Other reports identified that five or more pathologic positive neck nodes was also an adverse prognostic factor (Figure)[5]:

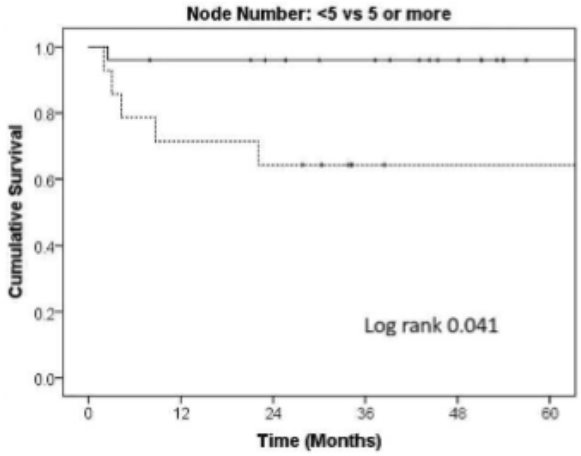


Fig. 3. Disease-free survival of surgical patients with pathological N3 disease from human papillomavirus–related oropharyngeal squamous cell carcinoma with less than five (solid line) versus five or more (dotted line) pathologically positive nodes.

Seventeen percent of patients with OPSCC have five or more positive neck nodes, but even these patients had a favorable five year disease-specific survival (DSS) of 80%.[6]

1.3 Acute and Long Term Toxicities of Surgery and Adjuvant Therapy for HPV-related OPSCC

The treatment-related toxicity burden experienced by patients with HPV-related OPSCC is substantial. Adverse events (AEs) due to surgery with modern trans-oral techniques usually resolve after 3-4 weeks. Swallowing function after TLM and adjuvant therapy was good at two years in 93% of patients with T1-3 disease but in only 40% of patients with T4 base of tongue (BOT) disease.[4] Shoulder dysfunction due to injury of cranial nerve XI is frequent but temporary in most cases, except those patients with bulky, infiltrative neck nodal disease.

In contrast to surgery, the toxicity of POACRT is much more significant. Acute AEs include mucositis, dysgeusia, dry mouth, weight loss, fatigue, renal dysfunction, myelosuppression, tinnitus, and high frequency hearing loss. Chronic AEs include xerostomia, dysgeusia, dental caries, difficulty swallowing, pain, hearing loss, carotid artery atherosclerosis, and fatigue. These AEs impair global patient-reported quality of life (PRQOL), and social, functional, physical, and emotional domains.

4. To document the measures of Quality of Life (QOL) at baseline, during treatment, and through one year after completion of treatment in each arm.
5. To determine the disease recurrence rate at 24 months post-treatment in each arm.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed HPV-related stages I-III OPSCC (8th edition of AJCC/UICC Staging Manual) or HPV-related neck node with unknown primary. HPV-related may be defined by p16 IHC stain and/or HPV-ISH or PCR using standard definitions of positive and negative test results. cT1N0 and cT2N0 excluded.
2. Primary tumor that will be resected via a transoral oral approach (conventional surgery, transoral laser microsurgery, transoral robotic surgery)
3. ECOG PS 0-2.
4. Normal organ and marrow function defined as:
    a. Creatinine clearance > 50 cc/min.
    b. ANC $\geq$ 1,000/mcL.
    c. Platelet count $\geq$100,000/mcL.
5. At least 18 years of age.
6. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.
7. Patient (or legally authorized representative) must be able to understand and willing to sign a written informed consent document.

3.2 Exclusion Criteria

1. cT1N0 or cT2N0 staging.
2. Prior curative therapy for HNSCC.
3. Patient must not have known distant metastatic disease at presentation.
4. History of prior invasive malignancy diagnosed within 2 years prior to study enrollment; exceptions are malignancies with a low risk of metastasis or death (e.g., expected 5-year OS > 90%) that were treated with an expected curative outcome, such as squamous cell carcinoma of the skin, in-situ carcinoma of the cervix uteri, non-melanomatous skin cancer, carcinoma in situ of the breast, or incidental histological finding of prostate cancer (TNM stage of T1a or T1b).
5. Receiving any other investigational agents.
6. Uncontrolled serious inter-current illness or serious psychiatric illness/social situations that would limit compliance with study requirements.

