Adjuvant De-escalation, Extracapsular spread, P16+, Transoral (A.D.E.P.T) Trial for Oropharynx Malignancy

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Adjuvant **D**e-escalation, **E**xtracapsular spread, **P**16+, **T**ransoral **(A.D.E.P.T)** Trial for Oropharynx Malignancy

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Version Date	Revision Summary
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02/27/13	*Amendment #1*
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Adjuvant **D**e-escalation, **E**xtracapsular spread, **P**16+, **T**ransoral **(A.D.E.P.T)** Trial for Oropharynx Malignancy

Principal Investigator Signature Page

Study Chair:	Jason Rich, MD	
	Signature of Investigator	Date
	Printed Name of Investigator	
	By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.	

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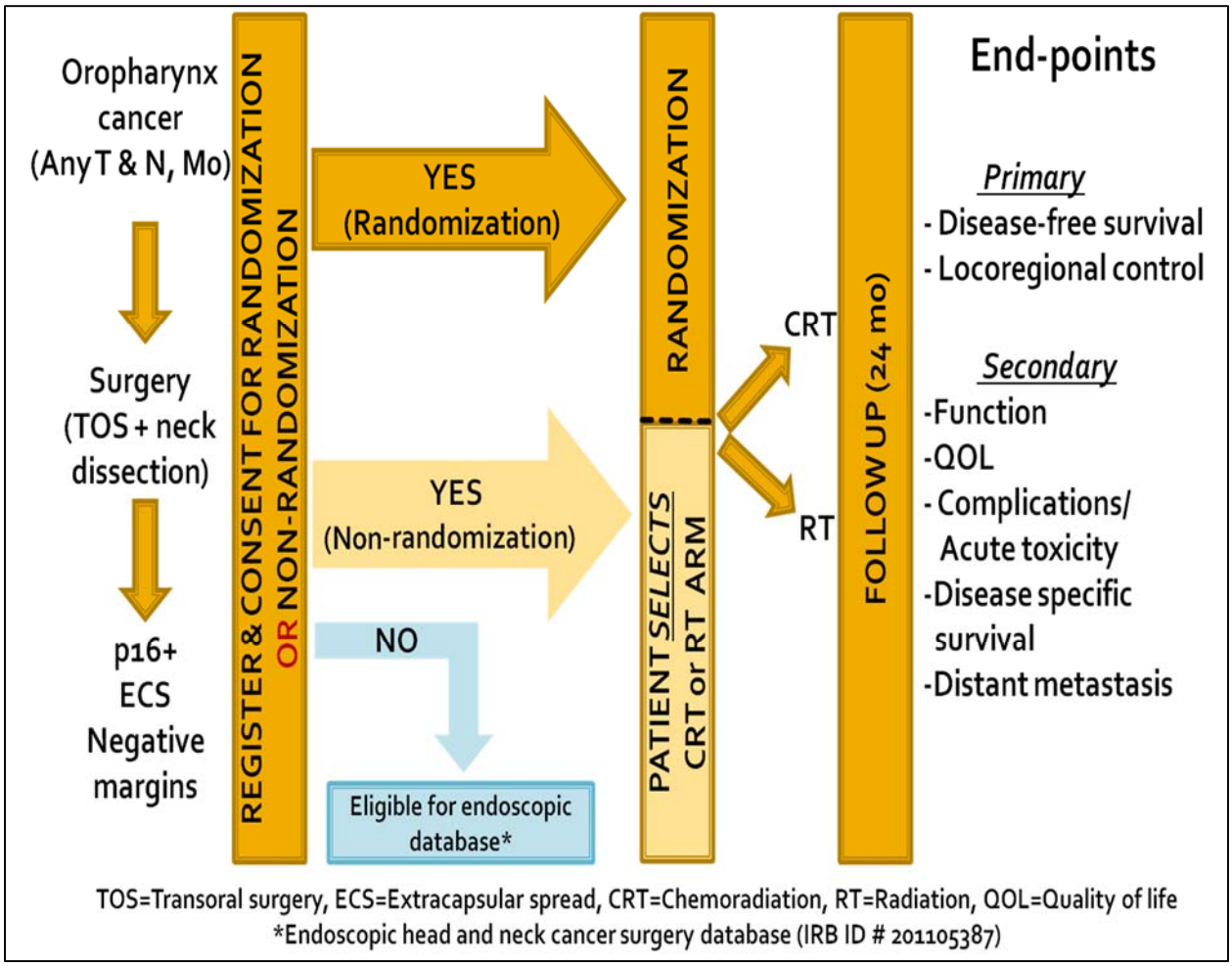
STUDY SCHEMA



1.0 INTRODUCTION AND BACKGROUND

1.1 Oropharynx Squamous Cell Carcinoma: Trends

Current head and neck cancer trends demonstrate emergence of a steadily progressive epidemic of human papillomavirus (HPV)-related oropharynx squamous cell carcinoma (OPSCC). This disease, with primary malignancies in the tonsil and tongue base runs counter to a declining incidence of classic, tobacco-associated cancers. HPV-related OPSCC incidence increased from 1973 to 2004 in the United States, particularly among younger (< 60 years) individuals, men, and whites (Figure 1) (1,2,3). A concomitant improvement in the population-based survival for OPSCC has been noted (3-6), despite almost universal neck node metastasis. The increasing incidence and improved survival are clearly shown to result from the increased proportion of OPSCCs caused by the HPV. Prevalence of HPV in oropharyngeal tumors increased substantially from 16.3% during the 1980s to 72.7% during the 2000s (3). Institutional incidence here at Washington University is approximately 90% (7). In comparison to non-HPV head and neck cancers, HPV-associated oropharyngeal tumors exhibit a distinct molecular biology, characterized by p16 over-expression, plus other favorable clinico-pathological attributes. Together, these translate into markedly improved disease control and survival rates (4-11).

