Clinical Research Project of Guangdong Medical University Affiliated Hospital

Project Name	Efficacy and Safety of Sapylin Versus Dexamethasone Atomized Inhalation for Concurrent Chemoradiotherapy-Induced Oral Mucositis in Patients With Nasopharyngeal Carcinoma: A Randomized, Parallel, Non-inferiority Clinical Trial		
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Efficacy and Safety of Sapylin Versus Dexamethasone Atomized Inhalation for Concurrent Chemoradiotherapy-Induced Oral Mucositis in Patients With Nasopharyngeal Carcinoma: A Randomized, Parallel, Non-inferiority Clinical Trial

I. Rationale

1.Background

Nasopharyngeal carcinoma (NPC), an epithelial malignancy originating from the nasopharyngeal mucosa, is one of the common head and neck malignancies. Globally, 70% of new cases occur in East and Southeast Asia[1]. Nearly 80% of global patients are concentrated in China, leading to its nickname, "China Cancer". Within China, it is highly prevalent in the southern regions, especially the Guangdong, Guangxi areas and Hong Kong, hence the common name "Guangdong Cancer". Currently, radiotherapy is the primary treatment modality for NPC. Seventy percent of patients are diagnosed at an advanced stage. For Locally Advanced NPC (LA-NPC), induction chemotherapy combined with Concurrent Chemoradiotherapy (CCRT) is the standard treatment regimen[1,2]. Since the adoption of induction chemotherapy combined with CCRT for LA-NPC patients, overall survival rates have improved[3,4]. However, over 20% of LA-NPC patients still experience treatment failure and have a 5-year survival rate lower than 5 years[5]. Furthermore, during radiotherapy, the radiation causes varying degrees of damage to the normal tissues adjacent to the tumor. Adverse reactions such as dry mouth and radiation-induced oral mucositis can reduce patient compliance. In severe cases, these can lead to clinical adverse outcomes such as reduced radiation dosage, treatment interruption, prolonged hospitalization, or even life-threatening situations, thereby negatively impacting the efficacy and quality of life associated with CCRT[6]. The INT0099 trial showed that 37% of patients receiving CCRT terminated treatment prematurely due to excessive toxicity[7].

Among radiation-induced adverse reactions, radiation-induced oral mucositis (RIOM) occurs in over 80% of patients undergoing radiotherapy. More than 50% of these patients even develop Grade 3-4 RIOM[8,9]. Current clinical strategies for the prevention and treatment of RIOM include oral care, gargling medications, nebulized inhalation drugs, and local application of epidermal growth factor. Nebulized drug therapy has become an important method in cancer supportive care due to its ability to increase local drug concentration, decrease blood drug concentration, and achieve better compliance. MASCC/ISOO, ESMO, and other authoritative guidelines agree that there is currently no specific drug for the prevention and treatment of RIOM. Treatment focuses primarily on symptom relief and reducing complications. Epidermal Growth Factor (EGF) and corticosteroids are recommended. However, the long-term use of corticosteroids increases the risk of fungal infection and tends to cause radiotherapy interruptions. There is an urgent need for a highly effective and low-toxicity drug to prevent and treat RIOM. Zhao Weiwei[10] and Chai Xieli[11], among others, concluded from relevant domestic and international studies that nebulized

inhalation therapy is a non-invasive, highly efficient, and low-side-effect approach in oncology treatment. However, the application of nebulized Sapylin is currently only reported in lung cancer, and its nebulized use in CCRT for NPC is rarely reported. Therefore, nebulized drug therapy for RIOM is one of the current research trends. Nishii et al.[12] found that local application of corticosteroids can relieve edema, inhibit inflammation, and alleviate patient symptoms. Systemic use of corticosteroids tends to reduce radiotherapy interruptions but does not decrease the incidence or severity of RIOM. However, long-term local use of corticosteroids increases the risk of oral fungal infections[12]. Nebulized traditional Chinese medicines lack multi-center clinical trials to evaluate their efficacy[13], thus limiting their application in NPC patients. However, a safer and more effective strategy is currently unavailable. Therefore, finding a drug with high efficacy and low side effects to improve RIOM in NPC patients and, consequently, enhance CCRT efficacy is crucial.

Sapylin (Group A streptococcus) is a Biological Response Modifier (BRM) with antitumor immune effects. Its main component is a lyophilized product of Group A streptococcus treated with penicillin. It effectively inhibits cancer cell proliferation, significantly enhances immune function, and increases the activity of various immune cells. It is widely used clinically to boost the immunity of cancer patients[14,15]. In recent years, Sapylin has been used as an immune adjuvant in various cancers, such as lung cancer[16-18], breast cancer[19], gastric cancer[20], and bladder cancer[21]. It has been shown to promote wound healing, enhance the efficacy of chemotherapy, and inhibit tumor cell proliferation. However, its role in tumor radiotherapy and its application in NPC patients are rarely reported. Sapylin (OK-432) is considered an adjuvant in cancer immunotherapy and has proven non-specific immune anti-tumor function. Additionally, Sapylin is believed to improve pleural fluid osmotic pressure and effectively reduce pleural effusion in some benign pulmonary diseases. To evaluate the effect of Sapylin on surgical treatment and immune function regulation in patients with thoracic malignancies, Tian et al.[22] investigated the clinical data of 71 patients who received Sapylin in the surgical area shortly after surgery. Local intraoperative application of Sapylin (OK-432) was found to enhance early postoperative immune function in patients with thoracic malignancies, promote postoperative recovery, and improve prognosis. This implies it can reduce postoperative chest drainage, shorten intubation and hospital stay, and decrease patient suffering. The conventional routes of Sapylin (OK-432) administration are intramuscular and subcutaneous injection, which can cause injection site pain and fever. Nebulized inhalation of Sapylin is non-invasive, highly efficient, and has low side effects. Moreover, it can exert its effects in improving RIOM and its antitumor activity by enhancing cellular immunity. This approach may be a safe and effective method for LA-NPC patients receiving induction chemotherapy combined with CCRT. This study is the first prospective, randomized controlled trial to evaluate the incidence rate, severity, efficacy, and survival analysis of RIOM in NPC patients receiving CCRT combined with nebulized Sapylin versus CCRT combined with nebulized Dexamethasone. It aims to provide innovative research evidence for the correct use of Sapylin in LA-NPC patients. This study provides scientific evidence for a prospective randomized investigation into whether nebulized Sapylin can reduce the incidence and severity of RIOM in LA-NPC patients.

2. Current Status of Domestic and International Research

(1) Current status of concurrent chemoradiotherapy for locally advanced NPC

Studies over the past 20 years indicate that concurrent chemoradiotherapy (CCRT) plays a crucial role in the treatment of LA-NPC. Both clinical studies and meta-analyses have confirmed that induction chemotherapy combined with CCRT offers significant survival benefits compared to radiotherapy alone, especially for patients with locally advanced disease. A Phase III clinical study enrolled 284 patients with Stage III and IV NPC without distant metastasis, randomly assigning them to a radiotherapy-alone group or an induction chemotherapy combined with CCRT group. The results showed that the locoregional failure rate and distant metastasis rate in the CCRT group were significantly lower than those in the radiotherapy-alone group. Furthermore, the 5-year nasopharyngeal failure-free survival rate (89.3%), failure-free survival rate (71.6%), and overall survival rate (72.3%) in the induction chemotherapy combined with CCRT group were significantly higher than those in the latter, with only a mild increase in Grade 3/4 acute toxicities[23]. A Phase III clinical study conducted by Chan et al.[24] reached similar conclusions, showing that the 5-year OS of the concurrent group was significantly higher than that of the radiotherapy-alone group, with a hazard ratio for death of 0.71, which further decreased to 0.51 in the T3-4 subgroup analysis. A meta-analysis comparing induction chemotherapy combined with CCRT versus radiotherapy alone (including a total of 1608 patients) showed that the relative risks (RRs) for death at 2, 3, and 5 years in the induction chemotherapy combined with CCRT group were [0.63, 95% CI (0.50–0.80)], [0.76, 95% CI (0.61–0.93)], and [0.74, 95% CI (0.62–0.89)], respectively [25]. Currently, induction chemotherapy combined with CCRT has become the standard treatment model for LA-NPC. The latest NCCN guidelines recommend induction chemotherapy combined with CCRT as one of the standard treatment regimens for LA-NPC[26]. However, studies have shown that CCRT is associated with higher toxicity compared to radiotherapy alone, and these toxicities can reduce patient compliance and treatment efficacy. Liu et al.[27] comprehensively analyzed 2605 patients across 8 studies and found that in the era of Intensity-Modulated Radiation Therapy (IMRT), the efficacy of induction chemotherapy combined with CCRT was comparable to that of induction chemotherapy combined with radiotherapy alone, but induction chemotherapy combined with CCRT had a higher incidence of Grade 3/4 toxicities during radiotherapy. Therefore, in the IMRT era, induction chemotherapy combined with CCRT might be replaced by new treatment mode combinations. Currently, several ongoing prospective randomized clinical studies are comparing the efficacy of induction chemotherapy combined with CCRT against other comprehensive treatment modes that do not utilize induction chemotherapy combined with CCRT under the premise of using IMRT technology, and the results are eagerly anticipated. Additionally, radiation-induced toxicity remains one of the primary reasons affecting the therapeutic efficacy and quality of life of LA-NPC patients; reducing the incidence and severity of toxicity has become an urgent topic in current research.

