SCHEMA

For patients with oropharyngeal cancer (OPC) or cancer of unknown primary (CUP):
Local p16 determination by immunohistochemistry is required.

For patients with laryngeal and hypopharyngeal primaries:
Analysis of p16 status is **not required.**

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STRATIFY

- Zubrod (ECOG) performance status: 0 vs. 1
- Smoking status: ≤ 10 pack-year vs. > 10 pack-year history
- T stage: T0-3 vs. T4
- Age: ≤ 50 vs. > 50 years

RANDOMIZE (1:1 in each cohort)

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Non-OPC/p16-negative OPC Cohort

Arm 1: IMRT/IMPT + High-dose cisplatin Q 3 weeks

Arm 2: IMRT/IMPT + Low-dose cisplatin weekly

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p16-positive OPC/CUP Cohort

Arm 3: IMRT/IMPT + High-dose cisplatin Q 3 weeks

Arm 4: IMRT/IMPT + Low-dose cisplatin weekly

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Notes: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Statistics and Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of SCCHN of the oropharynx, larynx, hypopharynx, or p16-positive unknown primary prior to registration; specimen from cervical lymph nodes with a well-defined primary site documented clinically or radiologically is acceptable; in patients with carcinoma of unknown primary this will be sufficient for pathologic confirmation without a clinically or radiographically defined primary site.

For patients with oropharyngeal cancer (OPC)/cancer of unknown primary (CUP):
P16 status based on local site immunohistochemical tissue staining is required. A cell block obtained from a fine needle aspiration (FNA) biopsy specimen may be used as the sole diagnostic tissue. Centers are encouraged to contact the pathology chair for clarification.

Note: Institutions must screen patients for p16 status by immunohistochemistry (IHC) in order to be eligible for the trial using a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. A rigorous laboratory accreditation process similar to the U.S. CLIA certification, such as the provincial accreditation status offered by the Ontario Laboratory Accreditation (OLA) Program in Canada, the College of American Pathologists (CAP), or an equivalent accreditation in other countries, is acceptable.

The p16 results must be reported on the pathology report being submitted. The p16 positivity is defined as > 70% of tumor cells showing strong nuclear and/or cytoplasmic immunostaining with p16 antibody.

For patients with laryngeal and hypopharyngeal primaries: Analysis of p16 status is **NOT** required;

3.1.2 Patients must have clinically or radiographically evident measurable disease at the primary site or at nodal stations. Simple tonsillectomy or local excision of the primary without removal of nodal disease is permitted, as is excision removing gross nodal disease but with intact primary site. Limited neck dissections retrieving ≤ 4 nodes are permitted and considered as non-therapeutic nodal excisions.

3.1.3 Clinical stage (AJCC, 8th ed.) as indicated in the tables below, including no distant metastases based on the following diagnostic workup:

- History/physical examination within 60 days prior to registration;

- One of the following imaging studies is required within 60 days prior to registration:
  1. CT scan of neck (diagnostic quality with contrast, unless contraindicated)
     OR
  2. MRI of the neck (diagnostic quality with contrast, unless contraindicated)
     OR
  3. FDG-PET/CT of the neck; the CT component should be of diagnostic quality with contrast, unless contraindicated.

  Note: A diagnostic quality CT or MRI with contrast or FDG-PET/CT scan of neck performed for the purposes of radiation planning may serve as both staging and planning tools.

- One of the following imaging studies is required within 60 days prior to registration:
  1. FDG-PET/CT of the chest; FDG-PET/CT scan is strongly preferred and highly recommended to be used for eligibility.
     OR
  2. Chest CT

- Exam with laryngopharyngoscopy (mirror or in office direct procedure acceptable) within 70 days prior to registration;

Eligibility by patient cohort:

Non-OPC/p16-negative OPC Cohort	
Tumor Site	**Clinical Staging (AJCC, 8th ed.)**
Larynx/Hypopharynx	T3-4 N0 or T1-4 N1-3 T2 N0 (hypopharynx only)
p16-negative OPC	T2N1, T1-4 N2-3, or T3-4 N0-1

p16-positive OPC/CUP Cohort		
Tumor Site	**Smoking Status**	**Clinical Staging (AJCC, 8th ed.)**
OPC	≤ 10 pack-years	T1-3 N2-3 or T4 N0-3
	> 10 pack-years	T1-2 N2-3 or T3-4 N0-3
CUP	Any	T0 N2-3

The following formula is used to calculate the pack-years during the periods of smoking in the patient's life; the cumulative total of the number of pack-years during each period of active smoking is the lifetime cumulative history.

Number of pack-years = [Frequency of smoking (number of cigarettes per day) × duration of cigarette smoking (years)] / 20

3.1.4 Age ≥ 18;

3.1.5 Zubrod (ECOG) performance status of 0-1 within 14 days prior to registration;

3.1.6 Adequate hematologic function within 30 days prior to registration defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
- Platelets ≥ 75,000 cells/mm^3
- Hemoglobin ≥ 8.0 g/dL (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dL is acceptable).

3.1.7 Adequate renal function within 30 days prior to registration defined as calculated creatinine clearance (CrCl) ≥ 50 mL/min by the Cockcroft-Gault formula:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg / dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

3.1.8 Adequate hepatic function within 30 days prior to registration defined as follows:

- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) (not applicable to patients with known Gilbert's syndrome);
- AST and ALT ≤ 1.5 x institutional ULN.

3.1.9 Known human immunodeficiency virus (HIV) infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months and CD4 T Cell count ≥ 200 cells/mm^3 are eligible for this trial. Testing is not required for entry into protocol.

3.1.10 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.11 Negative urine or serum pregnancy test (in persons of childbearing potential) within 14 days prior to registration. Childbearing potential is defined as any person who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

3.1.12 Willing to use highly effective contraceptives for participants of childbearing potential (participants who may become pregnant or who may impregnate a partner) during therapy and for 14 months (females); for 11 months (males) following last dose of cisplatin; this inclusion is necessary because the treatment in this study may be significantly teratogenic (See Section 9 for definition of highly effective contraception).

3.1.13 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

3.2 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.2.1 Patients with oral cavity cancer, nasopharynx cancer, or p16-negative cancer of unknown primary (CUP);

3.2.2 Recurrence of the study cancer;

3.2.3 Definitive clinical or radiologic evidence of distant metastatic disease;

3.2.4 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable, however, any prior exposure to cisplatin is excluded;

3.2.5 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.6 Severe, active co-morbidity defined as follows:

- Unstable angina requiring hospitalization in the last 6 months;
- Myocardial infarction within the last 6 months;
- New York Heart Association Functional Classification III/IV (Note: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification.);
- Persistent Grade 3-4 (CTCAE version 5.0) electrolyte abnormalities that cannot be reversed despite replacement as indicated by repeat testing;
- Patient must not have an active infection requiring IV antibiotics prior to registration;
- Other chronic renal disease like nephrotic syndrome, that could be worsened by cisplatin therapy;
- History of allogenic organ transplantation;
- Any symptomatic peripheral sensory neuropathy Grade ≥ 2 (CTCAE version 5.0);

3.2.7 Pregnancy and individuals unwilling to discontinue nursing.

Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf