who received fewer than 6 cycles of chemotherapy (32% vs. 14.0%, $P < 0.001$) (24). However, several studies have shown that there is no correlation between the number of chemotherapy cycles and survival outcomes in patients who received locoregional RT. Lin Shaojun and colleagues showed that patients treated with more than 4 cycles of chemotherapy had a median OS time of 26 months, and those who received fewer than 4 cycles had a median survival time of 22 months (P=0.16). However, additional studies showed that induction chemotherapy was an independent prognostic factor in patients treated with comprehensive treatment, and the risk of death for patients who received induction

chemotherapy was significantly lower than that for patients who did not receive induction chemotherapy (HR, 0.5; P = 0.007) (25). These findings suggest that induction chemotherapy might help improve survival for mNPC patients, but the survival outcomes might not be further improved with excessive cycles of systemic chemotherapy (>6).

In addition to the number of chemotherapy cycles, the dose of locoregional RT is also closely related to the OS of mNPC patients. As systemic chemotherapy is the main treatment for mNPC patients and locoregional RT is often used to control the symptoms of primary tumors, radical doses of locoregional RT are rarely used. Approximately 18.2-30.8% of patients were only treated with less than 66 Gy of locoregional RT (23,25). Lin Shaojun and colleagues reported that the median OS time of patients who received more than 65 Gy of radical RT was 27 months, which is significantly longer than that of patients who received less than 65 Gy of RT (median OS time: 12 months, P=0.05) (23). Our study also showed that in patients who received combined locoregional RT and systemic chemotherapy (n=176), radical locoregional RT (≥66 Gy) was associated with favorable survival outcomes (median survival time: 51.0 vs. 23.3, P=0.001). Moreover, according to the multivariable Cox model, more than 66Gy of radical RT is an independent prognostic factor (HR, 0.4, P = 0.001) (25). Therefore, according to the previous findings, moderate induction chemotherapy (approximately 6 cycles) and radical locoregional RT (≥ 66 Gy) should lead to significant survival benefits for mNPC patients.

Therefore, we designed this open-label multicenter randomized controlled clinical trial to compare the efficacy, therapeutic toxicity, and resulting quality of life of induction chemotherapy combined with radically dosed primary RT with those of systemic chemotherapy alone for the treatment of chemotherapy-sensitive mNPC

patients. The difference between therapies is intended to clearly answer the following clinical scientific question that currently needs to be addressed: "Can primary radical RT extend the survival time of NPC patients with distant metastasis?"

2.0 Objectives

2.1 The Primary Objectives

To evaluate and compare the short-term and long-term effects on OS between the chemotherapy plus RT group and chemotherapy alone group in chemotherapy-sensitive mNPC patients

2.2 The Secondary Objectives

To evaluate the tumor remission rates and progression-free survival between the chemotherapy plus RT group and the chemotherapy alone group in chemotherapy-sensitive mNPC patients and to evaluate and compare the acute toxicities including oral mucosa, dermatologic, hematologic, hepatic, and renal toxicities and long-term toxicities including neurotoxicity, ototoxicity, radiation damage, etc. between the chemotherapy plus RT group and the chemotherapy alone group in chemotherapy-sensitive mNPC patients.

3.0 Subject Enrollment

3.1 Eligibility Criteria

a. Histologically confirmed NPC
b. Clinically staged as T1-4N0-3M1, stage IVc at diagnosis (according to the 7^{th} AJCC edition)
c. No previous systemic chemotherapy
d. Age between 18-65 years
e. Adequate organ function (white blood cell count of at least $4.0x10^9$ per L; absolute neutrophil of at least $2.0x10^9$ per L; hemoglobin concentrations of at

least 90 g/L; platelet cell count of at least 100 $x10^9$ per L; aspartate transaminase and alanine transaminase levels less than 2.5 times the upper normal limit; and creatinine clearance rate at least 60 mL/min)

f. Satisfactory performance status: Karnofsky scale (KPS)>=70

g. Achieve a partial response (PR)/complete response (CR) after 3 cycles of chemotherapy

h. Properly informed about the investigational nature of this study and give written informed consent.