(2) Research progress on the treatment of radiation-induced oral mucositis

Due to the high incidence and pathogenesis of RIOM, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) released updated clinical practice guidelines for mucositis in 2020[28]. Subsequently, ESMO also updated its guidelines for the prevention and treatment of RIOM[29]. In China, the Radiation Oncology Branch of the Chinese Medical Association released the Expert Consensus on Prevention and Treatment Strategies for Radiation-Induced Oral Mucositis in 2019[13]. Clinical practice guidelines and expert consensus believe that: prevention is the priority

for RIOM, with good oral hygiene environment and care being the primary preventive measures; there is currently no specific drug for the prevention and treatment of RIOM, and treatment mainly lies in alleviating symptoms and reducing the occurrence of complications. Nutrition support, pain control, and the prevention and treatment of secondary infections are considered the cornerstones of RIOM management. The guidelines and consensus list drugs currently used domestically and internationally for the prevention and treatment of RIOM, such as analgesics, Epidermal Growth Factor (EGF), corticosteroids, Amifostine, and Leucogen, but analgesics have drawbacks such as short duration of action and significant side effects. Nishii et al.[12] found that local use of corticosteroids can reduce edema, inhibit inflammatory responses, and alleviate patient symptoms, but long-term use increases the risk of oral fungal infections; while systemic use of corticosteroids has a trend of reducing radiotherapy interruptions, it does not reduce the incidence and severity of RIOM. Nicolatou-Galitis et al.[30] found that when Amifostine is administered intravenously, there are side effects such as hypotension, nausea, and infusion-related reactions, whereas subcutaneous injection 60 minutes before radiotherapy in head and neck cancer patients, although significantly reducing side effects, lowers efficacy and compliance. Furthermore, due to inconsistent conclusions across studies and insufficient evidence levels, the guidelines and consensus do not yet recommend recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF), glutamine, and supersaturated calcium phosphate mouthwashes for the prevention of RIOM, nor do they recommend the local prophylactic use of antibiotics and hormones[13,31,32].

Therefore, the Chinese expert consensus on prevention and treatment strategies for radiation-induced oral mucositis believes that although much research has been conducted on the prevention and treatment of RIOM, many prevention and treatment strategies remain controversial due to the lack of large-scale multicenter randomized controlled trials. It looks forward to carrying out big data analysis of multicenter symptom management, with a view to discovering more complete risk factors for RIOM and finding safer and more effective prevention and treatment strategies[33], thereby improving the efficacy of concurrent chemoradiotherapy in patients with NPC.

(3) Research progress on the role of Sapylin in cancer

Currently, many studies have proven that Sapylin, as an immune adjuvant, has demonstrated definite efficacy and good prospects in various cancers, such as lung cancer [16-18], breast cancer [19], gastric cancer[20], and bladder cancer[21]. Xie Chuanhua[16], Zhang Lin[17], Li Xuezhen[18], and others observed the efficacy of nebulized Sapylin combined with chemotherapy in the treatment of advanced non-small cell lung cancer (NSCLC) and found that nebulized Sapylin inhalation can improve chemotherapy efficacy and the body's immune function without obvious side effects. Yano et al.[31] found through basic in vitro experiments that the cytotoxic effect of OK-432 on lung cancer cell lines increased in a dose-dependent manner and induced alveolar macrophages to produce various cytokines, namely IL-1, Tumor Necrosis Factor-α (TNF-α), and IL-6. Based on in vitro experiments, they subsequently treated 6 patients with bronchioloalveolar carcinoma with pulmonary metastasis via nebulized OK-432 inhalation and found that no adverse reactions were observed in any patients, and the production of TNF-α by alveolar macrophages or anti-tumor cytotoxic activity was enhanced; however, the clinical efficacy of nebulized Sapylin on bronchioloalveolar carcinoma still requires further study. Zhang[21] et al. treated the lung cancer cell line A549 with different concentrations of Sapylin and detected the proliferation, apoptosis, and signaling pathway expression of A549 cells. They found that Sapylin promoted apoptosis in a dose- and time-dependent manner and inactivated the PI3K/AKT and WNT3a/β-catenin signaling

pathways, suggesting that Sapylin has the effect of inhibiting lung cancer cell proliferation and promoting apoptosis. In addition, Li Dong et al.[18], through a retrospective analysis of 100 lung cancer patients with pleural effusion, found that intrapleural perfusion of Sapylin can reduce malignant pleural effusion, lower the levels of cellular inflammatory factors and tumor markers in serum and pleural effusion, and alleviate the toxicity of single-agent Cisplatin perfusion chemotherapy. Kong[19] et al. included 120 patients undergoing modified radical mastectomy for breast cancer in a prospective continuous cohort study and proved that Sapylin can stimulate the body to secrete various cytokines and promote wound healing. Studies abroad have also shown that the in vivo and in vitro application of the streptococcal preparation OK-432 can induce the production of tumor growth inhibitory factors in human monocytes[32]. Similar to the above results, Ono et al.[33] found through in vitro cell experiments that the streptococcal preparation can inhibit nucleic acid synthesis in tumor cells, thereby exerting an anti-tumor effect. Therefore, studying the effect of Sapylin on patients with NPC and evaluating its safety has important clinical significance.

Previously, through extensive literature review, we found that while Sapylin administered via traditional methods can reduce malignant pleural effusion and improve immunity in cancer patients, patients experience reactions such as injection site pain and fever. In contrast, the nebulized inhalation method is not only safe and effective but also improves the patient's immunity, inhibits tumor cell proliferation, and enhances the efficacy of tumor chemotherapy drugs. Furthermore, we have currently collected 32 clinical cases (16 cases in the CCRT + Sapylin group, 16 cases in the CCRT + Dexamethasone group). The results revealed that nebulized Sapylin inhalation can improve the efficacy of CCRT and prolong patient survival, improve the incidence and severity of RIOM in NPC patients, and show no obvious toxic side effects. However, the application of nebulized Sapylin in cancer treatment is currently only seen in lung cancer studies both domestically and internationally. Whether its application in NPC patients can improve the efficacy of concurrent chemoradiotherapy and what its safety profile is like are rarely reported domestically or internationally and require further research and exploration. Therefore, we intend to explore the impact of Sapylin on the efficacy of concurrent chemoradiotherapy and the incidence and severity of RIOM in NPC patients via nebulized inhalation, aiming to find a highly efficient, low-toxicity method for NPC specialists and patients that can reduce the occurrence and severity of RIOM and improve the efficacy of CCRT.

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II. Research Content

1. Research Objectives and Significance

1.1 Research Objectives

(1) Primary Objective: The primary objective evaluated will be the incidence and severity of RIOM.

(2) Secondary Objectives: Secondary objectives include the duration of RIOM, the completion rate of the planned treatment regimen, the incidence and severity of adverse events as graded by CTCAE V5.0, as well as changes in body mass index (BMI).