details of the pathology report, patients will be assigned to one of three adjuvant treatments. Arm 1 (ECE or positive margin but not clinical or pathologic T4 or clinical N3 disease) will be treated with POAmCRT (42 Gy RT + cisplatin 1 dose). Arm 2 (no ECE, no positive margins, and not clinical or pathologic T4 or clinical N3 disease) will be treated with POAmRT (42 Gy RT, no cisplatin). Arm 3 (clinical or pathologic T4 or clinical N3 disease) will be treated with POART (60 Gy RT). If there is pathologic evidence of ECE or positive margin, 3 cycles of cisplatin will be given concurrently with POART (60Gy).

Please note that because weight loss is the primary endpoint, a specific scale must be chosen at each facility. It is the responsibility of the research coordinator to ensure that the same scale is used for all patients at that facility. Patient weight will be assessed with clothes on (no outer layers such as jackets) and shoes off.

5.1 Baseline Assessment

The baseline assessment will include the following tests or procedures and must occur within 35 days (PET scan within 42 days) of enrollment:

1. Clinical examination to document extent of primary tumor by laryngoscopy performed in the office or in the operating room (depending on the ease of the exam and the primary tumor site) and palpable involved regional neck nodes.
2. Documentation of site of primary tumor (HPV-related oropharynx or CUP), location and level of clinically involved neck nodes (right or left neck, Level I-V), T stage (1-4), N stage (0-3), and overall clinical stage (I-III by AJCC Cancer Staging Manual Eighth Edition).
3. Documentation of demographic information, including gender (M/F), age (years), height (cm), weight (Kg), and BSA (m^2).
4. Documentation of baseline patient symptoms using NCI-CTCAE version 4.0.
5. Documentation of ECOG performance status (Appendix 1).
6. Completion of QOL questionnaires (Appendices 3, 4, 5, 6, and 7).
7. Documentation of Comorbidity Index (Appendix 2).
8. Laboratory evaluations: CBC, CMP, magnesium, PT/PTT, serum pregnancy test if patient is a female of childbearing potential.
9. CT scan of the neck (IV contrast preferred) to document and measure the extent of the primary tumor size and involved regional neck nodes.
10. FDG-PET/CT scan (whole body) to document and measure the FDG avidity at the primary tumor site and at the involved regional neck nodes.
11. OPTIONAL: Speech and swallowing assessment including a modified barium swallow (MBS) study and the Performance Status Scale for Head and Neck Cancer (PSS-HN) questionnaire (Appendix 8).

5.2 Standard of Care Surgery

- Dose Volume Histograms (DVHs):
  No more than 20% of any PTV should exceed 110% of the prescribed dose.
  DVH from PTVs must meet all prescription parameters.
  Normal structure DVHs should meet constraint parameters as listed above.

5.5.8 Daily Radiation Treatment

Arms 1 and 2: Patients will receive external beam radiation treatment delivered by a Varian linear accelerator once a day, five days a week, for 4 to 4 1/5 weeks as per routine clinical practice.

Arm 3: Patients will receive external beam radiation treatment delivered by a Varian linear accelerator once a day, five days a week, for 6 weeks as per routine clinical practice.

5.5.9 Quality Assurance

Treatment plan physics review and QA are required for each patient in accordance with current institutional standards for IMRT.

Daily set-up error will be minimized by the following clinically approved and commercially available patient setup techniques: immobilization mask, standard skin/mask alignment marks, and daily on-board imaging.

Per routine practice, daily cone beam CT scans will be acquired and compared with planning CT overlay.

These setup scans will be performed immediately prior to each treatment and the appropriate shifts will be made at that time.

5.6 Follow-Up Assessments after Adjuvant Therapy

Follow-up assessments will be planned at the following time points; actual follow up times may vary due to patient logistics and compliance:

- 6 weeks (+/- 1 week) following completion of adjuvant therapy
- 4 months (+/- 2 weeks) following completion of adjuvant therapy
- 6, 12, 18, 24, 30, 36, 48, and 60 months (+/- 6 weeks) following completion of adjuvant therapy
- annually thereafter for 5 years (total follow-up 10 years)

Patients with disease progression will only be followed for survival and will not stay on the above follow-up schedule. Their follow-up schedules will then be at the discretion of the investigator.