3.2 Exclusion Criteria

a. Recurrent metastatic nasopharyngeal carcinoma, which developed distant metastases after primary treatment.

b. Age > 65 or < 18 years

c. Prior RT, chemotherapy or surgery for the primary tumor or nodes

d. Progressive disease (PD)/stable disease (SD) after 3 cycles of chemotherapy

e. Pregnancy or lactation

f. Any severe intercurrent disease, which may cause unacceptable risk factors or affect compliance with the trial, for example, severe heart diseases (cardiac functional grade of 3 or lower), severe pulmonary dysfunction (pulmonary function grade of 3 or lower), renal diseases, severe metal diseases.

g. Other invasive malignant diseases within the past 5 years, other than excised basal cell skin carcinoma, cervical carcinoma in situ, and superficial bladder tumors (Ta, Tis, and T1)

3.3 Criteria for Removal from Protocol Treatment

a. More than a 2-week delay in treatment due to prolonged drug toxicity

b. Unacceptable toxicity

c. Disease progression

d. Intercurrent diseases that affect the assessments of clinical status to a significant degree or require discontinuation of the drugs, or both

e. Withdrawal from the study at any time for any reason

4.0 Treatment Plan

4.1 Chemotherapy

4.1.1 Cisplatin Plus Fluorouracil Regimen (Experimental and Control Arm)

Cisplatin is intravenously given at a dose of 100 mg/m^2 on day 1 and once every 3 weeks for a maximum of six cycles

Fluorouracil is given at a dose of 5 g/m^2 via a continuous intravenous infusion over 120 h once every 3 weeks for a maximum of six cycles.

Note:

* If severe tumor compression and destruction symptoms occur during follow-up, including severe pain, pathological fracture, etc., then according to the clinical needs to control local symptoms and improve quality of life, the appropriate treatment will be provided, including surgery, RT and local chemotherapy (e.g., TACE for the treatment of liver metastases).

4.1.2 Administration

To prevent the nephrotoxic effects of cisplatin, we apply a 4-day hydration protocol before and during the administration of cisplatin (D0-D3) and used furosemide (D1) and mannitol (D1-D2). We use antiemetic drugs, such as the 5-HT_3- receptor antagonist dexamethasone, to prevent chemotherapy-induced nausea and vomiting.

4.1.3 Dosage Adjustments

4.1.3.1 Patients will be examined and graded each day when chemotherapy is

administered and weekly while receiving RT for subjective/objective evidence of developing toxicity according to the CTCAE, v.3.0.

4.1.3.2 There is no dose escalation for cisplatin and fluorouracil.

Cisplatin Dose Levels		
-2	-1	Starting Dose
60 mg/m^2	80 mg/m^2	100 mg/m^2

Fluorouracil Dose Levels		
-2	-1	Starting Dose
3000 mg/m^2	4000 mg/m^2	5000 mg/m^2

Dose Adjustment for Hematologic Toxicity				
Absolute Neutrophil Count		Platelet Count	Cisplatin Dose Adjustment	Fluorouracil Dose Adjustment
>1.50x10^9/L	and	>75.00x10^9/L	Full dose	Full dose
1.00-1.49 x10^9/L	and/or	50.00-74.99 x10^9/L	Decrease 1 Level	Full dose
<1.00 x10^9/L	and/or	<50.00 x10^9/L	Decrease 2 Level	Decrease 1 Level

Dose Adjustment for Renal Toxicity				
Absolute Creatinine		Creatinine Clearance Rate[1]	Cisplatin Dose Adjustment	Fluorouracil Dose Adjustment
≤ 1.5x upper normal value	and/or	≥ 50 mL/min	Full dose	Full dose
> 1.5x upper normal value	and	40-50 mL/min	Decrease 1 Level	Full dose

> 1.5x upper normal value	and	<40 mL/min	Withhold drug[2]

Dose Adjustment for Mucosal Toxicity			
Oral Mucositis		Diarrhea	Fluorouracil Dose Adjustment
≤ Level 2	or	≤ Level 2	Full dose
Level 3	or	Level 3	Decrease 1 Level
Level 4	or	Level 4	Decrease 2 Level

[1]. The creatinine clearance is calculated with the Cockcroft formula.

[2]. If the creatinine clearance rate remains <40 mL/min, and/or the bilirubin level is more than 2 times the upper normal limit, then the patient will not receive additional cisplatin or fluorouracil.

4.2 Radiotherapy

Patients are examined and graded for subjective/objective evidence of acute toxicities according to the CTCAE toxicity criteria.