1.2 Research Significance

This study intends to explore the impact of nebulized Sapylin inhalation on the therapeutic efficacy of CCRT in patients with NPC via nebulized inhalation, observe the effect of nebulized Sapylin inhalation on the incidence and severity of RIOM, and evaluate the safety of nebulized Sapylin inhalation. This study aims to find a highly efficient and low-toxicity method for NPC specialists and patients to reduce the occurrence and severity of RIOM and improve the efficacy of CCRT.

2. Research Goals and Content

2.1 Research Goals

The purpose of this study is to investigate the effects of atomized inhalation of Sapylin versus Dexamethasone on the incidence and severity of RIOM, and to further evaluate the safety and effectiveness of aerosol inhalation of Sapylin and Dexamethasone in NPC patients receiving CCRT. This study will provide NPC specialists and patients with an efficient and low-toxicity method to reduce the occurrence and severity of RIOM and improve the efficacy of CCRT.

2.2 Research Content

Under the guidance of Randomized Controlled Trial (RCT) principles, patients will be divided into an experimental group and a control group. Patients will receive standardized treatment using the designed clinical treatment protocol, changes in patients' clinical observation indicators during treatment will be recorded, and follow-up records will be made according to the scheduled time to collect clinical data. Using statistical methods for comprehensive analysis, the results of this study will provide scientific research evidence for exploring methods to improve the occurrence and severity of RIOM and enhance the efficacy of CCRT.

3. Research Protocol

3.1 Study Design Type

Non-inferiority, parallel-design, randomized controlled clinical study.

3.2 Research Methods

(1) Incidence and Severity of RIOM

Guided by the principles of RCT, this study provides scientific research evidence to explore methods for improving the occurrence and severity of RIOM and enhancing the efficacy of CCRT. Specialized clinicians will observe whether patients develop RIOM and assess its severity during daily rounds, recording these in the progress notes. Grading will be performed using the WHO oral toxicity scale. The incidence and severity of RIOM will be statistically analyzed after the completion of concurrent chemoradiotherapy.

(2) Duration of Radiation-Induced Oral Mucositis (RIOM)

The duration of Radiation-Induced Oral Mucositis (RIOM) will be calculated from the day of its initial diagnosis (any grade) until the day it resolves to Grade 0 or baseline level, with this duration being assessed and documented daily in the medical records by the attending clinician during ward rounds.

(3) Completion Rate of Treatment Modalities

The completion rate of treatment modalities will be determined by recording the actual

administered dose and number of cycles of concurrent chemoradiation therapy (CCRT) versus the planned total regimen; this rate is calculated as two ratios: the actual administered dose divided by the planned total dose, expressed as a percentage, and the actual completed cycles divided by the planned total cycles, also expressed as a percentage.

(4) Adverse Events (AEs)

All observed adverse events (AEs) will be recorded and graded daily by the clinician based on patient complaints, physical examination, and laboratory test results, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 published by the National Cancer Institute (NCI).

(5) Change in Body Mass Index (BMI)

Patient height and weight will be measured by the nursing staff at a fixed time using the same calibrated instrument at two time points—before the initiation of CCRT (baseline) and upon completion of treatment—with the resulting BMI (kg/m^2) difference (*post-Treatment BMI-Baseline BMI*) constituting the change in BMI.

3.3 Inclusion and Exclusion Criteria and Sample Size Estimation

(1) Patient Selection: Meeting the diagnostic criteria for NPC; patients who have not yet received concurrent chemoradiotherapy; meeting the case inclusion and exclusion criteria; patients voluntarily joining this clinical trial and signing the informed consent form.

(2) Sample Size Estimation: The Delphi method is used to determine the non-inferiority margin of the observation endpoint. After consulting senior oncology practitioners, we defined an 8% reduction in the incidence of RIOM as a clinically acceptable non-margin of error. Under the conditions of test level a=0.05 and test efficacy 1-β=0.9, the proportion of cases in the two groups is 1:1. Using the module of non-destructiveness Tests for Two Proportions in PASS 15.0 statistical analysis software, we determined that a sample size of 81 was required per group. Considering a 10% loss to follow-up rate, we estimated that 90 cases would be required in each group, for a total of 180 cases.

3.4 Randomization Method

This study employs a block randomization method. Random sequences are generated by independent statistical personnel who are not involved in clinical procedures, utilizing statistical software. After patient enrollment, the research personnel access a centralized remote randomization system to obtain the patient's treatment assignment result, thereby allocating patients to either the Sapylin group or the Dexamethasone group at a 1:1 ratio. This procedure ensures the separation of random sequence generation and execution, maximizing the randomness and concealment of the allocation.

3.5 Clinical Treatment Protocol

(1) Experimental Group

Concurrent Radiotherapy Dose: Nasopharyngeal primary tumor site (PTVnx): 69.96Gy/2.12Gy/33F; High-risk planning target volume (PTV1): 60.06Gy/1.82Gy/33F; Low-risk

planning target volume (PTV2): 54.12Gy/1.64Gy/33F; Cervical lymph nodes (PTVnd): 66~69.96Gy/2~2.12Gy/33F; 5 times per week, for a total of 6-7 weeks.

Concurrent Chemotherapy: Cisplatin (80-100 mg/m^2, Q3W, 3 times during CCRT); Sapylin: 1 KE/time, nebulized, QD, starting from Day 1 of CCRT until the end of radiotherapy.

(2) Control Group:

Concurrent Radiotherapy Dose: Nasopharyngeal primary tumor site (PTVnx): 69.96Gy/2.12Gy/33F; High-risk planning target volume (PTV1): 60.06Gy/1.82Gy/33F; Low-risk planning target volume (PTV2): 54.12Gy/1.64Gy/33F; Cervical lymph nodes (PTVnd): 66~69.96Gy/2~2.12Gy/33F; 5 times per week, for a total of 6-7 weeks.

Concurrent Chemotherapy: Cisplatin (80-100mg/m^2, Q3W, 3 times during CCRT); Dexamethasone: 10mg/time, nebulized, QD, starting from Day 1 of treatment until the end of radiotherapy.

3.6 Patient Follow-up

(1) Observation and follow-up personnel will conduct patient follow-up via outpatient visits, telephone tracking, home visits, etc., to observe and evaluate the patient's RIOM grading, adverse effects, and weight changes

(2) Follow-up time requirements: The follow-up duration is set at 3 months, with assessments once a month.

4.Research Design

Study Period	Key Responsibilities
Jul 2022 - Jun 2024	1.Initiate recruitment; 2.Screen eligible NPC cases, determine baseline data and collect indicators, perform randomization, and complete the enrollment of the expected sample size; it is planned to recruit 90 patients in the 2 years (45 in the experimental group, 45 in the control group) and conduct follow-up observations on these subjects; 3.Follow up each enrolled case for 1 year; 4.The enrolled cases will proceed according to the trial steps designed for each group, including patient follow-up, disease assessment, and indicator collection and follow-up.
Jul 2024 - Jun 2026	1. Screen eligible NPC cases, determine baseline data and collect indicators, perform randomization, and complete the enrollment of the expected sample size; it is planned to recruit 90 patients in the second 2 years period (45 in the experimental group, 45 in the control group); 2. Follow up each enrolled case for 1 year, and perform data registration and statistics; 3. The enrolled cases will proceed according to the trial steps designed for each group, including patient follow-up, disease assessment, and indicator collection and follow-up.

Jul 2026 - Jul 2027	1. Statistical analysis, thesis writing, domestic and international exchange, and promotion application.

5. Study Subjects

Observe the data of NPC patients with complete clinical and pathological data who underwent concurrent chemoradiotherapy at the Head and Neck Tumor Ward of the Cancer Hospital of the Affiliated Hospital of Guangdong Medical University between July 2022 and July 2026.

6. Evaluation Indicators

(1) Primary Evaluation Indicator: Incidence and severity of RIOM.

(2) Secondary Evaluation Indicators: ①Duration of RIOM; ②Rate of completion of treatment measures; ③Adverse events classified according to CTCAE 5.0; ④Changes in BMI.

Adverse Event (AE) Any untoward medical occurrence in a subject during the clinical trial, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or temporary illness associated with the use of the drug, whether or not related to the drug.