5.6.1 Six Week (+/- 1 week) Assessment

1. Physical examination and weight (kg).
2. Serum creatinine (BMP).
3. Documentation of ECOG performance status.
4. Documentation of narcotic and PEG tube usage.
5. Documentation of patient symptoms using NCI-CTCAE version 4.0.
6. Completion of QOL questionnaires
7. CT Neck.
8. OPTIONAL: Speech and swallowing assessment

5.6.2 Four Month (+/- 2 weeks) Assessment

1. Physical examination and weight (kg).
2. Documentation of ECOG performance status.
3. Documentation of narcotic and PEG tube usage.
4. Completion of QOL questionnaires.
5. OPTIONAL: Speech and swallowing assessment

5.6.3 Six to Sixty Month (+/- 6 weeks) Assessments

1. Physical examination and weight (kg).
2. Documentation of ECOG performance status.
3. Documentation of narcotic and PEG tube usage.
4. Completion of QOL questionnaires (to occur at 6, 12 and 24 month visits only).
5. CT scan of neck and chest (IV contrast preferred) to be done at 6, 12, 18, 24, and 36 months (+/- 6 weeks) following completion of therapy. CXR (PA and Lateral) may be substituted for CT chest if unable to obtain the latter.
6. OPTIONAL: Speech and swallowing assessment (to occur at 6, 12, and 24 month visits only). These will include MBS at 6 months post-adjuvant therapy, PSS-HN questionnaires at 6, 12, and 24 months, and Fiberoptic Endoscopic Evaluation of Swallowing (FEES) as clinically indicated.

5.6.4 Annual Assessments Subsequently

1. Physical examination and weight (kg).
2. Documentation of ECOG performance status.

5.7 Evaluations for Toxicity and Disease Relapse

All patients who receive any study treatment (starting point of “study treatment” is

first dose of post-operative RT) are evaluable for toxicity. Patients are evaluated from first day of study treatment until five years after the conclusion of treatment, or death.

All patients who undergo surgery are evaluable for disease relapse.

5.8 General Concomitant Medication and Supportive Care Guidelines

Primary prophylaxis with G-CSF or Neulasta is not permitted; however it can be used in a non-prophylactic setting following neutropenia. Use of erythropoietin is not permitted.

5.9 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum pregnancy test within 35 days of enrollment.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 1 month following the last day of study treatment.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 1 month after the last day of study treatment, the investigator must be notified in order to facilitate outcome follow-up.

5.10 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for the duration of surgery and RT +/- cisplatin until one of the following criteria applies:

- Documented and confirmed disease progression
- Death

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

9.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

9.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

9.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies

to increase enrollment to reach 7 additional patients on Arm 1, or 20 additional patients onto any arm, whichever comes first.

10.3 Accrual

We perform surgery in 60-80 patients per year at Washington University with similar characteristics and estimate approximately 30-40 patients/year may be eligible for and will participate in this trial. We anticipate enrollment of approximately 2-3 patients per month.

10.4 Statistical Analyses

10.4.1 Patient Disposition

The number of patients discontinued, the reasons for discontinuation, and the amount of therapy administered will be summarized by patient and by reason for discontinuation by arm.

10.4.2 Protocol Deviations

All significant deviations will be summarized by patient and by type of deviation.

10.4.3 Demographics and Baseline Characteristics

Subject demographic and clinical characteristics will be summarized to characterize the population. Descriptive summaries will include means, standard deviations, medians, ranges for continuous variables and frequency and percentage for categorical variables. They are presented by total and each arm, respectively.

10.4.4 Endpoint Analysis

The primary endpoint is percent weight loss. Weight (kg) will be collected weekly during radiation within each arm. The percent weight loss from the baseline is calculated at any post-baseline. The generalized estimating equation (GEE) model with identity link function will be used to analyze this percent weight loss data, in which the correlation among the repeated measures from the same patient need be considered. The autoregressive of first order as working correlation structure will be used. The GEE model includes baseline weight and time points. The p-value is estimated to assess whether the percentages of weight loss across all time points are different. Least square means for percent weight loss at each time point and mean differences between any time points will be estimated, and their standard errors will be calculated within the use of GEE sandwich method when accounting for within-patient correlation.