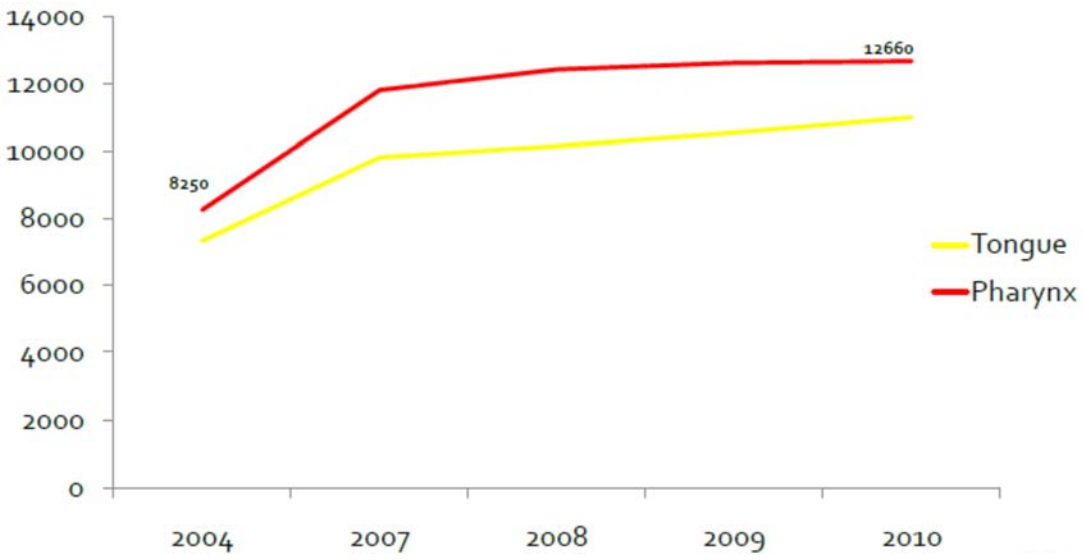


Figure 1. Trends in annual incidence of OPSCC in US. Jemal A, Cancer Statistics (SEER) 2004 – 2010 (2)

1.2 Transoral Approach to Oropharynx Cancers

Independently, but co-incident with this rise in OPSCC, there has been a marked improvement in surgical methods for oropharynx resection, most procedures now using a minimally invasive approach.

Surgical resection with adjuvant radiotherapy was the main modality of management for OPSCC in the past. Classic surgical management of cancer in the oropharynx included open *en bloc* "commando" resections. These entailed external incisions through the face and neck, transection of the musculoskeletal framework, displacement and disruption of cranial nerves and sophisticated reconstruction for wound closure and functional restoration. Such procedures were time- and resource-consuming, had an appreciable complication rate and were often associated with a certain degree of functional and aesthetic morbidity.

Advances in technology have driven a transition in the treatment paradigm of oropharyngeal cancers from the open surgical resection and non-surgical treatment towards minimally invasive transoral (through the mouth) approaches, which in 2012 is represented by transoral laser microsurgery (TLM) and transoral robotic surgery (TORS). First performed by Panje in 1984, TLM for OPSCC was then popularized further in Europe by Iro, Eckel and Steiner et al (12). Use of a robot to aid in transoral tumor resection is the alternative technology, with feasibility first reported in 2006 (13, 14).The end result from the patient's perspective, however, is identical, i.e., resection of all known primary tumor to a negative margin. Hundreds of such transoral procedures have been performed at Washington University (11).

In addition to locoregional control and survival being comparable to open surgery, transoral approaches have minimized morbidity, functional deficits, and cost. TLM allows primary tumor-targeted treatment with optimum disease control for all resectable OPSCC tumors (T1-T4a). It is also allows reduced blood loss, rapid wound healing, shorter hospital stay, and faster rehabilitation. Tracheotomy is avoided except for extensive oropharyngeal resections where occasional swelling occurs, or flap reconstruction required.

Swallowing, oral function and speech is usually maintained by endoscopic procedures because there is less disruption of the neuromuscular structure of the pharynx. Laser wounds also heal with less scarring than conventional surgical wounds: improved quality of life is likely to follow. The surgical approach also facilitates decision-making for adjuvant therapy, allowing many cases to be adjuvant therapy de-escalated, based on precise pathological staging and prognostication.

1.3 p16 as a Surrogate Biomarker in HPV-related OPSCC

The distinct molecular characteristics between HPV-related and non-HPV associated OPSCC suggest different pathways of carcinogenesis. p16 gene functions as a cell-cycle checkpoint regulator and a tumor suppressor gene. Inactivation of p16 has been found to be the earliest change occurring in the molecular progression model of head and neck carcinogenesis due to effects of mutagens like tobacco. In HPV-related HNSCC, the oncoprotein E6 binds and degrades tumor suppressor gene products of p53 whereas the HPV oncoprotein E7 binds and degrades tumor suppressor gene products of pRB. pRB negatively regulates p16 promoter. Therefore, there is over-expression of p16 in case of HPV-mediated carcinogenesis since HPV causes absence of functional pRB (15-18).

As p16 over-expression is very rarely seen in non-HPV related OPSCC, it is considered a surrogate marker for HPV-positive OPSCC. p16 immunohistochemistry (IHC) also represents a less expensive and simpler alternative and can be applied to routinely fixed and processed tissues. It is also the frequently recommended/reported strategy for assessing HPV positivity in comparison to HPV polymerase chain reaction (PCR) (19).

OPSCC tumors characterized by p16 over-expression have been recognized to possess a favorable clinical and molecular biology in several published studies (4-11). p16 staining is now routinely performed for OPSCC primary tumors and/or their neck metastases, diagnosed at Washington University.

1.4 Extracapsular Spread in Head and Neck Squamous Cell Carcinoma: Dilemma #1

Extracapsular spread (ECS) in nodal metastases is traditionally one of the most important negative prognosticators in p53 mutant head and neck cancer, the presence of which is believed to endow a higher degree of aggressiveness and reduced survival outcomes (20-24). However, there is a significant degree of uncertainty regarding criteria that define the phenomenon of ECS and/or its extent. This also obfuscates the determination of differences in prognostic impact, relative to variations in the extent of nodal metastasis. Literature review of ECS and its detected extent in head and neck squamous cell carcinoma (HNSCC) metastases reveals that there is little consistency in the pathological definition of either the presence of ECS or the pathological sub-categories of microscopic vs. macroscopic ECS. Most of the studies that categorize extent of ECS show a trend towards visibly macroscopic spread into soft tissues and/or desmoplastic response, vs. microscopic ECS, as the significant negative prognosticator. Routine reporting/measurement of extracapsular spread varies markedly both in quantity and character, between institutions and even between one institution's pathologists. Nonetheless, this prognosticator, however reported, has been a common trigger for escalated adjuvant therapy in "traditional," p53 mutant head and neck cancer.