Serious Adverse Event (SAE) All serious adverse events occurring during the clinical trial must be recorded in the Serious Adverse Event (SAE) report. The occurrence of any of the following conditions should be considered a serious adverse event:

① Results in death;

② Is life-threatening;

③ Requires inpatient hospitalization or prolongation of existing hospitalization;

④ Results in persistent or significant disability/incapacity;

⑤ Results in a congenital anomaly or birth defect;

⑥ Other.

Causality Assessment of Adverse Events While recording in detail any abnormal symptoms, signs, laboratory tests, or other special examinations occurring during the clinical study, a causality assessment should be performed. According to the criteria for adverse reaction/event analysis, the causality assessment is classified as: 1-Definitely related; 2-Probably related; 3-Possibly related; 4-Probably unrelated; 5-Definitely unrelated.

① Is there a reasonable temporal relationship between the start of medication and the appearance of the suspected adverse reaction?

② Does the suspected adverse reaction fit the known adverse reaction profile of the drug? ③ Can the suspected adverse reaction be explained by the effects of concomitant medications, the patient's clinical condition, or other therapies?

④ Does the suspected adverse reaction disappear or alleviate after stopping or reducing the drug?

⑤ Does the same reaction reappear after re-exposure to the suspected drug?

Causality Determination Criteria: Determined sequentially according to the above indicators 1-5.

Causality Determination Table for Adverse Reactions					
Judgment Result	Assessment Indicators				
	①	②	③	④	⑤
Definitely Related	+	+	−	+	+

Probably Related	+	+	−	+	?
Possibly Related	+	+	+	±	?
Probably Unrelated	+	−	±	±	?
Definitely Unrelated	−	−	+	−	−
Remarks: "+" indicates affirmation/positive; "–" indicates negation/negative; "±" indicates difficult to affirm or deny; "?" indicates unknown/unclear.					

The relationship between adverse events (including serious adverse events) and the drug should be determined whenever possible. If the assessment determines the relationship to be definitely related, probably related, or possibly related, the event will be considered an adverse reaction caused by the drug, and its severity will be used to determine if it should be classified as a serious adverse event.

7. Data Management and Statistical Analysis Plan

(1) Data Management

Original case report forms (CRFs), once data entry and verification are completed as required, shall be archived and saved in numerical order, and furnished with a retrieval catalog, etc., for inspection. Electronic data files, including databases, verification programs, analysis programs, analysis results, code books, and descriptive documents, should be classified and saved, with multiple backups stored on different disks or storage media, and properly preserved to prevent damage. All original records shall be preserved for the period stipulated by China's Good Clinical Practice (GCP).

(2) Statistical Analysis

① General Principles: One-sided tests will be used for superiority tests, while two-sided tests will be used for other statistical tests. Quantitative indicators will be described using the number of cases, mean, standard deviation, median, minimum, and maximum. Categorical indicators will be described using the number of cases and percentages. All statistical analyses will be conducted using SPSS 26.0 statistical software.

② Statistical Analysis Populations

Full Analysis Set (FAS): Refers to the ideal set of subjects that closely adheres to the intention-to-treat principle (including all randomized subjects who have received at least one treatment). This data set is formed by excluding randomized subjects using minimal and reasonable methods. For example, cases with no follow-up observation data after enrollment (no medication received) may be excluded. For the estimation of missing values for primary variables, such as case data where the entire treatment process was not observed, the last observation carried forward (LOCF, or "carry-forward") method will be used to impute missing trial data. The number of subjects evaluated for efficacy at the endpoint in each group will remain consistent with the number at the start of the trial.

Per Protocol Set (PPS): Includes all cases that comply with the trial treatment protocol, have good compliance (used the trial drug quantity between 80% and 120%), completed the required fields in the CRF, have measurable primary variables, have no missing baseline variables, and have no major violations of the trial protocol.

Safety Analysis Set (SS): Includes all enrolled cases that have used the study medication at

least once and have safety records after drug administration. This data set is used for safety analysis.

In this trial, baseline data will be analyzed using the FAS. Primary efficacy endpoints will be analyzed simultaneously on the FAS and PPS. Safety evaluation will be conducted using the SS.

③ **Statistical Analysis Methods**

A. **Enrollment and Completion Status** The enrollment and completion status for each center will be listed, including whether enrolled cases met the inclusion and exclusion criteria. The actual number of enrolled cases, excluded cases, and dropped-out cases for each center will be counted individually, and the FAS, PPS, and SS will be defined.

B. **Baseline Balance Analysis** Baseline is defined as before radiotherapy (-7 to 0 days). A comparability analysis of the basic demographic characteristics, general conditions, and baseline status (pre-treatment) at the time of enrollment will be conducted for the experimental and control groups. Specifically, quantitative data conforming to a normal distribution will use the independent samples t-test, quantitative data conforming to a skewed distribution will use non-parametric tests, ordinal data will use the Kruskal-Wallis test, and categorical data will use the χ^2 test or Fisher's exact test.

C. Comparison of Factors Affecting Trial Evaluation

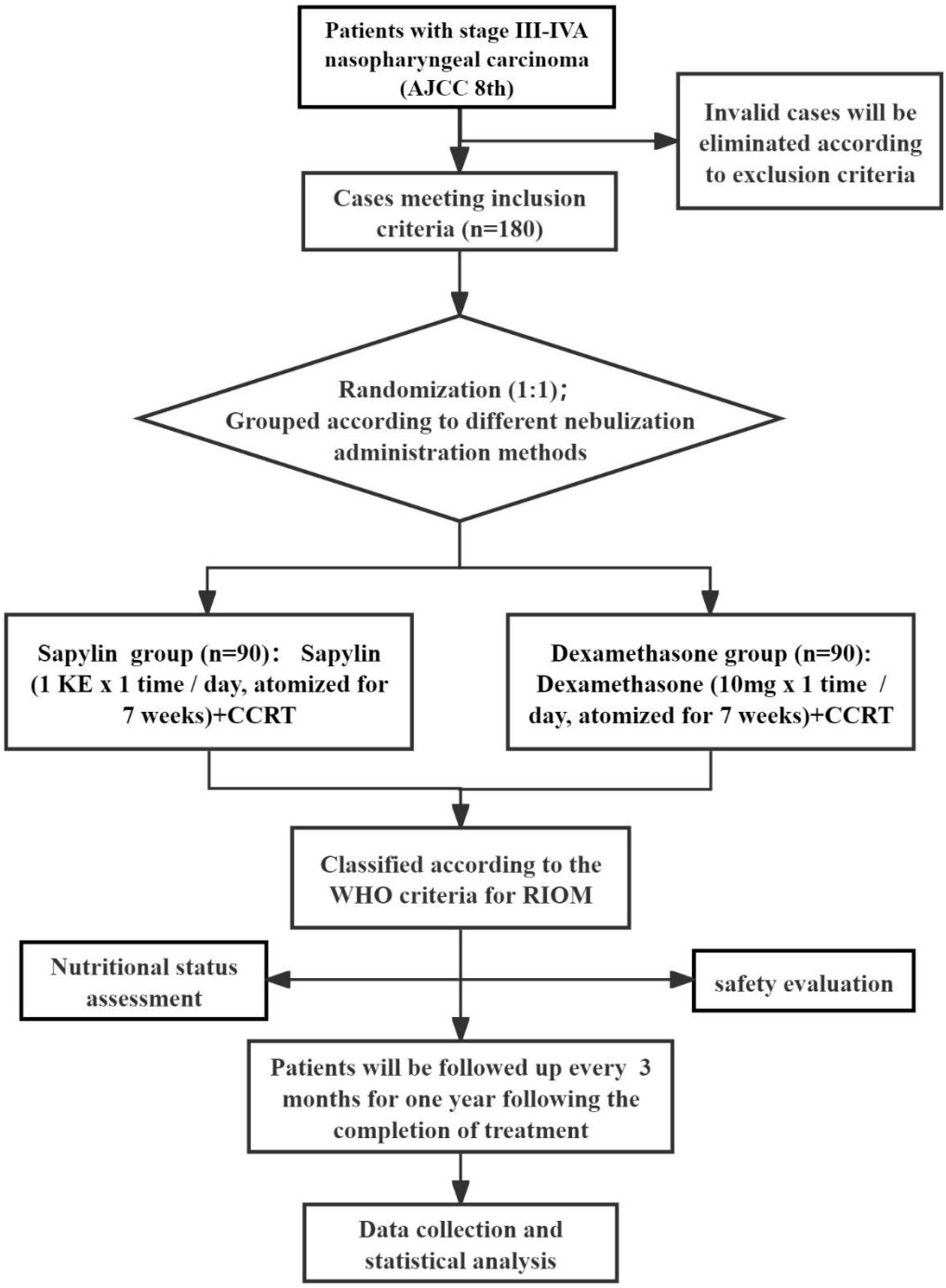
a. Analysis of Concomitant Medication Use The frequency and percentage of concomitant medication use will be listed for the cases. Group comparison will be performed using the χ^2 test or Fisher's exact test.

b. Analysis of Medication Compliance The frequency and percentage of cases with medication compliance < 80%, and > 120%、 80% ~ 120% will be listed. Group comparison will be performed using the χ^2 test or Fisher's exact test.

c. Time Exposed to Treatment Treatment duration (days) = Time of last dose – Time of first dose + 1.