4.2.1 Radiotherapy Adjustments for Nonhematologic Toxicity:

The side effects of RT may include mucositis and skin reactions. The investigators manage these conditions according to the clinical practice at the institution. We do not allow RT dose modifications. Treatment interruptions are allowed if the symptomatic mucositis or skin reactions that occur warranted a break in treatment, as judged by the attending clinician. The treatment is completed according to the protocol and allowed for treatment breaks up to and including 14 days. If the break exceeds 14 days, the patient will be removed from the protocol treatment, the completion of treatment is at the discretion of his or her physician, but the patient will be still followed up and included in the

analysis.

4.2.2 Radiotherapy Adjustments for Hematologic Toxicity:

RT will be withheld until the absolute neutrophil count is >500 and platelet count is >25000.

4.2.3 Target Volume Determination for IMRT:

RT is required to be given through IMRT techniques. The target volumes are delineated using pre-chemotherapy imaging data according to a previously described institutional treatment protocol and in accordance with the International Commission on Radiation Units and Measurements reports 50 and 62. The principles of target volume determination for IMRT and prescribed dose and fractionation are as follows:

Term	Definition	Note
Gross tumor volume (GTV)	The gross tumor determined by physical examination, imaging (including MRI and PET/CT) and endoscopic findings, including GTVnx and GTVnd	
GTVnx	The sum of the primary tumor volume and enlarged retropharyngeal nodes	
GTVnd	Volume of the clinically involved gross lymph nodes	
CTV1	GTVnx plus an additional anterior, superior, inferior and lateral margin of 5 mm to 10 mm and additional posterior margins of 2 mm to 3 mm (the range of extension was determined by the	The volume also included the entire mucosal stratum and 5 mm of the nasopharyngeal

	characteristics of the adjacent structures)	submucosal stratum
CTV2*	CTV1 plus an additional anterior, superior, inferior and lateral margin of 5 mm to 10 mm and an additional posterior margin of 2 mm to 3 mm (the range of extension was determined by the characteristics of the adjacent structures), as well as the GTVnd plus possible tumor-draining lymph node groups that were at risk for potential microscopic spread of disease	The range for prophylactic neck radiation extended from the involved lymph node groups to 1 or 2 adjacent groups
PTV	Generally, PTVnx, PTVnd, PTV1, and PTV2 refers to GTVnx, GTVnd, CTV1, and CTV2 plus an additional margin, an anterior, superior, inferior, lateral extension of 5 mm, and a posterior extension of 3 mm, respectively	
Organs at risk	Brainstem, temporal lobe, lens, eyeballs, optic nerves, optic chiasm, pituitary, parotid gland, temporomandibular joint, mandible, larynx, oral cavity, salivary gland, and inner and middle ear	Organs could be added or removed according to the actual situation

*Level Ib was electively irradiated if the following conditions were met: (1) the level Ib lymph nodes (LNs) were involved; (2) the level IIa LNs had extracapsular extension or a diameter ≥ 3 cm; (3) there was extensive nodal disease on the ipsilateral neck; or (4) the soft or hard palate, oral cavity, or ipsilateral nasal cavity was grossly involved.

4.2.4 Prescribed Dose and Fractionation:

All patients are treated with IMRT using a simultaneously integrated boost with 5 fractions per week. The prescribed doses are 66–70 Gy to the planning target volume (PTV), 56-66 Gy to PTV1, 50-60 Gy to PTV2, and 60–66 Gy to the PTV of the involved cervical LNs in 28 to 33 fractions.

4.2.5 Normal Tissue Dose Constraints:

Normal Tissue Dose Constraint Structure

Structure	Dose constraints
Spinal cord	Dmax* ≤ 45 Gy
Spinal cord_PRV	D1~ ≤ 54 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$^{\omega}$ < 8Gy
Pituitary	Dmax ≤ 60 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

PRV=planning organ-at-risk volume.

[*]Maximum point dose to the target volume.

[≈]Dose received by 1% of the target volume.

[ω]Mean dose to the target volume.

[&]At least 50% of the gland received <30 Gy (was achieved in at least gland)

4.3 Salvage Therapy

Second- or third-line chemotherapy will be provided for patients with disease progression. Local treatment for metastatic lesions, including definitive RT, surgical resection, ablation, or other treatments are used for some patients to control local symptoms and eliminate metastases in the bone, liver, lungs, or other organs. Additionally, locoregional RT are also offered in the chemotherapy alone group.

Observation and Assessment

During the initial screening period, eligible mNPC patients are treated with a cisplatin plus fluorouracil regimen. After 3 cycles of chemotherapy, an efficacy evaluation will be performed, and a second screening process (screening confirmation period) will be also performed. The patients who are evaluated to achieve CR or PR after 3 cycles of chemotherapy will be officially registered and enrolled. Patients who are not sensitive to chemotherapy (evaluated as having SD or PD after 3 cycles of chemotherapy) will be excluded.