1.5 Adjuvant Therapy for HNSCC with ECS: Dilemma #2

Extracapsular spread is considered an indication for chemoradiotherapy (CRT) based on two prospective trials (RTOG 9501 and EORTC 22931) of patients with "high-risk" HNSCC published in 2004 (25, 26). Unfortunately, no subset analyses by tumor primary site or risk factors (ECS vs. positive margins) were reported in either of the trials. Oropharynx was the primary site in only 30% of cases in the EORTC (26), and 42% in the RTOG trial (25). ECS as a "high-risk" criterion was present in only 57% of patients in EORTC (26). What is worse, its prevalence in the RTOG trial (25) could not even be estimated, because patients with ECS and or ≥ 2 positive lymph nodes were clustered together. These studies were not powered to stratify for these variables, nor was HPV status taken into account. Thus, the findings and conclusions from the trials are too general, and obscure the relevance of ECS as a risk factor or adjuvant therapy determinant in an individual patient, especially with HPV-related OPSCC.

To compound the problem, addition of chemotherapy resulted in a 2-fold or more increase in treatment-related severe acute toxicity compared to radiotherapy (RT) alone, from 34% in the RT group to 77% in the CRT group in RTOG (25), and from 21% to 41% in the EORTC trial (26). Neither the RTOG trial nor the EORTC trial found significant reduction in distant metastasis in "high-risk" patients receiving CRT (20%, CRT versus 23%, RT) and (21%, CRT vs. 25%, RT), respectively. Finally, in the ten-year report from RTOG 9501, a subset analysis of the OPSCC patients with ECS showed no significant chemotherapy treatment effect. (27).

1.6 ECS in p16+ OPSCC

Our TLM database research on oncologic outcomes of OPSCC patients treated by primary surgery (in the form of TLM ± neck dissection) and adjuvant therapy, revealed p16 positivity as the strongest (favorable) prognosticator in multivariate analyses, with reduction in risk of death by 90-96% (HR=0.04-0.10) (7,11). Despite their high prevalence there was a lack of prognostic significance for both nodal metastasis, and ECS in those metastases (7, 11, 28, 29). Level of functional preservation in terms of swallowing was high, in general, for the study cohort but progressive, statistically significant reduction in swallowing function was observed as adjuvant treatment intensified (7, 11), in line with the prospective RTOG trials.

In a focused, 152 patient cohort study, all with p16+ oropharyngeal cancer, we further confirmed that ECS was not a predictor of poor prognosis (28). Excellent locoregional control (97%) and survival outcomes (3-year disease-free survival: 90%, disease-specific survival: 93%) were observed for this cohort. Presence of ECS, both as measured from the routine pathology reports and by using a stringent histological grading, failed to show any significant reduction in disease-free survival (DFS) (3-year DFS; ECS (routine report)-positive vs. negative: 89% vs. 94%, p=0.21 (Figure 2); ECS(stringent grading)-positive vs. negative: 92% vs. 97%, p=0.08). Notably, addition of chemotherapy in the adjuvant treatment regimen was not associated with any benefit to survival both for the overall cohort and for patients with ECS. The 3-year DFS was 91.8% for ECS-positive patients who received CRT, and 94.5% in patients who received RT (p=0.74) (Figure 3). The probability of disease control by type of adjuvant treatment was also similar in patients with extracapsular spread who received CRT compared to those receiving RT alone (p=0.96) (Figure 4). These findings were also intuitively reasonable if our first premise (that ECS is not prognostic) was correct, since the commonest indication for chemotherapy was extracapsular spread.

In our ***Cancer*** publication (29), the above findings were confirmed in a case-matched study, where again there was complete overlap of the curves for all ECS patients (measured by stringent histological grading) in the CRT vs. RT alone groups, matched for T stage and surgical margins and with no significant differences in other potentially relevant variables such has age, smoking history and N stage. Subsequent studies from several centers in United States and worldwide (University of Pittsburgh, Memorial Sloan Kettering Cancer Center, Mayo Clinic Cancer Center, University of Prague), have since duplicated our

finding, to also find no adverse risk associated with ECS in the HPV+ OPSCC patient (30-34).