The number of cases, mean, standard deviation, median, minimum, and maximum will be calculated. Group comparison will be performed using the independent samples t-test or the Wilcoxon rank-sum test.

8. Study Steps and Technical Route



9. Data Confidentiality Plan

All records related to the subject's identity shall be kept confidential, and these materials will not be made public beyond the scope permitted by relevant laws and/or regulations. The subject's name will not be provided to the sponsor. Only the subject's number and initials of the name will be recorded on the case report form. If the subject's name appears in any other document (e.g., pathology reports), it must be redacted before providing copies of the documents to the sponsor. Study reports stored on computers must comply with local data protection laws. Patients will be

notified in writing that representatives of the sponsor, Ethics Committee/Institutional Review Board, or drug regulatory authorities may review their medical records to verify the information collected. All personal information involved in the review will be kept strictly confidential and will comply with local data protection laws. If the study results are published, the patient's personal identity will remain confidential. The investigator will retain a list to verify patient records.

III. Study Participant Recruitment

1. Inclusion Criteria

(1) stage III-IVa NPC (AJCC 8th edition) diagnosed via pathology in a tertiary hospital;
(2) no previous radiotherapy, chemotherapy, surgery, immunization, or targeted therapy;
(3) Karnofsky Performance Status score ≥80;
(4) intact and normal oral mucosa before treatment;
(5) age 18–75 years;
(6) voluntary participation and provision of informed consent in person;
(7) routine blood examination: white blood cell count $\geq 4.0\times10^9$/L, hemoglobin ≥100g/L, neutrophil count $\geq 1.5\times10^9$/L, and platelet count $\geq 100\times10^9$/L;
(8) biochemical examination: total bilirubin ≤1.5×the upper limit of the normal range (ULN), alanine aminotransferase and aspartate aminotransferase ≤2×ULN, and estimated glomerular filtration rate ≥60 mL/min.

2. Exclusion Criteria

(1) with other malignant tumors in the past or present and/or distant metastasis during treatment;
(2) who have undergone surgery, chemoradiotherapy, and targeted immunotherapy;
(3) with a history of asthma, rash, urticaria, and other allergic diseases;
(4) with a history of autoimmune diseases, connective tissue diseases, and diabetes mellitus that significantly affect the healing of the oral mucosa;
(5) with concomitant diseases, such as heart disease, kidney disease, and acute infectious diseases, which are judged by the investigator to seriously endanger the safety of patients or affect the completion of the study;
(6) who are breastfeeding, pregnant, or planning to become pregnant during the study;
(7) with known allergies to the therapeutic agents and penicillin used in the trial;
(8) with mental or nervous system diseases or poor compliance will be excluded from the study.

3. Withdrawal and Termination Criteria

3.1 Withdrawal determined by the investigator

Withdrawal determined by the investigator refers to situations where it is inappropriate for an already enrolled patient to continue the trial, and the investigator decides to withdraw the patient from the trial:

① The patient is unsuitable to continue receiving the trial treatment;
② The patient has poor compliance;
③ Occurrence of a serious adverse event or emergency unblinding in the trial;
④ Use of protocol-prohibited medications during the trial.

3.2 Subject initiated withdrawal

In accordance with the informed consent form, the subject has the right to withdraw from the trial midway. A subject is also considered "withdrawn" if they do not explicitly request to withdraw but are lost to follow-up by no longer receiving medication and testing. The reason for withdrawal should be ascertained and recorded whenever possible. Examples include: feeling the treatment is ineffective; finding certain adverse reactions intolerable; having commitments preventing continuation of the clinical study; economic factors; or being lost to follow-up without stating a reason. Regardless of the reason, the case report form for the withdrawn patient should be retained.

3.3 Handling of Dropouts

When a patient drops out, the investigator must fill in the reason for dropout in the CRF. They should contact the patient whenever possible, complete all feasible assessment items, and fill in the end-of-treatment follow-up record form, recording the time of the last dose if possible. For dropouts due to an adverse event that is ultimately judged to be related to the study drug following follow-up, this must be recorded in the CRF and the sponsor notified. No replacement cases are needed for dropouts.

3.4 Criteria for Case Exclusion

① Case selection does not meet the inclusion criteria;

② The trial medication was never used;

③ No data exists after randomization or major indicators are missing, or the data is obviously incomplete;

④ Use of medications prohibited by the trial protocol, making efficacy evaluation impossible.

4. Duration of Participation (Time per session and total time)

This study is expected to last 5 years, including an 48-month enrollment period. Each patient will be followed up for 12 months after stopping treatment.

(1) Planned date for enrollment of the first patient: July 30, 2022.

(2) Planned date for enrollment of the last patient: July 1, 2026.

(3) Planned date for the last patient's exit or trial conclusion: July 1, 2027.

(4) Estimated report date: July 20, 2027.

(5) Follow-up duration: 12 months; Primary endpoint: Incidence and severity of RIOM; Secondary endpoints: ①Duration of RIOM; ②Rate of completion of treatment measures; ③Adverse events classified according to CTCAE 5.0; ④Changes in BMI

Follow-up frequency: The follow-up period is 1 year; The first follow-up is 1 month after concurrent chemoradiotherapy; thereafter, follow-up visits are every 3 months. RIOM incidence rate, severe RIOM incidence rate, ORR, and PFS.

5. Recruitment Process (Including recruitment procedure and start time, recruitment materials, expected number of recruits)

(1) Patient selection: Meeting the diagnostic criteria for NPC; patients who have not yet received concurrent chemoradiotherapy; meeting the inclusion and exclusion criteria; patients voluntarily joining this clinical trial and signing the informed consent form.

(2) Expected number of recruits: The Delphi method is used to determine the non-inferiority margin of the observation endpoint. After consulting senior oncology practitioners, we defined an

8% reduction in the incidence of RIOM as a clinically acceptable non-margin of error. Under the conditions of test level a=0.05 and test efficacy 1-β=0.9, the proportion of cases in the two groups is 1:1. Using the module of non-destructiveness Tests for Two Proportions in PASS 15.0 statistical analysis software, we determined that a sample size of 81 was required per group. Considering a 10% loss to follow-up rate, we estimated that 90 cases would be required in each group, for a total of 180 cases.

(3) Planned date for enrollment of the first patient: July 30, 2022; Planned date for enrollment of the last patient: July 1, 2026; Planned date for the last patient's exit or trial conclusion: July 1, 2027.

IV. Risk/Benefit Assessment

1. Benefits (Individual and Societal Benefits)

This study intends to explore the impact of nebulized Sapylin inhalation on the therapeutic efficacy of CCRT in patients with NPC via nebulized inhalation, observe the effect of nebulized Sapylin inhalation on the incidence and severity of RIOM, and evaluate the safety of nebulized Sapylin inhalation. This study aims to find a highly efficient and low-toxicity method for NPC specialists and patients to reduce the occurrence and severity of RIOM and improve the efficacy of CCRT.

2. Risks

(1) Efficacy and adverse reaction risks;

(2) Time risk;

(3) Policy risk;

(4) Personnel risk.