5.1 Initial Screening Period

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

the trial, including the following:

a. Medical history review

b. Personal data collection

c. Review of present medications and treatment

d. Body examinations, including height, weight, and vital signs

e. Physical examination of the head and neck region, including the nasopharyngeal and cervical LNs

f. Physical examination of the nervous system

g. Nasal endoscopy and lesion biopsy

h. Biopsy or needle aspiration of distant metastases

i. Blood routine

j. Urine routine

k. Blood biochemistry

l. Imaging test of the tumor (enhanced MR or enhanced CT of the head and neck (CT was indicated only in patients with contraindications to MRI))

m. PET/CT is compulsorily required during the initial screening period*

*Patients who underwent PET/CT examinations did not need chest X-rays, abdominal ultrasonography, or ECT bone scans.

5.2 Screening Confirmation Period

a. PET-CT, MRI and/or CT of the primary tumor and distant metastases, which is performed after treatment, and CR, PR, SD, or PD is evaluated according to the RECIST version 1.1 criteria.

b. Physical examinations of the head and neck region, including the nasopharyngeal and cervical LNs

5.3 During Treatment

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

a. MRI and/or CT of the primary tumor and distant metastases, which is performed after treatment, and CR, PR, SD, or PD is evaluated according to the RECIST version 1.1 criteria. The chest films and abdominal ultrasonography are reexamined after treatment. PET-CT and ECT bone scans are performed as clinically indicated.

b. General conditions

c. Acute and late toxicities assessment (NCI-CTC, version 3.0), including for hematological toxicity, gastrointestinal reactions, hepatotoxicity, nephrotoxicity, mucositis, neurotoxicity, ototoxicity, etc.

d. Peripheral neuropathy

e. Laboratory tests: blood routine and blood biochemistry are required within 1 week prior to each cycle of chemotherapy and once per week during treatment.

6.0 Follow-Up and Recording of Events

After completing treatment, the patients are followed up every 2 to 3 months until death to evaluate the patients' recent and long-term efficacy and safety profiles.

Follow-up method: Record of the patient's examination data, a doctor's letter with signature to document the visit, or a doctor's follow-up records collected by telephone

Follow-up content: Routine examination of the nasopharyngeal lesions and LNs, and B-mode ultrasound, chest X-ray, and CT or MR examinations of the distant metastases every 3 months. PET/CT or bone scintigraphy are performed when clinically indicated. The treatment responses are also evaluated according to the RECIST criteria. The earliest date of detecting symptomatic late toxicities 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) are recorded.

7.0 Security Measures and Quality Control

a. Provide a systemic learning program for every member in the research group Assigned one doctor in each center to lead tumor staging, which must be in accordance with the 7th edition AJCC guidelines and to ensure that every patient enrolled is eligible. Patients are assigned to their groups based on random numbers
b. Make a monitoring plan for adverse effects and an emergency plan
c. Research plan is made by all participating centers and approved by the ethics committee
d. Develop various standard operation procedures related to this study
e. Establish a standardized evaluation system to unify the diagnostic criteria, curative effect judging criteria, etc.
f. Establish professional statistical plans
g. Research staff members are trained before the study
h. Ensure that every participating center conducts the study at the same pace
i. Arrange a quality controller to create a quality control plan and regularly check on the study
j. Set up a coordination committee, curative effect judging group and follow-up team

8.0 Statistical Analysis

8.1 Endpoint Definitions

8.1.1 Primary Endpoint

OS is defined as the time from random assignment to death from any cause, or the patient was censored at the date of the last follow-up.

8.1.2 Secondary Endpoints

8.1.2.1 Progression-free survival (PFS): PFS is defined as the time from random assignment to the date of documented local or regional relapse, distant metastasis, or death from any cause, whichever occurs first.