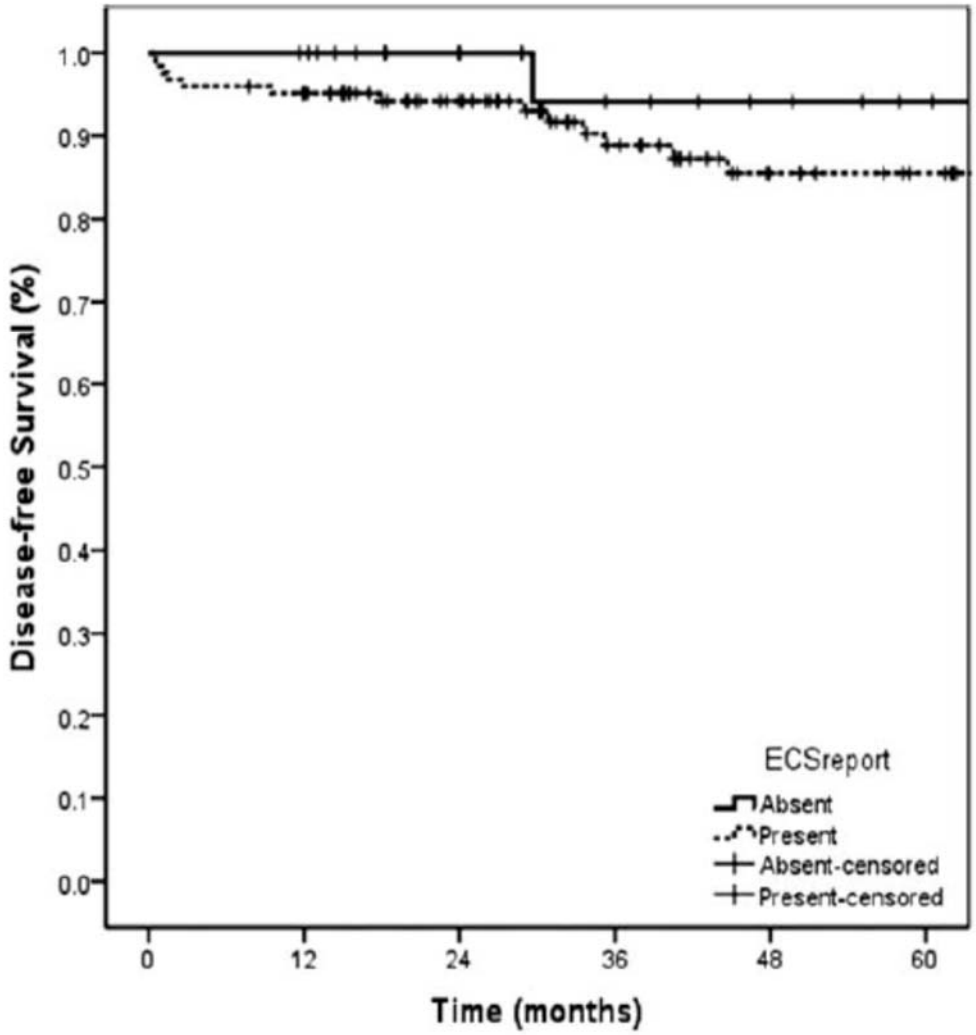


Figure 2. Kaplan-Meier disease-free survival (DFS) estimates are shown for the study cohort stratified according to the presence (N=124) or absence (N =28) of extracapsular spread (ECS) measured from routine reporting (ECSreport) (p= .21).

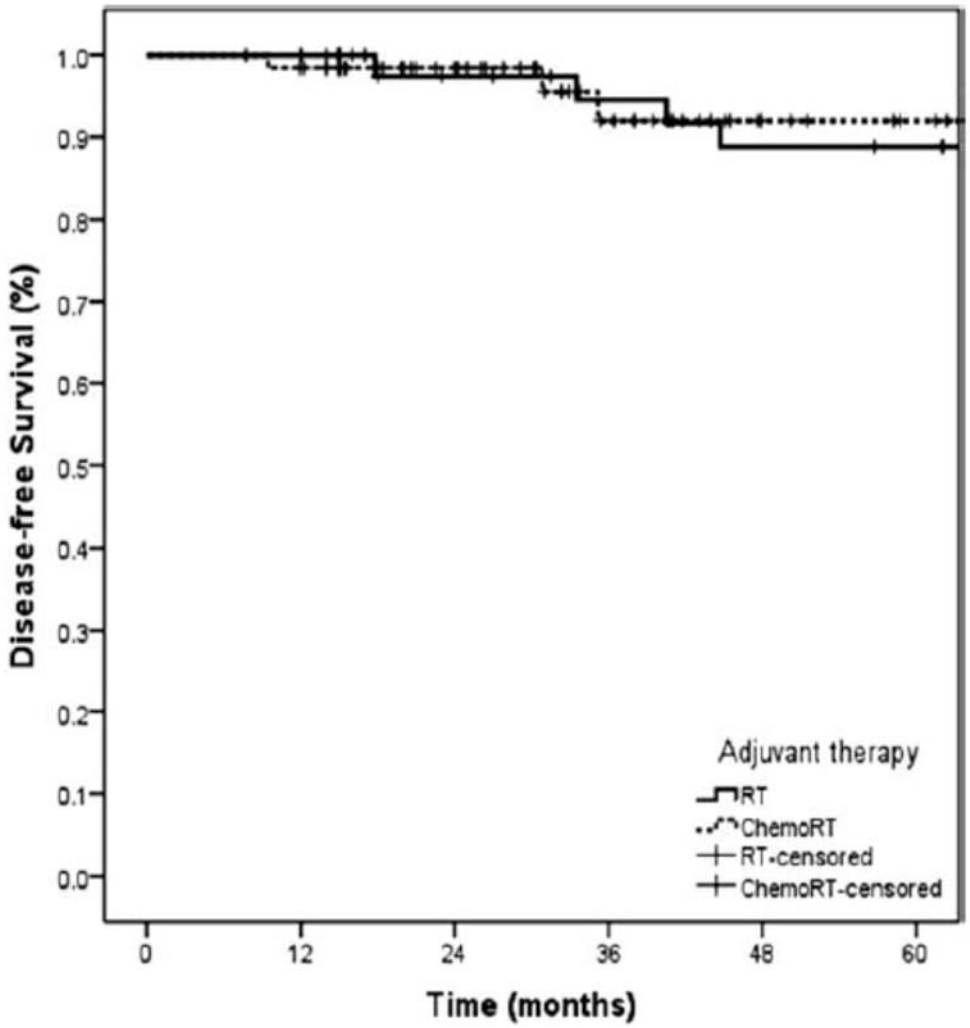


Figure 3. Kaplan-Meier DFS estimates are shown for patients who had positive ECSreport results stratified according to the receipt of adjuvant chemoradiotherapy (ChemoRT) (N=65) versus radiotherapy alone (RT) (N=48) (p= .74).