Mitigation Measures: Flexibility (high variability); diverse services; low cost; shortened research time; expanded research resources; and the ability to adapt to and meet strict GCP requirements, etc.

3. Protection of Special Populations (Women, children, the elderly, and other special populations such as incarcerated individuals, etc., risk and protection)

The study population for this project consists of NPC patients aged 18-75. The research personnel will conduct risk assessment for women, the elderly, and other special populations, and implement corresponding risk protection measures.

V. Ethical Issues in the Study

1. Ethics Approval

This clinical trial has followed the Declaration of Helsinki and China's relevant clinical trial research norms and regulations. The implementation of this trial protocol has been approved by the Ethics Committee of the principal clinical research unit prior to the start of the trial.

2. Informed Consent

Before any patient is selected for this study, the investigator must fully and comprehensively introduce the study's objectives, procedures, and possible risks to the patient's family members or their designated representatives in written form. Patients and their family members should be informed that they have the right to withdraw from the study at any time. A written Patient

Informed Consent Form (included as an appendix to the protocol) must be provided to every patient and family member before enrollment. The investigator must obtain informed consent before any patient or family member enters the study, and the informed consent form must be retained as a clinical trial document for inspection.

VI. Annual Plan

Study Period	Key Responsibilities
Jul 2022 - Jun 2024	1.Initiate recruitment; 2.Screen eligible NPC cases, determine baseline data and collect indicators, perform randomization, and complete the enrollment of the expected sample size; it is planned to recruit 90 patients in the 2 years (45 in the experimental group, 45 in the control group) and conduct follow-up observations on these subjects; 3.Follow up each enrolled case for 1 year; 4.The enrolled cases will proceed according to the trial steps designed for each group, including patient follow-up, disease assessment, and indicator collection and follow-up.
Jul 2024 - Jun 2026	1. Screen eligible NPC cases, determine baseline data and collect indicators, perform randomization, and complete the enrollment of the expected sample size; it is planned to recruit 90 patients in the second 2 years period (45 in the experimental group, 45 in the control group); 2. Follow up each enrolled case for 1 year, and perform data registration and statistics; 3. The enrolled cases will proceed according to the trial steps designed for each group, including patient follow-up, disease assessment, and indicator collection and follow-up.
Jul 2026 - Jul 2027	1. Statistical analysis, thesis writing, domestic and international exchange, and promotion application.

VII. Assessment Indicators

The primary assessment indicator is the incidence and severity of RIOM. The secondary assessment indicators are: (1) duration of RIOM, (2) rate of completion of treatment measures, (3) adverse events classified according to CTCAE 5.0, and (4) changes in BMI.

VIII. Preliminary Research Foundation and Working Conditions

The research team conducted a retrospective study on 32 NPC (NPC) patients from 2016 to 2019. The study observed the effect of nebulized Sapylin and Dexamethasone on the incidence rate of RIOM (radiation-induced oral mucositis) and the efficacy of CCRT (Concurrent

Chemoradiotherapy) during concurrent chemoradiotherapy. Results showed: The CCRT combined with nebulized Sapylin group had a lower incidence rate of RIOM and Grade III-IV RIOM compared to the CCRT combined with nebulized Dexamethasone group (43.75% vs 68.75%) and (12.5% vs ≥31.3%), respectively. Furthermore, the CCRT combined with nebulized Sapylin group was superior to the CCRT combined with nebulized Dexamethasone group in terms of objective response rate (ORR) (87.5% vs 62.5%), median overall survival (OS) (53.7M vs 46.4M), and median progression-free survival (PFS) (27M vs 23M). Moreover, comparison of the efficacy and survival analysis between the CCRT combined with nebulized Sapylin group and the CCRT combined with nebulized Dexamethasone group revealed that the nebulized Sapylin inhalation group showed a trend toward reducing the incidence rate of Grade III-IV RIOM and enhancing CCRT efficacy in NPC patients, with no obvious toxic side effects observed. Therefore, this project will conduct a non-inferiority, parallel-design, randomized controlled study of nebulized Sapylin versus nebulized Dexamethasone for the prevention and treatment of radiation-induced oral mucositis in NPC.

(I) Research Methods

1. Study Subjects

Data of NPC patients with complete clinical and pathological data who underwent concurrent chemoradiotherapy at the Head and Neck Tumor Ward of the Cancer Hospital of the Affiliated Hospital of Guangdong Medical University between May 2016 and December 2019 were observed.

1.1 Inclusion Criteria:

(1) stage III-IVa NPC (AJCC 8th edition) diagnosed via pathology in a tertiary hospital;
(2) no previous radiotherapy, chemotherapy, surgery, immunization, or targeted therapy;
(3) Karnofsky Performance Status score ≥80;
(4) intact and normal oral mucosa before treatment;
(5) age 18–75 years;
(6) voluntary participation and provision of informed consent in person;
(7) routine blood examination: white blood cell count $\geq 4.0\times10^9$/L, hemoglobin ≥100g/L, neutrophil count $\geq 1.5\times10^9$/L, and platelet count $\geq 100\times10^9$/L;
(8) biochemical examination: total bilirubin ≤1.5×the upper limit of the normal range (ULN), alanine aminotransferase and aspartate aminotransferase ≤2×ULN, and estimated glomerular filtration rate ≥60 mL/min.

1.2 Exclusion Criteria

(1) with other malignant tumors in the past or present and/or distant metastasis during treatment;
(2) who have undergone surgery, chemoradiotherapy, and targeted immunotherapy;
(3) with a history of asthma, rash, urticaria, and other allergic diseases;
(4) with a history of autoimmune diseases, connective tissue diseases, and diabetes mellitus that significantly affect the healing of the oral mucosa;
(5) with concomitant diseases, such as heart disease, kidney disease, and acute infectious diseases, which are judged by the investigator to seriously endanger the safety of patients or affect the completion of the study;
(6) who are breastfeeding, pregnant, or planning to become pregnant during the study;
(7) with known allergies to the therapeutic agents and penicillin used in the trial;
(8) with mental or nervous system diseases or poor compliance will be excluded from the study.

2. Treatment Methods: NPC patients will undergo CCRT, divided into the CCRT combined with nebulized Sapylin group and the CCRT combined with nebulized Dexamethasone group.

2.1 CCRT combined with nebulized Sapylin group:

Concurrent Radiotherapy Dose: Nasopharyngeal primary tumor site (PTVnx): 69.96Gy/2.12Gy/33F; High-risk planning target volume (PTV1): 60.06Gy/1.82Gy/33F; Low-risk planning target volume (PTV2): 54.12Gy/1.64Gy/33F; Cervical lymph nodes (PTVnd): 66 ~ 69.96Gy/2 ~ 2.12Gy/33F; 5 times per week, for a total of 6-7 weeks.

Concurrent Chemotherapy: Cisplatin (80-100mg/m^2, Q3W, 3 times during CCRT); Sapylin: 1 KE/time, nebulized, QD, starting from Day 1 of CCRT until the end of radiotherapy.

2.2 CCRT combined with nebulized Dexamethasone group:

Concurrent Radiotherapy Dose: Nasopharyngeal primary tumor site (PTVnx):

69.96Gy/2.12Gy/33F; High-risk planning target volume (PTV1): 60.06Gy/1.82Gy/33F; Low-risk planning target volume (PTV2): 54.12Gy/1.64Gy/33F; Cervical lymph nodes (PTVnd): 66 ~ 69.96Gy/2 ~ 2.12Gy/33F; 5 times per week, for a total of 6-7 weeks.

Concurrent Chemotherapy: Cisplatin (80-100mg/m^2, Q3W, 3 times during CCRT); Dexamethasone: 10mg/time, nebulized, QD, starting from Day 1 of treatment until the end of radiotherapy.

3. Observation Indicators: The primary observation indicator is the RIOM incidence rate. The secondary observation indicators are: Grade III-IV RIOM incidence rate; RIOM onset time and duration; assessment of adverse reactions, ORR, and PFS for both regimens.

