

Study Protocol and Statistical Analysis Plan

A Phase 1 Trial of Multimodal Evaluation-Guided Surveillance-Intervention with Endoscopic Selective Neck Dissection for Post-RT N3 NPC

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1. Protocol Synopsis

Item	Description
Study Design	Prospective, single-center, single-arm, open-label, interventional phase Ib study
Primary Purpose	Treatment
Study Population	Patients aged 18-70 years with pathologically confirmed N3 nasopharyngeal carcinoma
Planned Enrollment	50 participants
Study Strategy	Multimodal follow-up evaluation after radiotherapy, including clinical assessment, conventional imaging, EBV DNA testing, and contrast-enhanced ultrasound (CEUS). Participants with suspicious residual cervical lymph nodes and surgical indications undergo endoscopic selective neck dissection (ESND).
Primary Objective	To evaluate the safety and feasibility of the multimodal evaluation-guided surveillance-intervention strategy combined with ESND.
Secondary Objectives	To describe preliminary clinical outcomes, including disease progression, locoregional recurrence, distant metastasis, and survival.
Follow-up	Every 3 months during the first 3 years after radiotherapy, every 6 months in years 3-5, and annually thereafter when applicable.
Study Period	Enrollment planned from August 2022 to June 2024; follow-up and data collection planned through May 2026; publication and study close-out through October 2028.

2. Background and Rationale

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy of the head and neck that is closely associated with Epstein-Barr virus infection and is endemic in southern China and Southeast Asia. Although induction chemotherapy and concurrent chemoradiotherapy have improved locoregional control, patients with N3 disease remain at high risk of treatment failure, including residual disease and distant metastasis.

Post-radiotherapy cervical lymph node assessment remains challenging. Conventional imaging may have difficulty distinguishing viable residual tumor from post-radiotherapy edema, fibrosis, scarring, necrosis, or inflammatory changes. Contrast-enhanced ultrasound (CEUS) provides dynamic information on lymph node microvascular perfusion and may complement routine post-treatment assessment.

For patients with suspected residual cervical nodal disease, neck dissection is an established salvage treatment option. Endoscopic selective neck dissection (ESND) is a minimally invasive surgical approach based on the principles of selective neck dissection and may reduce surgical trauma while allowing pathological confirmation and removal of suspicious residual lymph nodes. This study evaluates a multimodal evaluation-guided surveillance-intervention strategy combining post-radiotherapy lymph node assessment and conditional ESND in suitable patients.

3. Objectives

3.1 Primary Objective

To evaluate the safety and feasibility of a multimodal evaluation-guided surveillance-intervention strategy in patients with N3 NPC after radiotherapy.

3.2 Secondary Objectives

To describe preliminary clinical outcomes, including disease progression, locoregional recurrence, distant metastasis, and survival.

4. Study Design

This is a prospective, single-center, single-arm, open-label phase Ib interventional study. All participants enter a multimodal follow-up evaluation pathway after completion of standard radiotherapy. ESND is performed only in participants whose follow-up evaluation suggests suspicious residual cervical lymph nodes and who are suitable for surgery.

There is no randomization, no internal control group, and no masking. The allocation is not applicable because the study has one arm.

4.1 Sample Size

The planned sample size is 50 participants. The sample size is primarily based on the precision of estimating the primary safety endpoint, particularly the incidence of grade 3 or higher procedure-related adverse events. Assuming a grade 3 or higher procedure-related adverse event rate of approximately 10%, a sample size of 50 participants provides an estimated two-sided 95% confidence interval precision of approximately $\pm 8.3\%$. Given the exploratory nature and feasibility considerations of this phase Ib study, 50 participants are considered appropriate. Survival outcomes will be analyzed exploratorily.