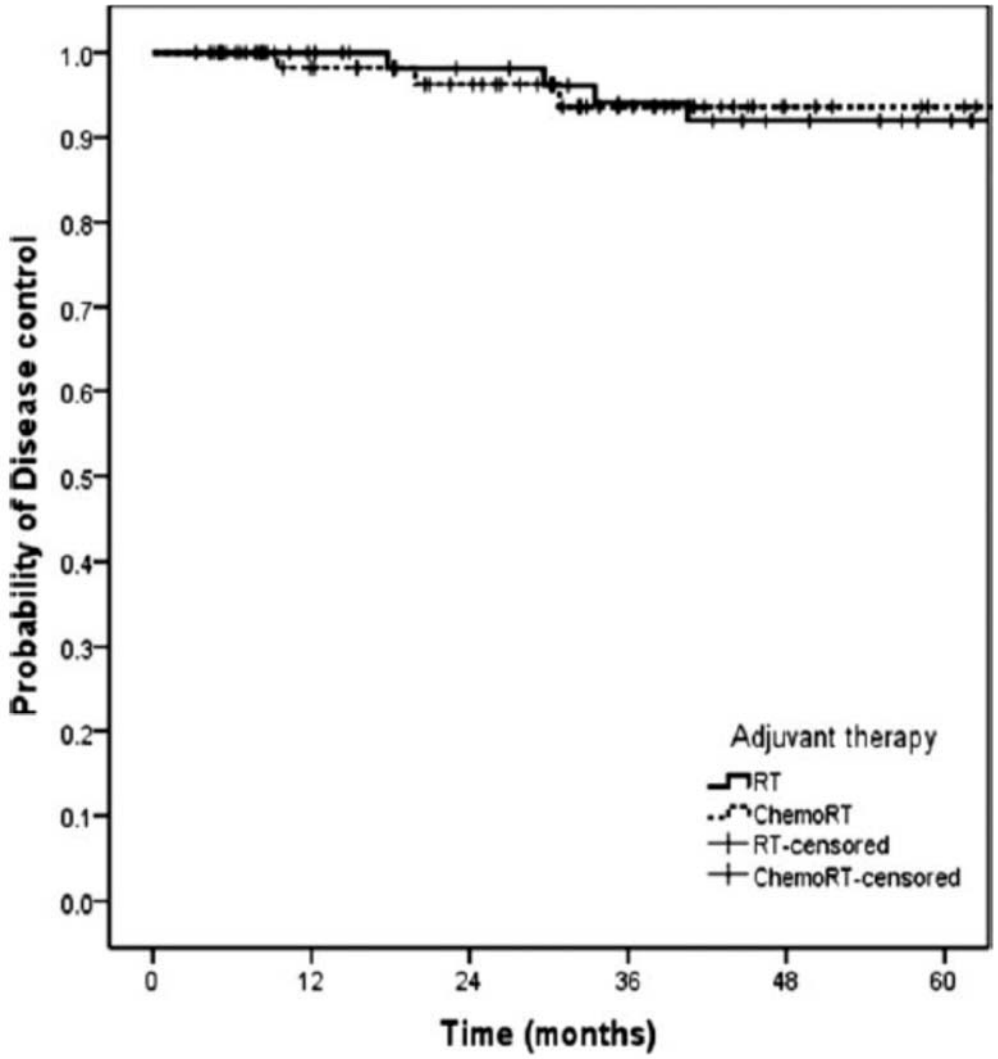


Figure 4. Kaplan Meier estimates for probability of disease control by type of adjuvant treatment in patients with extracapsular spread who received CRT compared to those receiving RT alone (p=0.96)

1.7 Quality of Life and Functional Outcomes

With the improved prognosis and younger age of onset associated with HPV-positive squamous cell carcinoma of the oropharynx, awareness of the impact of acute and long-term toxicity (*viz* swallowing disability) of therapy and its influence on quality of life are increasing (35). Given the markedly increased severe acute toxicity measured in prospective studies (25, 26) when chemotherapy is added to postoperative adjuvant radiotherapy, assessment of symptoms and their impact on patient-reported quality of life is important to this trial. In a long term study comparing toxicities in trials of nonsurgical management of head and neck cancers, chemoradiotherapy regimens showed up to 500% more acute toxicity burden versus standard postoperative radiotherapy (36). Late sequelae, with an increase in swallowing dysfunction in the concurrent chemotherapy versus radiation alone have also been reported (37).

1.8 Study Rationale and Summary Statement

Advanced nodal stage and extracapsular spread are considered to be markers of poor prognosis and survival outcomes in HNSCC, which are triggers for up scaling treatment intensity in adjuvant settings. Being a category 1 recommendation by the National Comprehensive Cancer Network (NCCN), presence of ECS in postoperative OPSCC patients is frequently treated with chemoradiotherapy (38, 39). This recommendation is based on the two prospective trials discussed above (25, 26). Most importantly, however neither of these trials takes into account HPV status. Furthermore, the updated long-term i.e. 5-year results for one of these trials, the RTOG 9501, demonstrated that both locoregional control ($p=0.086$) and DFS rates ($p=0.098$) were not statistically significant and only trends toward improvement with the addition of adjuvant chemotherapy to the postoperative regime were observed (40). This renders these data somewhat obsolete, and of dubious practical contemporary relevance.

Recent literature on surgically treated HPV-positive malignancy of the tonsil and tongue base has identified pathological attributes which exhibit prognostic relevance, but distinct from traditional tobacco-related head and neck cancer. The degree of aggressiveness added to the disease by presence of extracapsular spread is reduced or eliminated in exclusively p16+ surgically treated OPSCC cohorts, matched for other prognostic variables. As a consequence, chemotherapy is not associated with better survival, locoregional control or distant metastatic rate. This finding is especially pertinent with the expanding use of transoral procedures which, by minimally invasive means, eradicate all known primary disease simultaneous with selective neck dissection and preserve swallowing.

In view of this change in prognosticators and the questions it creates regarding the indications for adjuvant chemotherapy, it is now critical to perform prospective research that will inform future management options.

1.9 ADEPT Study Planning, 2-10-2012

Following many months of comprehensive institutional meetings involving all relevant specialties (head and neck surgery, medical and radiation oncology, pathology) plus Siteman Cancer Center/Biostatistics Core staff, a one day Multidisciplinary Multicenter Planning Meeting was hosted at Washington University on 2-10-2012. Fifty five people attended from all relevant specialties from the six noted Academic Medical Centers invited to participate in ADEPT.

At that event, a comprehensive plan for the ADEPT trial was discussed in detail (see attached Agenda) and consensus built on inclusion/exclusion criteria, data collection, treatment protocols and end-points of interest. The protocol herewith submitted is the product of that convocation of experts.

2.0 OBJECTIVES

The broad objective of this study is to demonstrate that de-intensified adjuvant therapy (i.e., radiotherapy alone) following minimally invasive surgical resection of p16+, ECS-positive oropharyngeal cancer is not inferior to chemotherapy-containing adjuvant protocols, using disease free survival and locoregional control as primary outcome measures.

The secondary hypothesis is that toxicity will be lower and function/quality of life better in the de-intensified, radiation alone group.

The specific aims are to compare in a prospective trial, the two postoperative regimens of i) cisplatinum-based chemoradiotherapy to ii) radiotherapy alone, whilst maintaining excellent oncologic outcomes and minimizing toxicity.

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Patient must have histologically confirmed p16 positive squamous cell carcinoma of the oropharynx (OPSCC). (See Section 4.0.)

2. Patient must have undergone transoral resection of their T1-4a oropharynx primary to a negative margin, and a neck dissection(s).

3. Patient's disease must be pathological N-stage positive.

4. Patient's disease must show extracapsular spread (ECS) in their nodal metastasis. (See Section 4.0.)

5. Patients with synchronous primaries are included.

6. Patients with unknown primaries are included if the diagnosis and resection of a primary site in the oropharynx is made from an endoscopic or robotic surgical procedure(s).
7. Patients with recent excisional node biopsies/neck dissections are included if material is evaluable for extracapsular spread.