The secondary endpoints include proportion of PEG tube placements for all enrolled patients, the serum creatinine changes in patients receiving POAmCRT, proportion of the narcotics administration of patients 6 weeks after POAmCRT, the measures of Quality of Life (QOL), and RFS. Proportions of PEG tube placements for all enrolled patients and the narcotics administration of patients 6 weeks after POAmCRT and their associated 95% confidence intervals will be calculated assuming a binomial distribution[23]. The serum creatinine is measured at the baseline and six weeks after POAmCRT. The paired t-test will be considered to test the change. QOL are measured at baseline/during treatment/one year after completion of treatment on all arms. Similarly, the GEE model will be used to analyze the longitudinal QOL data.

Disease recurrence rate at 24 months post-treatment (DRR-24) in each arm is calculated for each arm. The proportion and 95% CI from binomial distribution will be shown for Arm 1. If 95% upper CI is smaller than 20%, then the risk of disease recurrence is deemed as acceptable. If 95% lower CI is larger than 20%, then the risk of disease recurrence is deemed as unacceptable. Given our small sample size, there are some uncertainties. Therefore, we do not test the hypothesis about (DRR-24) but provide a preliminary data for planning future studies.

Data on the toxicity in each arm will be collected for each subject, including frequency, type, and severity of adverse events. All analyses were conducted using SAS (SAS Institute, Cary, NC) at the two-sided 5% significance level.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	**Submission Schedule**
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Surgery Form	Time of surgery
QOLs Forms	Baseline Interim assessment Day 1 of RT (-7/+0) Day 22 after start of RT (Arm 1 & 2 +/- 2 days; Arm 3 +/- 5 days) Day 36 after start of RT (Arm 1 & 2 +/- 2 days; Arm 3 +/- 5 days) 6 weeks after completion of adjuvant therapy 4 months after completion of adjuvant therapy 6 months after completion of adjuvant therapy 12 months after completion of adjuvant therapy 24 months after completion of adjuvant therapy

Toxicity Form	Continuous
Weight Form	Baseline, weekly during treatment, and at each follow-up visit
Treatment Summary Form	Completion of treatment
Follow Up Form Narcotics Form PEG Form	6 weeks, 4 months, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, and 48 months after the completion of adjuvant therapy
RECIST Form	Baseline, 6 weeks after completion of adjuvant therapy, and 6 months after completion of adjuvant therapy

12.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

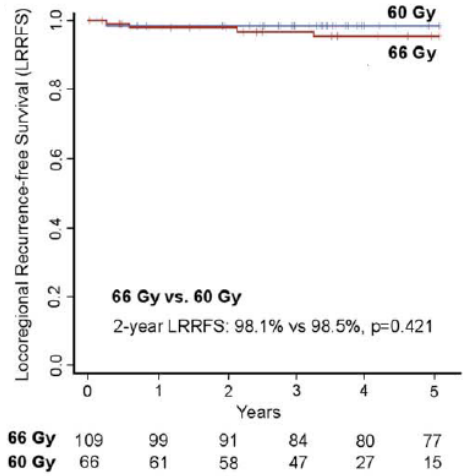
The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

1.4 Steps Already Taken to Reduce Treatment-Related AE in Patients with HPV-related OPSCC

The goal of primary surgery is to remove all gross disease at the primary tumor site and remove the involved and at risk neck nodes, to result in a state of microscopic disease. Nearly all cases can be performed by trans-oral procedures (TLM or TORS), which are much mess morbid compared to open surgical techniques. The vast majority of patients with HPV-related OPSCC do not need to undergo reconstruction procedures and their associated morbidities. Reconstruction procedures using free- or pedicle-flaps are usually only required for management of bulky or infiltrative tumors (T4 or N3).