4. Statistical Methods

① General Principles: One-sided tests will be used for superiority tests, while two-sided tests will be used for other statistical tests. Quantitative indicators will be described using the number of cases, mean, standard deviation, median, minimum, and maximum. Categorical indicators will be described using the number of cases and percentages. All statistical analyses will be conducted using SPSS 26.0 statistical software.

② Statistical Analysis Populations:

Full Analysis Set (FAS): Refers to the ideal set of subjects that closely adheres to the intention-to-treat principle. It includes all randomized subjects who have received at least one treatment. The number of subjects evaluated for efficacy at the endpoint in each group will remain consistent with the number at the start of the trial.

Per Protocol Set (PPS): Includes all cases that comply with the trial treatment protocol, have good compliance (used the trial drug quantity between 80% and 120%), completed the required fields in the CRF, have measurable primary variables, have no missing baseline variables, and have no major violations of the trial protocol.

Safety Analysis Set (SS): Includes all enrolled cases that have used the study medication at least once and have safety records after drug administration. This data set is used for safety analysis.

In this trial, baseline data will be analyzed using the FAS. Primary efficacy endpoints will be analyzed simultaneously on the FAS and PPS. Safety evaluation will be conducted using the SS.

(II) Preliminary Research Work

1. Clinical and Pathological Features of NPC Patients Receiving Chemotherapy:

A retrospective study reviewed 32 NPC patients with complete clinical and pathological data who underwent concurrent chemoradiotherapy at the Head and Neck Tumor Ward of the Cancer Hospital of the Affiliated Hospital of Guangdong Medical University between May 2016 and December 2019. NPC patients were predominantly male (63.8%), with an average age of 51±15 years. The pathological types of NPC were mainly undifferentiated non-keratinizing carcinoma (90.2%) and differentiated non-keratinizing carcinoma (6.35%). The vast majority of NPC patients were TNM stage III-IVa.

2. Observation of treatment efficacy, prognosis, RIOM incidence, and severity in NPC patients:

Table 1 Efficacy and Survival Analysis of CCRT combined with Nebulized Sapylin Group versus CCRT combined with Nebulized Dexamethasone Group in the Treatment of Locally Advanced NPC

Group	N	PR+CR	PD	Median OS (months)	Median PFS (months)
CCRT + Sapylin Neb.	16	14	1	53.7M	27M
CCRT + Dexamethasone Neb.	16	0	3	46.4M	23M

CCRT: Concurrent Chemoradiotherapy、PR: Partial Remission/Response、CR: Complete Remission/Response、PD: Progressive Disease、OS: Overall Survival、PFS: Progression-Free Survival

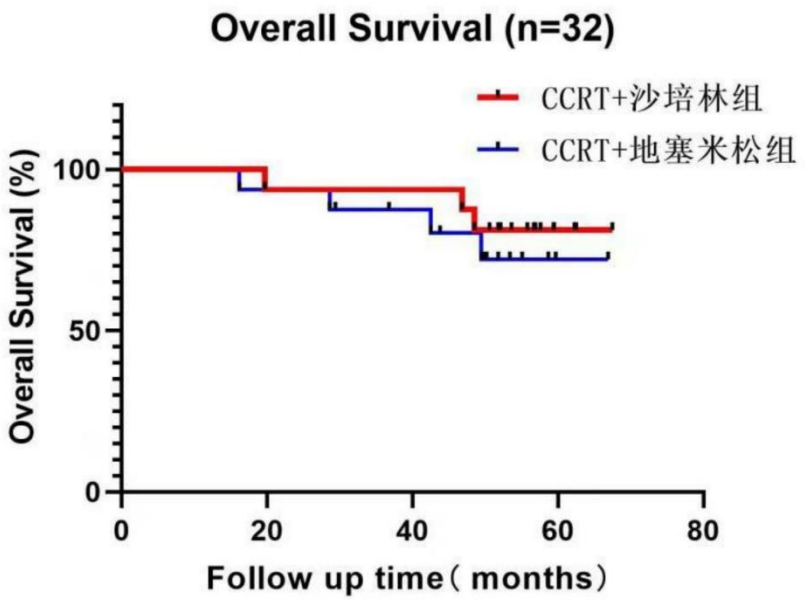


Figure 1 Survival Analysis of CCRT combined with Nebulized Sapylin Group versus CCRT combined with Nebulized Dexamethasone Group in the Treatment of Locally Advanced NPC.

Table 2 Grading of Toxic/Adverse Reactions (CTCAE Version 5) in CCRT combined with Nebulized Sapylin Group versus CCRT combined with Nebulized Dexamethasone Group in the Treatment of Locally Advanced NPC.

Adverse	**CCRT + Sapylin Neb.**					**CCRT + Dexamethasone Neb.**				
Event	0	I	II	III	IV	0	I	II	III	IV
Anemia	2	4	7	3	0	1	3	7	5	0
White blood cell decreased	4	4	6	2	0	4	3	5	4	0
Neutrophil count decreased	16	0	0	0	0	12	0	4	0	0
Platelet count decreased	15	0	1	0	0	12	2	1	1	0
Weight loss	0	8	8	0	0	1	6	6	3	0
Vomiting	5	6	5	0	0	2	4	6	3	1
Nausea	5	8	3	0	0	3	5	5	3	0
RIOM	9	1	4	2	0	5	2	4	3	2

The results from Table 1 show that the treatment response rate in the CCRT combined with nebulized Sapylin inhalation group was higher than in the Dexamethasone group, suggesting that nebulized Sapylin inhalation can improve the efficacy of CCRT and prolong patient OS. The results from Table 2 show that a comparison of common adverse reactions between the two groups suggests that the CCRT combined with nebulized Sapylin inhalation group can reduce the incidence and severity of RIOM, and can reduce overall adverse reactions.

(III) Conclusion

1.The combined use of nebulized Sapylin during concurrent chemoradiotherapy in NPC patients reduces the incidence and severity of radiation-induced oral mucositis.

2.The combined use of nebulized Sapylin during concurrent chemoradiotherapy using Cisplatin as the main chemotherapy regimen in NPC patients shows a trend toward improving the efficacy of chemoradiotherapy and prolonging patient survival compared to the use of nebulized Dexamethasone.

IX. Other Issues to be Explained

1. Form of Publication of Results and Authorship Arrangements

All data and results obtained from this study, as well as all intellectual property rights, belong to the sponsor. The sponsor may utilize these materials in various forms. At the same time, researchers may use the data obtained from this study independently for scientific purposes, but must consult with the sponsor and obtain the sponsor's written consent before publication. The sponsor acknowledges the right of the investigator to publish the study results after the study is completed. The research results will be published in the form of a paper. It is expected that 1 paper will be published in an SCI-indexed or Chinese scientific and technological core professional journal, 2 master's students will be trained, and relevant academic achievements will be shared and reported at relevant academic conferences.

2. Other Issues to be Explained

The first affiliation for authorship shall be the Affiliated Hospital of Guangdong Medical University, and the intellectual property rights belong to the Affiliated Hospital of Guangdong Medical University.

X. Investigator Information Table

1. Principal Investigator

Name	Telephone Number	Email Address
Haiqing Luo	13729196345	hqluo@126.com

Project Secretary: Donghong Yang ; **Contact Number:** 15812356223 ; **Email :** ydh192@sina.com

2. Project Team Members (including Principal Investigator)

Name	Affiliation	Degree	Title	Project Task Assignment	Ethics Training	GCP Training
Haiqing Luo	Affiliated Hospital of Guangdong Medical University	Ph.D.	Chief Physician, Associate Professor	Overall Responsibility, Project Design, Implementation Guidance	Received	Received
Xuesong Chen	Affiliated Hospital of Guangdong Medical University	Bachelor's Degree	Chief Physician	Project Implementation Monitoring	Received	Received
Liren Hu	Affiliated Hospital of Guangdong Medical University	Bachelor's Degree	Associate Professor	Statistical analysis of patient survival data	Received	Received
Jiayuan Wu	Affiliated Hospital of Guangdong Medical University	Master's Degree	Deputy Chief Physician	Patient follow-up, data statistics	Received	Received
Donghong Yang	Affiliated Hospital of Guangdong Medical University	Master's Degree	Deputy Chief Physician	Project Secretary	Received	Received
Guihua Yi	Affiliated Hospital of	Master's Student	None	Case enrollment and screening	Received	Received