5. Study Population

5.1 Inclusion Criteria

1. Aged 18 to 70 years.
2. Pathologically confirmed nasopharyngeal non-keratinizing carcinoma (differentiated or undifferentiated, i.e., WHO Type II or III).
3. Tumor staged as TanyN3M0 according to the 8th Edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system.
4. ECOG performance status 0–1.
5. No previous neck dissection.
6. Adequate hematologic, hepatic, and renal function, defined as: white blood cell count $\geq 4.0 \times 10^9/L$, absolute neutrophil count $\geq 2.0 \times 10^9/L$, hemoglobin ≥ 90 g/L, platelet count $\geq 100 \times 10^9/L$, aspartate aminotransferase and alanine aminotransferase $\leq 2.5 \times$ the upper limit of normal, and creatinine clearance ≥ 60 mL/min
7. Written informed consent provided prior to study enrollment

5.2 Exclusion Criteria

1. Ongoing receipt of other antitumor treatment or concurrent participation in another interventional clinical trial.
2. Pregnancy or breastfeeding
3. Severe concomitant disease that may, in the investigator's judgment, pose an unacceptable risk or compromise study compliance, including severe cardiac disease, severe pulmonary dysfunction, significant renal disease, or severe psychiatric illness.
4. History of another invasive malignancy within 5 years before enrollment, except for adequately treated basal cell carcinoma of the skin, cervical carcinoma in situ, or superficial bladder tumors (Ta, Tis, or T1).

6. Standard Anticancer Treatment Before Follow-up Evaluation

Participants receive standard therapy according to guideline-based care. Treatment may include cisplatin-based induction chemotherapy followed by intensity-modulated radiotherapy (IMRT) with concurrent cisplatin-based chemoradiotherapy (CCRT). Adjuvant therapy may be considered according to clinical practice. For epidermal growth factor receptor-positive patients, nimotuzumab may be administered during induction chemotherapy at the investigator's discretion according to institutional standards.

Radiotherapy is delivered using IMRT. Target delineation and dose constraints are performed according to institutional radiotherapy standards. Treatment-related toxicities are monitored during treatment and follow-up.

7. Study Intervention Strategy

7.1 Multimodal Cervical Lymph Node Follow-up Evaluation

After completion of radiotherapy, participants undergo prospective multimodal evaluation. The evaluation includes clinical assessment, conventional imaging such as MRI or CT, plasma EBV DNA testing, CEUS, and biopsy when clinically feasible.

Multimodal findings are integrated to determine whether cervical lymph nodes are low suspicion, intermediate suspicion, high suspicion, or very high suspicion for residual viable disease. The integrated assessment by multidisciplinary discussion is used to guide possible ESND.

7.2 Contrast-Enhanced Ultrasound

CEUS is performed to evaluate cervical lymph node microvascular perfusion and enhancement patterns. The protocol uses an ultrasound contrast agent administered intravenously according to clinical practice, followed by dynamic observation of contrast wash-in and wash-out and recording of dynamic imaging data.

CEUS imaging features include enhancement homogeneity, enhancement intensity, centripetal perfusion, focal non-perfusion, and time-intensity curve parameters. CEUS images are assessed by experienced radiologists.

7.3 Multimodal Risk Assessment

The multimodal assessment integrates CEUS features and parameters, MRI/CT findings, plasma EBV DNA status, and lymph node volume changes. Higher scores suggest a greater probability of residual viable tumor. Supplementary modifiers, including nodal trend, EBV DNA trend, nodal necrosis, extranodal extension, and biopsy results, may be used to refine risk classification.

7.4 Endoscopic Selective Neck Dissection

Participants whose follow-up evaluation suggests suspicious residual cervical lymph nodes and who are suitable for surgery undergo ESND. ESND is performed under general anesthesia using a minimally invasive endoscopic approach with a postauricular route, selected according to nodal location, anatomical feasibility, and surgeon judgment.

The dissection extent is lesion-oriented and guided by radiologic, CEUS, and integrated multimodal evaluation. Commonly involved levels include II to IV, with extension to levels Ib or V when clinically indicated. Radical neck dissection is not planned. Preservation of key structures, including the internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle, is prioritized unless direct tumor invasion is suspected intraoperatively. All surgical specimens are submitted for pathological assessment.

8. Follow-up Schedule and Assessments

Participants are followed prospectively after standard anticancer treatment and radiotherapy. During the first 3 years after radiotherapy, follow-up evaluations are generally performed at least every 3 months. Thereafter, follow-up is performed every 6 months until death, loss to follow-up, withdrawal of consent, or the study data cutoff date, whichever occurs first.