8. Patient must be ≥ 21 years of age.

9. ECOG performance status ≤ 2 (Karnofsky ≤ 60%; see Appendix A).

10. Patients must have normal organ and marrow function as defined below:

    - leukocytes ≥3,000/mcL
    - absolute neutrophil count ≥1,500/mcL

- platelets	≥100,000/mcL
- total bilirubin	<1.5 X upper normal institutional limit
- AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
- creatinine	within normal institutional limits
OR	
- creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

11. Patient (or legally authorized representative) must be able to understand and willing to sign a written informed consent document.

3.2 Exclusion Criteria

1. Patient must not have pathologically N stage negative disease.

2. Patient must not have outside nodal tissue from previous neck biopsy/neck dissections in which ECS cannot be confirmed or denied.

3. Patient must not have a true unknown primary in which permanent section results are negative for malignancy in completely excised ipsilateral oropharyngeal tissue (palatine and lingual tonsil).

4. Patient must not have known distant metastatic disease at presentation.

5. Patient must not have gross residual and/or microscopic disease present after surgery including re-resection(s), per the operative and pathology report.

6. Patient must not have transoral robotic surgery (TORS) for a T3 or T4 primary tumor.

7. Patient must not have a history of prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years; noninvasive cancers (for example, carcinoma in situ of the oral cavity, larynx, breast or cervix are all permissible) are permitted even if diagnosed and treated < 3 years ago.

8. Patient must not have had previous systemic chemotherapy for the study cancer. (**Note:** prior chemotherapy for a different cancer is allowable).

9. Patient must not be receiving any other investigational agents.

10. Patient must not have had any prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields

11. Patient must not have any life-threatening comorbid illnesses e.g. stroke with major sequelae or myocardial infarction/ unstable angina within the preceding 3 months

or psychiatric illness/social situations that would limit compliance with study requirements.

12. Patient must not be pregnant or breastfeeding. If a woman of childbearing potential, patient must agree to use medically acceptable forms of contraception.

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

After the patients have signed the consent form, they become eligible for entry into the study when they meet each of the criteria listed above. In particular, patients with p16 positive oropharyngeal tumors meet eligibility only after their surgery and pathology specimen analysis, in which presence of ECS in nodal metastasis must be centrally verified. The consent process allows for patients to participate in either the randomized or non-randomized pathways, according to their choice. Following this, registration will be performed. Patients must not start any protocol-specific intervention, the first of which is central pathological review of their neck dissection specimen, prior to consent. Patients who do not consent to participate either on the randomized or on the nonrandomized pathways will be excluded from ADEPT and advised to receive adjuvant therapy regimens of their and their physicians' choice, but will be eligible for close follow-up on the minimally invasive, endoscopic head and neck cancer surgery database (HRPO# 201105387).

The following steps must be taken:

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

Once the patient has been entered in the Siteman Cancer Center database, the WUSM coordinator will forward verification of enrollment and the UPN via e-mail.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by e-mailing/faxing (email preferable) the information listed below to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and e-mail address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials

5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Dispatch date of sample shipment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by e-mail or fax within one business day. Verification of eligibility and pre-registration should be kept in the patient chart.

Patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

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 case report forms (CRFs).

4.4 Registration for Study Therapy

4.4.1 Patients Who Consent for Participation on the Randomized Pathway

Patients with p16+ OPSCC and extracapsular spread will be registered for ADEPT after they consent for participation and randomization. If found to meet all other eligibility criteria, they will be randomized to either of the two study treatment arms. Patients will undergo radiation oncology and medical oncology consults prior to randomization. The same UPN will be used for randomization (for details of randomization, see Section 5.3).

4.4.2 Patients Who Consent for Participation on the Non-Randomized Pathway

Patients with p16+ OPSCC and extracapsular spread will also be registered for ADEPT if they give consent to participate, but refuse randomization *and select* the ADEPT treatment arm of their choice, adjuvant radiation or chemoradiation. The treatment regimens will be exactly the same as specified in the protocol for randomized patients. These patients will comprise the observational cohort for ADEPT.

Each of these patients will be identified with a unique patient number (UPN) ending in the letters NR (non-randomized). All data will be recorded with this

identification number on the appropriate CRFs. The reason(s) for refusal of randomization will be documented and recorded in the CRF.

4.4.3 Patients Who Refuse to Undergo the Assigned Treatment Arm after Randomization

In addition to patients who consent for ADEPT's non-randomized pathway, there may be patients who initially choose to be randomized but change their decision after randomization. Such patients who refuse to be treated in the arm to which they are randomized but who still want to receive treatment as specified in the study protocol for the other arm will be allowed to participate in the study. These patients will be considered as the study's prospective observational cohort.

4.5 Companion Protocol for All p16+ Patients

A separate companion protocol is anticipated for use in those institutions where identification of all presenting p16+ OPSCC cases can be accomplished. The lead investigators of this study will support this protocol, which will track treatment pathways for those patients who are not eligible for, or who do not randomize on the ADEPT protocol.

This will be implemented to determine an answer to a separate question, i.e. what fraction of patients with p16+ OPSCC proceed forward with the transoral surgery/neck dissection treatment paradigm, and what proportion , for whatever reason, do not.

4.6 Study Track Log

All p16+ OPSCC patients detected to have ECS after the surgical resection and who meet all other eligibility criteria will be offered the opportunity to participate in the trial. If the patient refuses to consent and participate, the reason and refusal will be recorded in a separate log. Reason for non-participation will also be recorded if there is failure to randomization and/ or treatment initiation after the patient consents. A Study Track Log will be created in the form of an Excel spreadsheet without any identifying information. The log will have the columns as shown in the table below. The first column labeled as "Serial Number" will be entered as sequentially increasing numbers such as Non-participant 1, Non-participant 2, etc…Other participating centers will be asked and encouraged to maintain a similar Study Track Log and the template for the spreadsheet will be sent to them for uniformity.

Serial Number	Primary surgeon's initials	Time of trial proposal (Month-Year e.g. Jan-13)	Reason for refusal to participate
Non-participant 1			
Non-participant 2			

5.0 STUDY PROCEDURES

5.1 Surgery Guidelines

5.1.1 Surgery Guidelines for Primary

Transoral resection of the primary will be performed to a negative margin with resectional tools of the surgeon's choice, although robotic techniques will not be used for larger, T3 or T4 primaries. The surgeon will attempt to achieve a clear margin around the primary (which will vary in dimension, and does not need to be recorded). A negative surgical margin in the oropharynx will be verified by intraoperative frozen section taken from the margins of the patient's wound or the specimen.

