1. Resectable oropharynx carcinoma, p16+ by IHC, PS 0-1
2. Credentialed of surgeon required as part of site participation, neck levels dissected and nodal yield (> nodes/neck)
3. Radiotherapy will be given with an intensity modulated radiotherapy (IMRT) technique. Standard ECOG credentialing through QARC will be required.
4. Stratify by current/former smoking history(<10pk-yr vs. >10pk-yr)
5. Low risk: T1-T2, N0-N1, 0-1 metastatic lymph nodes, negative margins
6. High risk: >1mm ECS or >5 metastatic lymph nodes, positive margins
7. Intermediate risk: Close (<3mm) margins, <1mm ECS, 2-4 metastatic lymph nodes.
8. If ≥ 2 events are observed among the first ten patients registered on Arm A within one year, currently enrolled and subsequently enrolled low risk patients who have not progressed will be treated with IMRT 50 Gy

Accrual: 377
Registration to Surgery (Arm S)

1. Age \( \geq 18 \) years.
2. ECOG performance status of 0 or 1.
3. Patients must have newly diagnosed, histologically or cytologically confirmed squamous cell carcinoma or undifferentiated carcinoma of the oropharynx. Patients must have been determined to have resectable oropharyngeal disease. Patients with primary tumor or nodal metastasis fixed to the carotid artery, skull base or cervical spine are not eligible.
4. Patients must have AJCC TNM tumor stage III, IV a, or IV b (with no evidence of distant metastases) as determined by imaging studies (performed < 4 weeks prior to pre-registration) and complete head and neck exam. The following imaging is required: CT scan with IV contrast or MRI.
5. Primary: patients must have measurable disease of the primary by both clinical and radiographic methods. To meet this criteria, a lesion must be > 2 cm in at least one dimension by clinical exam AND by radiographic exam with CT or MRI. If radiographic exam utilizes spiral CT, lesion must be > 1 cm in at least one dimension. Nodes: although it is required that patients must have nodal stage beyond N0 confirmed by clinical or radiographic methods, measurable nodal disease is not required.
6. Carcinoma of the oropharynx associated with HPV as determined by p16 protein expression using immunohistochemistry (IHC) performed by a CLIA approved laboratory. Using p16 antibody obtained from Roche mtm laboratories AG (CINtec, clone E6H4) is recommended.
7. No prior radiation above the clavicles.
8. Patients with a history of a curatively treated malignancy must be disease-free for at least two years except for carcinoma in situ of cervix and/or non-melanomatous skin cancer.
9. Patients with the following within the last 6 months prior to pre-registration must be evaluated by a cardiologist and/or neurologist prior to entry into the study. Congestive heart failure > NYHA Class II? CVA/TIA? Unstable angina? Myocardial infarction? (with or without ST elevation)
10. Patients must not have evidence of extensive or “matted/fixed” pathologic adenopathy on preoperative imaging.
11. Patients must have acceptable renal and hepatic function within 4 weeks prior to registration.
12. Women must not be pregnant or breast-feeding due to the teratogenicity of chemotherapy.
13. Patients must not have uncontrolled diabetes, uncontrolled infection despite antibiotics or uncontrolled hypertension within 30 days prior to pre-registration.

Registration/Randomization to Step 2 - Arms A, B, C, and D

1. Histopathologic assessment of surgical pathology must include examination for perineural invasion (PNI) and lymphovascular invasion (LVI) and reported as absent or present. The absence or presence of extracapsular spread (ECS) requires gross and microscopic assessment and is defined to be:
   - absent (negative or nodal metastasis with smooth/rounded leading edge confined to thickened capsule/pseudocapsule
   - present - minimal (tumor extends <1 mm beyond the lymph node capsule), or
   - present - extensive (Gross, tumor extends >1 mm beyond the lymph node capsule (includes soft tissue metastasis)

2. Patients must have ECOG performance status 0 or 1.
3. Patient must be registered/randomized within 5-7 weeks following surgery.
4. Women of childbearing potential and sexually active males are strongly advised to an accepted and effective method of contraception