Assessment	Timing/Comment
Medical history and symptoms	At each follow-up visit
Physical examination	At each follow-up visit
Nasopharyngoscopy	As clinically indicated and according to follow-up schedule
Plasma EBV DNA	During routine follow-up according to institutional practice
CEUS of cervical lymph nodes	Integrated into routine cervical lymph node surveillance when feasible
MRI or CT of nasopharynx and neck	According to follow-up schedule and clinical indication
Chest and abdominal imaging/bone scan	According to follow-up schedule and clinical indication
Adverse event assessment	Throughout study participation and post-ESND follow-up when applicable

9. Outcome Measures

9.1 Primary Outcome Measure

Outcome	Definition/Assessment	Time Frame
Safety and feasibility of the multimodal evaluation-guided surveillance-intervention strategy	Safety is assessed by adverse events and postoperative complications related to radiotherapy, follow-up evaluation, CEUS, and ESND when applicable. Feasibility is assessed by successful implementation of multimodal cervical lymph node evaluation and completion of indicated ESND in eligible participants.	From enrollment through post-radiotherapy follow-up and 30 days after ESND when applicable.

9.2 Secondary Outcome Measures

Outcome	Definition	Time Frame
Progression-free survival	Time from enrollment to disease progression, recurrence, distant metastasis, or death from any cause, whichever occurs first.	From enrollment to event or last follow-up.
Locoregional recurrence-free survival	Time from enrollment to locoregional recurrence or death from any cause, whichever occurs first.	From enrollment to event or last follow-up.
Distant metastasis-free survival	Time from enrollment to distant metastasis or death from any cause, whichever occurs first.	From enrollment to event or last follow-up.
Overall survival	Time from enrollment to death from any cause. Participants alive at last follow-up will be censored.	From enrollment to death or last follow-up.

10. Safety Monitoring and Adverse Event Reporting

Adverse events (AEs) are any unfavorable medical occurrences after informed consent, whether or not considered related to the study intervention. Serious adverse events (SAEs) include events resulting in death, life-threatening events, hospitalization or prolonged hospitalization, persistent or significant disability, or other medically important events.

Toxicity and postoperative complications are assessed according to standard clinical criteria, including CTCAE version 5.0 when applicable. Acute events may include bleeding, wound infection, wound effusion, allergic reaction, or other procedure-related complications. Late events may include nerve injury, lymphatic or chyle leak, head and neck edema, flap necrosis, neck movement disorder, or other sequelae.

AEs and SAEs are collected from informed consent through the study observation period. For participants undergoing ESND, AEs are recorded through 30 days after the last study intervention; SAEs are followed for up to 90 days after the intervention or until initiation of another antitumor treatment, whichever occurs first. SAEs are reported within 24 hours of investigator awareness according to institutional and ethics committee requirements.

The study team maintains a safety management process including event recording, reporting, clinical management, review, and corrective actions when needed. Participants with ongoing study-related AEs or SAEs are followed until resolution, stabilization, return to baseline, or until no further information can reasonably be obtained.

11. Risk Minimization and Quality Assurance

CEUS is performed by experienced clinicians using standardized procedures. Participants are monitored for contrast reactions and other procedure-related risks. ESND is performed by experienced head and neck surgeons using established surgical principles and perioperative safety measures.

Quality control procedures include standardized CEUS acquisition, independent review by experienced radiologists when feasible, storage of imaging data, standardized surgical documentation, pathology review of surgical specimens, and regular review of safety events by the study team. Study data are recorded in source documents and case report forms and are managed according to institutional requirements.

12. Data Management and Confidentiality

Study-related data are recorded accurately, completely, and in a timely manner in source records and case report forms. Data include eligibility information, baseline characteristics, treatment and follow-up assessments, imaging findings, CEUS results, surgery records, pathology findings, adverse events, and outcome events.

Participant confidentiality is protected. Records are stored securely and are accessible only to authorized study personnel, monitors, auditors, ethics committee representatives, or regulatory authorities as permitted by applicable laws and institutional policies. Publicly posted documents will not contain names of study participants or direct participant identifiers.