Reconstruction is at the surgeon's discretion but may include primary closure, local, regional pedicled or free flap repair.

5.1.2 Surgery Guidelines for Unknown Primary

In cases going forward to surgery with an unknown primary, preliminary microscopic or telescopic endoscopy under anesthesia frequently reveals areas of suspicion. The laser can be used to make precise exploratory incisions into deeper layers of lingual or palatine tonsillar tissue to expose an occult submucosal carcinoma. Once exposed, these small lesions may be confirmed by frozen section and excised to a negative margin, completeness confirmed by frozen-section margin re-evaluation, taken from the defect. If the primary is not identified by frozen section, the ipsilateral palatine and lingual tonsil(s) and/or remnants are excised and submitted for pathological section.

If the primary is discovered on permanent section, the case may remain in the study, as long as a negative margin is achieved. Patient with unknown primaries where the submitted tissue is negative on the permanent section pathological report must be considered ineligible for randomization and excluded from the study.

5.1.3 Surgery Guidelines for the Neck

At the same surgical session as the TLM, patients with clinically positive necks or with a high risk of occult metastasis will undergo neck dissection. A selective neck dissection including levels II through IV lymph nodes is the standard minimum procedure. Neck dissections may be extended to other levels e.g. IB or V depending upon the clinical and/ or image-based evidence of nodal disease. The selective neck dissection may be converted to a modified or radical, if necessary. Especially with tumors of the tongue base and/ or other oropharyngeal site approaching or extending across the midline, patients may undergo a contralateral elective neck dissection, either simultaneous or staged. Retropharyngeal lymph nodes, if detected

pre- or intra-operatively (usually for tonsil or oropharyngeal wall primaries), may be removed transorally through the posterior aspect of the pharyngeal defect.

5.2 Pathological Evaluation of Surgical Specimen

5.2.1 p16 Immunohistochemistry

Immunohistochemistry for p16 will be performed on the oropharyngeal squamous cell carcinoma surgical specimens on representative 4mm sections cut from formalin-fixed, paraffin-embedded tissue blocks using a monoclonal antibody to p16 (MTM Laboratories; monoclonal) on autostainers according to standard protocols, with appropriate positive controls. Positive p16 expression will be defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells.

5.2.2 Neck Dissection Specimen

The neck dissection will be grossed in according to the standard institutional procedure. All lymph nodes will be inspected grossly for evidence of ECS and nodal sectioning designed accordingly. Participating center pathologists will perform the initial histopathological screening for ECS, and if positive, the case will be registered and informed consent presented to the patient at the participating center. If consent is obtained, all sections showing metastatic carcinoma in neck dissection material will be submitted for central review and presence of ECS confirmed and graded. Randomization will be based on the results of this central review/confirmation, not on the results of institutional review.

Extracapsular spread, the primary determinant of eligibility, will be defined in a range from absence of the nodal capsule up to soft tissue metastasis which obliterates the entire lymph node. It should be noted that some of the study pathologists do not consider a thickened, fibrous capsule or pseudocapsule with no intervening normal lymphoid tissue to represent “true” ECS, so it is anticipated that those institutions will submit fewer patients for central review. However, from institutions where this finding is considered to be ECS, those patients will be allowed in the trial. To account for this differential in classification, all ECS data will be stratified for extent of ECS based on central review and strict definitions, which will enable an ultimate discriminating analysis of all grades of ECS represented in the trial. It should be noted that our preliminary published data demonstrate that neither the presence of, nor varying degrees of ECS make any difference to oncologic outcome in the presence of adjuvant therapy, which will be delivered to all patients in this trial.

All hematoxylin and eosin slides that show metastatic carcinoma in neck dissection material shall be sent for central review (along with the corresponding outside pathology report) shall be sent to the lab of Dr. James Lewis, Jr. at the address below:

Vanderbilt University Hospital
1211 Medical Center Drive
Room 3020D – Surgical Pathology
Nashville, TN 37232-7415
(615) 322-2302
james.lewis@vanderbilt.edu

Prior to shipment, confirm with the Washington University research coordinator that specimens should be shipped to Dr. Lewis. The back-up central reviewer will be Dr. Rebecca Chernock at Washington University. The WU research coordinator will provide shipping instructions to Dr. Chernock if required.

The outside institution slides will be retained at the central site until all data is accumulated.

5.2.3 Margin Reporting

The margins of the primary resection will be determined and recorded as positive, negative or "close" (<5mm) in the final resection or re-resection specimen, according to institutional practices. Patients with final positive margins are ineligible.

5.2.4 Tumor Banking

Tumor banking is allowed for patients in this protocol and data reflecting tissue entered into a participating institution's tumor bank will be collected as part of the database. Every patient who consents to participate in this protocol will be offered the opportunity to participate in the site specific tumor bank protocol (at Washington University, the tumor bank protocol for head and neck cancer [Tissue Acquisition Protocol, TAP] is IRB protocol #201102323). Linked translational studies in future, covered under separate protocols will thus be facilitated.

5.3 Treatment Randomization

Patients will be randomized 1:1 to concurrent chemoradiation or radiotherapy using a formal probability model implemented by SAS proc plan. Assignments will be balanced within blocks of random size.

Furthermore, the treatment arms will be stratified by T-stage (T1-T2 vs. T3-T4) and smoking history (≤ 10 pack years vs.>10 pack years).

After eligibility and registration is completed, each patient will be added to the randomization table, created by the study statistician at Washington University, incorporating all patients from the primary and secondary sites. This process will assign the treatment arm, centralize and balance assignment of patients to the two treatment arms, and allow for patient-initiated withdrawals following randomization. The secondary sites will be able to access their patient enrollee's randomization result via a website which will create access to information for a particular patient via their UPN. All this information will be communicated to each secondary site via the secondary site packet.

5.4 Radiotherapy Treatment Planning and Administration

All patients regardless of arm assignment will receive radiotherapy as detailed below.

5.4.1 Dose Specifications

The prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size (total of 30 fractions). The daily dose of 2 Gy will be prescribed such that 95% of the Planning Target Volume 60 (PTV60) volume receives at least 60 Gy. PTV52 also may be defined. The spinal cord dose may not exceed 48 Gy to any volume larger than 0.03 cc.

5.4.2 Technical Factors

1. *Linear accelerator:* Megavoltage energy photon beam irradiation is required.
2. *CT simulator*
3. *Image Guidance for IGRT:* Daily image guidance of IMRT may be used.
4. *Proton beam*: Proton beam is not allowed due to insufficient published data on its use in an adjuvant setting for head and neck cancer patients. If data become available during the study supporting proton beam treatment for head and neck cancer patients, a protocol amendment to allow this technology will be considered.