8.1.2.2 Short-term response: Treatment response is assessed by imaging by independent image committee every three cycles until disease progression. The nasopharyngeal tumor, cervical LN, and distant metastasis responses are observed and evaluated by physical examinations, nasopharyngoscopy, and MRI/CT imaging. Tumor response is classified according to the RECIST criteria, version 1.1. CR is defined as the disappearance of all target lesions. Any pathological LNs (whether target or nontarget) must have been reduced in the short axis to <10 mm. PR is defined as an at least 30% decrease in the sum of diameters of the target lesions, with the baseline diameter sum serving as the reference. PD is defined as an at least 20% increase in the sum of diameters of the target lesions, with the smallest sum during study serving as the reference (including the baseline sum). In addition to a 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 disease progression). SD is defined as both insufficient size reduction to qualify as PR and an insufficient increase to be considered PD, with the smallest diameter sum during the study serving as the reference. Proportion of patients who have a confirmed objective response are defined as a CR or PR from the first evaluation after 3 cycles of chemotherapy with PF until disease progression or death according to the RECIST 1.1 criteria). Proportion of patients who achieve disease control are defined as an objective response and stable disease.

8.1.2.3 Safety indicators: Acute toxicities are assessed according to the

NCI-CTC version 3.0. The acute toxicities include hematologic toxicity, mucositis, allergic reactions and other adverse events and serious adverse events. Late radiation toxicities are assessed using the RTOG and EORTC late radiation morbidity scoring scheme. The late toxicities include neurotoxicity, ototoxicity and other complications and sequelae.

8.2 Sample Size Estimate

To confirm the superiority of systemic chemotherapy plus RT over systemic chemotherapy alone regarding OS. On the basis of previous reports[22,23,24], we assume that 2-year OS rate is 51.0% for patients treated with systemic chemotherapy alone, and 70.0% for patients treated with systemic chemotherapy plus radiotherapy, with a target hazard ratio (HR) of 0.530. The log-rank test is used to calculate the sample size. The expected length of the accrual period is 3 years, and the expected maximum length of follow-up is 5 years. The two-sided type I error is 0.05 ($\alpha = 0.05$), and the power is 0.90 (1-β). After accounting for a 10% dropout rate, we estimat that a total of 204 participants are needed, (102 participants in each group), in order for 104 events to be observed for the primary analysis of overall survival.

8.3 Independent Trial Data Monitoring Committee (IDMC)

The PI hired Professor Yi-Min Liu as the IDMC for this study. After the enrolled patients are registered, all patient information will be sent to the IDMC, who manage the database, and is involved in the statistical analysis, data interpretation, and toxicity data review. As per institutional (SYSUCC) practice, the data is to be reviewed once a year to evaluate safety. Futility is also assessed to avoid over-treatment of patients with metastatic disease. For the final analysis, this is to

be performed by the investigators (Rui You and Sze Huey Tan).

Members of the Independent Data Monitoring Committee (IDMC).

Position	**Name**	**Job Title**	**Specialty**
Chairman	Yi-Min Liu	Department of Radiotherapy Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University/Professor	Radiotherapy Oncology
Member	Wen Chen	School of Public Health, Sun Yat-sen University/Professor	Health Statistics
Member	Gang Li	Department of Otorhinolaryngology, Southern Medical University Nanfang Hospital/Professor	Otorhinolaryngology
Member	Yi Pan	Department of Radiotherapy Oncology, Guangdong Provincial People's Hospital/Professor	Radiotherapy Oncology
Member	Jing-Qi Chen	The Ethics Committee and Department of Medical Oncology of the Second Affiliated Hospital of Guangzhou Medical University Chairman/Professor	Oncology

8.4 Stratification/Randomization Scheme

8.4.1 Stratification

Patients are stratified according to treatment centers (Sun Yat-sen University Cancer Center, Guangdong Provincial People's Hospital, and The First Affiliated Hospital, Sun Yat-sen University), the number of metastatic lesions (1-2 vs ≥3) and treatment response (complete response vs partial response).

8.4.2 Randomization

The patients who are evaluated achieving CR or PR after 3 cycles of chemotherapy are officially registered, enrolled and randomized. The eligible patients are randomized using a 1:1 allocation to a chemotherapy plus RT arm and a chemotherapy alone arm. Stratified randomization is performed within each stratum based on the number of metastatic lesions, the treatment centers and treatment response. The randomized block design is conducted by the data management team, and the data management team choose the block size so that each block contains an equal proportion of patients. This procedure helps to ensure both randomness and investigator blinding (the block sizes are known only by the data management treatment), as recommended by Friedman et al (Friedman J, Furberg, C, DeMets D. Fundamentals of clinical trials. New York: Springer-Verlag; 1998). Randomization is performed by the data management team, and the results are placed in opaque, sealed envelopes labeled by stratum, which are only unsealed after patient registration. The patients are identified by a unique subject number that remains consistent for the duration of the study.

8.5 Case Report Form (CRF)

The required CRF is designed before the study to record the detailed medical history, treatment outcomes and follow-up information; the CRF is designed to be

easy to fill in and to save in the database.

8.6 Analytical Approach

The results of our study are analyzed by the intention-to-treat (ITT) approach, and all eligible patients are analyzed according to the randomization scheme, including the patients whose treatment plan is changed from chemotherapy plus RT to chemotherapy alone. The Kaplan-Meier estimator is used to estimate the survival function from lifetime data, and the log-rank test is used to compare the differences in survivals between the two groups. The response rates and incidence of toxicities are compared by the chi-square test. The Cox proportional-hazards model is used to calculate the hazard ratios and 95% confidence intervals. The statistical tests are two-sided, and a P value < 0.05 is considered statistically significant.

The analyses included the following:

General information: The distribution and equilibrium of general factors, such as age, sex, and disease stage, are assessed.

Adverse effects:

Acute and late toxicities, sequelae and complications in each arm are assessed according to NCI-CTC version 3.0

Short-term effects:

CR, PR, SD, PD, overall response rate, and disease control rate are evaluated with the RECIST criteria.

Long-term curative effects:

24-months OS and PFS rates, median OS, median PFS are calculated according to follow-up data.

9.0 Ethical Considerations

9.1 This study was approved by an appropriate institutional ethics committee.

9.2 Informed consent is obtained from the individual patients. A copy of the consent form and contact number for the investigators and ethics committee are available to the patients upon request.

9.3 The advantages and disadvantages of chemotherapy plus RT in treating mNPC patients are mentioned below:

9.3.1 Advantages:

a. Chemotherapy plus RT is expected to bring significant survival benefits to mNPC patients.

b. Locoregional RT is expected to significantly improve the compressive and destructive symptoms caused by nasopharyngeal and cervical tumors, such as headache and bleeding.

c. Locoregional RT might help minimize the metastatic spread of NPC cells.

d. Active locoregional RT is beneficial for the patients' determination to fight cancer and improve their mental state.

9.3.2 Disadvantages:

a. Chemotherapy plus RT increases the financial burden for mNPC patients.

b. Locoregional RT causes radiation injuries such as dry mouth and sore throat, thereby affecting the quality of life of some patients.

9.4 Chemotherapy plus RT is expected to bring significant survival benefits to patients [22-25], to control local symptoms, to reduce further distant metastasis and to improve the patient's mental state, thus greatly benefiting patients, their family and society. Moreover, previous studies have shown that most NPC patients could tolerate RT well and that the complications from radiation were acceptable, especially in the IMRT era. Although RT could increase the economic

burden of patients to a certain extent, distant metastases of NPC are incurable, and proportionally, the RT costs are relatively low over the course of long-term treatment. More importantly, if the use of locoregional RT can help patients achieve a longer tumor remission time and a better survival outcome, then the use of RT will lower the cost of treatment and thus the overall cost. Therefore, the advantages of using locoregional RT for mNPC will outweigh the disadvantages.

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Appendix I

STAGING CRITERIA – the 7th AJCC edition

Tumor

• T1 - confined to the nasopharynx, or the tumor extends to the oropharynx and/or nasal cavity without parapharyngeal extension

• T2 - tumor with parapharyngeal extension (posterolateral infiltration, i.e., beyond the pharyngobasilar fascia)

• T3 - involves the bony structures and/or paranasal sinuses

• T4 - intracranial extension and/or involvement of the cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space

Nodes

• N1 - unilateral nodes (6 cm or less) above the supraclavicular fossa, and/or retropharyngeal LNs 6 cm or less (unilateral or bilateral)

• N2 - bilateral nodes (6 cm or less) above the supraclavicular fossa

• N3a - lymph nodes greater than 6 cm

• N3b - extension to the supraclavicular fossa (defined as the triangular region described by Ho and bounded by the superior margin of the sternal head of the clavicle, the superior margin of the lateral end of the clavicle, and the point where the neck meets the shoulder. These features are present in some level IV as well as level V tumors.)

Overall stage

• I - T1 N0

• II - T1-T2 N1, T2 N0 (i.e., T2 or N1)

• III - T3 N0-2, or T1-3 N2 (i.e., T3 or N2)

• IVA - T4 N0-2

- IVB - N3
- IVC - 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 normal activity; some signs or symptoms of disease
70	Cares for self; unable to normal activity or to do active work
60	Requires occasional assistance but is able to care for most of his or her 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