13. Statistical Analysis Plan

13.1 Analysis Sets

- Full Analysis Set (FAS): all enrolled participants, analyzed according to the intention-to-treat principle when applicable. Baseline characteristics and efficacy-related exploratory outcomes will be summarized using the FAS.
- Safety Analysis Set (SAS): all enrolled participants with available safety records. For surgery-specific safety analyses, participants who undergo ESND and have postoperative safety records will be included in the relevant surgery safety subset.

13.2 General Statistical Principles

This is an exploratory phase Ib study. Statistical analyses will be primarily descriptive. Continuous variables will be summarized using mean, standard deviation, median, interquartile range, minimum, and maximum as appropriate. Categorical variables will be summarized using counts and percentages. Two-sided 95% confidence intervals may be provided for key proportions and time-to-event estimates when appropriate.

13.3 Baseline Characteristics

Baseline demographic and clinical characteristics will be summarized for the FAS. Variables may include age, sex, ECOG performance status, TNM stage, treatment details, EBV DNA status, imaging findings, and cervical lymph node characteristics.

13.4 Primary Outcome Analysis

Safety will be summarized by the incidence, severity, seriousness, relationship to study procedures, and outcome of AEs and SAEs. Procedure-related adverse events, radiotherapy-related toxicities, CEUS-related reactions, and postoperative complications will be tabulated. The incidence of grade 3 or higher procedure-related adverse events will be reported with 95% confidence intervals when appropriate. Feasibility will be summarized by the proportion of participants completing planned multimodal follow-up evaluation and, among those with suspicious residual cervical lymph nodes and surgical indications, the proportion completing ESND as planned.

13.5 Secondary Outcome Analysis

Progression-free survival, locoregional recurrence-free survival, distant metastasis-free survival, and overall survival will be estimated using the Kaplan-Meier method when data are sufficient. Median survival times, event rates at selected time points, and 95% confidence intervals may be reported. Participants without an event at the data cutoff will be censored at the last disease assessment or last known follow-up, as appropriate.

13.6 Missing Data

Missing data will not be imputed for the primary descriptive analyses. The number of participants with missing data for each variable will be reported where relevant. For time-to-event analyses, participants without events will be censored at the last available follow-up date.

13.7 Subgroup and Exploratory Analyses

Exploratory analyses may describe outcomes by multimodal evaluation category. If comparisons are performed, they will be considered exploratory and interpreted cautiously because the study is not powered for formal between-group comparisons.

14. Ethics and Informed Consent

The study is conducted in accordance with the principles of the Declaration of Helsinki and applicable Chinese regulations for biomedical research involving human participants. The protocol was approved by the Medical Ethics Committee of West China Hospital of Stomatology, Sichuan University. Written informed consent is obtained before study participation. Participants may refuse participation or withdraw consent at any time without penalty or loss of medical rights and benefits.

15. Selected References

1. Cui XW, Jenssen C, Saftoiu A, Ignee A, Dietrich CF. New ultrasound techniques for lymph node evaluation. *World J Gastroenterol*. 2013;19(30):4850-4860.
2. Trillaud H, Bruel JM, Valette PJ, et al. Characterization of focal liver lesions with SonoVue-enhanced sonography: international multicenter study in comparison to CT and MRI. *World J Gastroenterol*. 2009;15(30):3748-3756.
3. Nakase K, Yamamoto K, Hiasa A, Tawara I, Yamaguchi M, Shiku H. Contrast-enhanced ultrasound examination of lymph nodes in different types of lymphoma. *Cancer Detect Prev*. 2006;30(2):188-191.
4. Ling W, Nie J, Zhang D, et al. Role of contrast-enhanced ultrasound in the diagnosis of cervical lymph node metastasis in patients with nasopharyngeal carcinoma.
5. Relevant CSCO and NCCN guideline recommendations for nasopharyngeal carcinoma and salvage neck dissection are considered in the study rationale.

16. Public Posting Statement

This document is intended for public posting as a Study Protocol with Statistical Analysis Plan. It has been prepared without participant names, medical record numbers, signatures, or other direct participant identifiers.