	Guangdong Medical University					
Qianbing Luo	Affiliated Hospital of Guangdong Medical University	Master's Student	None	Filling out the patient CRF	Received	Received
Ningxin Huang	Affiliated Hospital of Guangdong Medical University	Master's Student	None	Filling out the patient CRF	Received	Received
Haifeng Tang	Affiliated Hospital of Guangdong Medical University	Master's Student	None	Patient follow-up, data statistics	Received	Received
Jiaqi He	Affiliated Hospital of Guangdong Medical University	Master's Student	None	Manuscript writing	Received	Received

XI. Appendices

(1) Appendix 1: NPC TNM Staging Criteria (AJCC 8th)

(2) Appendix 2: Radiation Therapy Oncology Group (RTOG) Grading Criteria for Acute Radiation Morbidity of Mucosa

(3) Appendix 3: CTCAE Version 5 Adverse Event Grading Criteria (Partial Content)

(4) Appendix 4: Performance Status Rating Scale (Karnofsky Score)

(5) Appendix 5: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Applicant's Commitment and Signature: I guarantee the authenticity of the application content. If funding is obtained, I will fulfill the responsibilities of the principal, strictly abide by the relevant regulations such as the institutional and national GCP principles, effectively ensure the time dedicated to the research, earnestly carry out the work, submit relevant materials on, and consciously perform annual summaries and final reports. I will assume full responsibility for any false reporting or violation of regulations.

Appendix 1: NPC TNM Staging Criteria (AJCC 8th)

Regional Lymph Node (N) Staging	
T_X	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal involvement.
T2	Tumor with extension to parapharyngeal space.

Regional Lymph Node (N) Staging	
T3	Tumor involves bony structures of skull base and/or paranasal sinuses.
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle.

Primary Tumor (T) Staging	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s), ≤ 6 cm in greatest dimension, above the caudal border of cricoid cartilage, and/or unilateral or bilateral retropharyngeal lymph node(s), ≤ 6 cm in greatest dimension.
N2	Bilateral metastasis in cervical lymph node(s), ≤ 6 cm in greatest dimension, above the caudal border of cricoid cartilage.
N3	Metastasis in a lymph node(s) > 6 cm in greatest dimension and/or extension below the caudal border of cricoid cartilage.

Distant Metastasis (M) Staging	
M0	No distant metastasis
M1	Distant metastasis

NPC TNM Staging			
Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T0, T1	N1	M0
II	T0 ~ 2	N0 ~ 1	M0
III	T2	N2	M0

NPC TNM Staging			
Stage	T	N	M
III	T0 ~ T2	N0 ~ 2	M0
IVa	T3	N0 ~ 3	M0
IVa	T4	N3	M0
IVb	Any T	Any N	M1

Appendix 2: Radiation Therapy Oncology Group (RTOG) Grading Criteria for Acute Radiation Morbidity of Mucosa

	0	I	II	III	IV
Mucosal appearance	No change over baseline	Erythema	Patchy mucositis、With inflammatory sero-sanguinous discharge	Confluent fibrinous mucositis	Ulceration、Hemorrhage、Necrosis
Pain level	No change over baseline	Mild pain	Moderate pain	Severe pain	
Pain management	No change over baseline	No analgesic required	Analgesic required	Requiring narcotic analgesic	

Appendix 3: CTCAE Version 5 Adverse Event Grading Criteria (Partial Content)

Adverse Event	Grade				
	1	2	3	4	5
HGB	< LLN-10.0g/dL < LLN-6.2mmol/L < LLN-100g/L	< 10.0 − 8.0g/dL < 6.2 − 4.9mmol/L < 100 − 80g/L	< 8.0 − 6.5g/dL < 4.9 − 4.0mmol/L < 80 − 65g/L	< 6.5g/dL < 4.0mmol/L < 65g/L	Death
WBC	< LLN-3000/mm^3 < LLN-3.0×10^9 /L	< 3000-2000/ mm^3 < 3.0 − 2.0×10^9 /L	< 2000-1000/ mm^3 < 2.0 − 1.0×10^9 /L	< 1000/ mm^3 < 1.0×10^9 /L	Death
PLT	< LLN-75,000/mm^3 < LLN-75.0×10^9 /L	< 75,000-50,000/mm^3 < 75.0 − 50.0×10^9 /L	< 50,000 − 25,000/mm^3 < 50.0 − 25.0×10^9 /L	< 25,000/mm^3 < 25.0×10^9 /L	Death
Nausea	Loss of appetite without	Decreased oral intake; no significant	Inadequate oral caloric or fluid intake;	Life-threatening consequences	Death

	alteration in eating habits	weight loss, dehydration, or malnutrition; requires intravenous (IV) fluids for < 24 hours	requires IV fluids, tube feeding, or TPN (Total Parenteral Nutrition) for ≥ 24 hours		
Episodes	1-2 episodes in 24 hours (separated by 5 minutes)	3-5 episodes in 24 hours (separated by 5 minutes)	≥6 episodes in 24 hours; requires nasogastric tube feeding, total parenteral nutrition (TPN), or hospitalization	Life-threatening consequences; requires urgent intervention	Death
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; requires hospitalization; marked increase in ostomy output compared to baseline; limiting instrumental activities of daily living	Life-threatening consequences; requires urgent intervention	Death
Oral Mucositis	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Appendix 4: Performance Status Rating Scale (Karnofsky Score)

Score	Performance Status
100	Normal, no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	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.

Score	Performance Status
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

Note 1: A higher score indicates a better performance status and a greater ability to tolerate the side effects of treatment, thereby increasing the likelihood that the patient can undergo aggressive therapy. Conversely, a lower score indicates a poorer performance status. If the score falls below 70, many effective anti-tumor treatments may not be feasible.

Note 2: This scale is adapted from the original table developed in 1948 by Dr. Karnofsky and Dr. Burchenal for the objective assessment of chemotherapy efficacy.

Appendix 5: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Therapeutic Response	
Complete remission (CR)	Disappearance of all target lesions, no new lesions, and normalization of tumor marker levels, maintained for at least 4 weeks.
Partial remission (PR)	At least a 30% decrease in the sum of the longest diameters of target lesions, maintained for at least 4 weeks.
Stable disease (SD)	The change in the sum of the longest diameters of target lesions does not meet the criteria for either PR or Progressive Disease (PD).
Progressive disease (PD)	At least a 20% increase in the sum of the longest diameters of target lesions compared to the smallest sum recorded, or the appearance of one or more new lesions.

Measurable Lesions: Lesions that can be measured in diameter using clinical or imaging methods, according to the RECIST criteria. For example, intrapulmonary lesions ⩾10mm on chest X-ray, ⩾20mm on conventional CT or MRI scan, or ⩾10mm in diameter on helical CT scan.

Evaluable Lesions: Includes unidimensionally measurable lesions, masses with unclear boundaries, small lesions whose diameter cannot be measured (such as miliary or patchy lesions in the lung), lesions whose diameters are both less than ⩾10mm, and masses whose diameter is less than the scanning interval, etc.

Non-Evaluable Lesions: Includes osteoblastic metastases, pleural effusion, ascites, pericardial effusion, lymphangitis carcinomatosa in the lung, and previously irradiated lesions without progression.

Notes:

① Changes in slice thickness of CT or MRI scans may affect the measurement and detection of new lesions. The standard should be 5mm thin-slice CT. To reduce detection error, imaging should be performed before and after treatment, whenever possible, using the same equipment, the same examination method, and marked by tumor diameter.

② Enrolled patients must have at least one bidimensionally measurable lesion. If there are multiple measurable lesions in the head and neck but not all can be evaluated, up to 3 lesions may be selected for evaluation before enrollment, and the rest should be observed as evaluable lesions.

③ The lesion status determined before drug administration, and the method of its evaluation, will be applied throughout the entire trial process for efficacy assessment and cannot be changed.

④ Lesion measurement should be performed using unified technical methods. Each evaluation should be compared with the baseline measurements taken at enrollment, and the best response should be recorded. Cases where efficacy is difficult to evaluate should be handed over to the clinical lead unit for comprehensive evaluation by an independent expert panel.