The goal of POART is to eliminate microscopic tumor in at risk zones that may have been left behind after surgery. A series of studies in patients with OPSCC showed that changes in radiation technique, doses, and port volumes can be safely performed without loss of efficacy and resulted in improvement in PRQOL and reduction in toxicity. The shift from 3D CRT to IMRT resulted in a reduction in grade 3 acute (mucositis, dysphagia, and pain) and delayed (xerostomia and dysphagia) toxicities.[7] Elimination of POART to the primary tumor site resulted in a risk of local recurrence of 3% in patients with T1-2 disease compared to 17% in patients with T3-4 disease.[6] Rates of temporary percutaneous endoscopic gastrostomy (PEG) tube requirements were 6% with no primary bed radiation vs 41% with primary bed radiation. These data support elimination of radiation to the primary tumor bed in patients with T1-2 disease. In HPV-related OPSCC, no difference in local-regional recurrence-free survival occurred between post-operative adjuvant IMRT doses of 60 Gy compared to 66Gy (98.5% vs 98.1% at 2 years, respectively).[8]



In OPSCC patients with a clinically uninvolved contralateral neck, eliminating coverage of POART to the contralateral high level II neck and retropharyngeal

7. Pregnant and/or breastfeeding. A negative serum or urine pregnancy test is required at screening for all female patients of childbearing potential.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN AND SCHEDULED ASSESSMENTS

Patients with HPV-related OPSCC will undergo resection of the primary tumor site and involved/at risk regional neck nodes. Based on the clinical and pathologic staging and the

Patients will undergo a typical preoperative workup in preparation for surgery, including routine lab work, electrocardiogram, and a preoperative assessment by anesthesiology. Patients will undergo surgical resection of the primary tumor via a transoral approach, including conventional transoral surgery, transoral laser microsurgery (TLM), or transoral robotic surgery (TORS). The choice of surgical technique will be based on surgeon preference, tumor characteristics, and tumor site. Margin status will be assessed intra-operatively on frozen section and confirmed on permanent section.

At the time of transoral resection, patients will also undergo surgical management of cervical lymph nodes via a conventional selective neck dissection. For oropharyngeal tumors, this most often includes dissection of Levels II-IV. If the tumor approaches within one centimeter of midline, the patient will undergo bilateral neck dissections.

The pathology report documents margin status, perineural invasion, lymphovascular invasion, and extracapsular extension (ECE). Margins will be considered positive if gross or microscopic disease is present at the margins based on the surgical pathologist's judgement. ECE will be defined as tumor extending beyond the lymph node capsule into the surrounding soft tissue (AJCC 8th Edition Staging Manual). ECE will be measured when possible; however, extensive ECE or soft tissue metastases may preclude this measurement.

5.3 Interim Assessment

The interim assessment will include the following tests or procedures and should occur within 14-42 days of surgery:

1. Clinical examination.
2. Documentation of key data from the pathology report: T (1-4) and N (0-3) stage, ECE status (+/-) and extent of ECE (mm), margin status (+/-).
3. Arm assignment (based on pathology data)
4. Documentation of patient symptoms using NCI-CTCAE version 4.0; please note that AEs considered at least possibly related to surgery need not be recorded.
5. Documentation of ECOG performance status.
6. Completion of QOL questionnaires.
7. Documentation of Comorbidity Index.
8. Laboratory evaluations: CBC, BMP, magnesium, PT/PTT.
9. OPTIONAL: Speech and swallowing assessment including MBS and PSS-HN questionnaire.

5.4 Postoperative Adjuvant Chemotherapy

5.4.1 ARM 1 ONLY - Cisplatin (one dose) + 21 doses of RT

The dose of cisplatin will be given on the same day as one of the initial 5

- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

6.0 PHARMACEUTICAL INFORMATION

6.1 Cisplatin (CDDP, Platinol-AQ®)

6.1.1 Cisplatin Description

Molecular formula: PtCl2H6N2
Molecular weight: 300.1.

6.1.2 Clinical Pharmacology

The mechanism of action of cisplatin has not been clearly elucidated. However the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis, and to a lesser degree, RNA and protein synthesis. It has also been shown that Cisplatin binds to DNA and produces inter-strand cross-links. Also cisplatin is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle. Additional information can be found in the package insert.

6.1.3 Supplier

Cisplatin is commercially available as 1 mg/mL in both 50 mL multiple dose vial and 100 mL multiple dose vial.

6.1.4 Dosage Form and Preparation

The stability of cisplatin in solution is dependent upon the chloride ion concentration present in the diluent. Cisplatin should be diluted into an IV solution containing NaCL at a minimum chloride ion concentration of 0.040 mol/L (0.2% NaCL). Needles, syringes, catheters and IV administrations sets containing aluminum must be avoided during preparation and administration due to cisplatin-aluminum reaction causing precipitation and

that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

9.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

9.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

9.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

9.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.