5.4.3 Localization, Simulation, and Immobilization

Patients must have an immobilization device (e.g., Aquaplast mask) made prior to treatment planning CT scan.

The treatment planning CT scan should be performed with IV contrast if possible so that the major vessels of the neck are easily visualized. The treatment planning CT scan must be performed with the immobilization device and in the treatment position.

5.4.4 Target and Normal Tissue Volume Definitions

Clinical Target Volume 60(CTV60): This volume will receive 2 Gy per day. CTV60 will include the primary tumor bed (for T3 or T4 disease only; T1 and T2 patients will receive neck only irradiation) (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, and pathologic findings). This volume may approach the skin but should not approach < 3mm. It is recognized that after surgery, there can be considerable distortion of normal anatomy. If possible, map preoperative Gross Target Volumes (GTV) onto the postoperative radiation therapy planning CT scan to help guide target delineation.

CTV60 will include the ipsilateral pathologically positive neck node basins with ECS. If both sides of the neck are proven pathologically positive, CTV60 will include both sides). This generally means encompassing nodal levels 2a, 3, and 4 for all cases. Nodal levels 1, 2b, 5a, and 5b are included in CTV60 in selected circumstances. If neck dissection clearly demarcates nodal level, the nodal level(s) outside of the involved level may receive a subclinical dose.

CTV52: This will include all other regions felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. For example, this would apply to the contralateral hemineck being irradiated electively, or ipsilateral level(s) of the neck outside of the level with pathologically involved lymph nodes. This volume should not approach the skin < 3 mm. This volume will receive 1.7 Gy per day.

PTV: In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered but is generally not recommended. It is also allowable to define two PTVs for a given CTV:

1) PTV Planning, which extends beyond the skin surface and is used for planning treatment segments
2) PTV Evaluation, which does not reach the skin surface within 2 mm and is used for evaluation of the dose volume histogram to determine if treatment goals have been met.

The minimum CTV-to- PTV expansion with daily IGRT is 3-5 mm.

5.4.5 Definition of Normal Tissues/Organs at Risk (OARs)

1. Spinal Cord: The cord begins at the cranial-cervical junction (i.e., the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.
2. Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRVbrainstem = brainstem + 3 mm in each dimension.
3. Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The oral cavity will be defined as a composite structure consisting of the anterior 1⁄2 to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and palate.
4. Parotid Glands: Parotid glands will be defined based on the treatment planning CT scan. Parotid gland volume will not include any portion of any of the CTVs, although they can overlap the PTVs.
5. Glottic/Supraglottic Larynx (GSL): This will be defined as a "triangular prism shaped" volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.
6. Mandible: This includes the entire bony structure of the mandible from TMJ through the symphysis.
7. Unspecified Tissue outside the Targets: This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

5.4.6 Treatment Planning and Delivery

IMRT dose constraints to normal structures:

1. Spinal Cord: The PRVcord should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 50 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.

2. Brainstem: The PRVbrainstem should not exceed 52 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than the other critical structures listed below.
3. Lips: Reduce the dose as much as possible. The mean dose should be < 20 Gy. For non- oral cavity cancers, the maximum dose will be < 30 Gy. For non-oral cavity cancers, the mean dose should be < 30 Gy. For oral cavity cancers, the mean dose should be < 50 Gy. Efforts should be made to avoid hot spots (> 60 Gy) within the oral cavity.
4. Parotid Glands: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 20 Gy.
5. Glottic and Supraglottic larynx (GSL): Reduce the dose as much as possible. In patients with resected oral or oropharyngeal carcinoma, it is recommended that the dose to the larynx should be kept < 45 Gy whenever feasible.
6. Mandible: Reduce the dose as much as possible. It is recognized that particularly for some oropharynx tumors especially those extending forwards beyond the anterior tonsil pillar, laterally to the medial pterygoid muscle or forwards into the deep floor of mouth, significant portions of the mandible will overlap the CTVs and/or PTVs; however, hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 60Gy, recognizing that this is the maximum dose and only a small volume of the mandible in some patients will get 60 Gy

5.5 Chemotherapy Administration

For patients randomized to receive chemoradiotherapy, cisplatin at 40 mg/m^2 will be given intravenously (IV) over 60 minutes on Days 1, 8, 15, 22, 29, and 36 of radiation therapy (6 doses for a total of 240 mg/m^2). Cisplatin can be given prior to or after the patient's radiation on each day of chemotherapy delivery at the treating physician's discretion. Cisplatin administration outside of these specified time points during radiation is only allowed in the event of holidays or scheduling conflicts that do not permit drug and radiation delivery on the specific date. Subsequent chemotherapy doses should follow the protocol specified days of treatment. Cisplatin is administered concurrent with radiation therapy. In the event that radiation therapy is held, no cisplatin will be administered.

Note: Carboplatin and other agents (cetuximab or taxanes) cannot be substituted for cisplatin.

Laboratory studies required <7 days of the start of each cycle: complete blood count and differential (to calculate absolute neutrophil count) and chemistry (to include creatinine).

Dose reduction will be considered for patients developing severe toxic adverse effects (see Section 5.5.3).

Criteria to receive the first dose of cisplatin include:

- creatinine clearance $\geq$ 60 mL/min (by Cockcroft-Gault) or serum creatinine within normal limits
- ECOG performance status $\leq$ 2
- no active serious infections
- absolute neutrophil $\geq$ 1500/mcL
- platelets $\geq$ 100,000/mcL

Patients who do not meet these criteria may not receive cisplatin.

5.5.1 Premedication Administration

Premedication with palonosetron (0.25 mg IVPB) and dexamethasone (20 mg IVPB) is recommended prior to each dose of cisplatin.

Hydration consisting of 1L IVF NS + 10 meq KCL/L + 8 meq $MgSO_4$/L over 60 minutes before and after cisplatin is recommended. Additionally, 1L IVF NS over 60 minutes on the two days following cisplatin is recommended.

5.5.2 Cisplatin Administration

Cisplatin shall be given at a dose of 40 mg/m^2 IV over 60 minutes.

5.5.3 Cisplatin Dose Modifications

Neutropenia: If on the day of scheduled weekly cisplatin the absolute neutrophil count (ANC) is < 1000/mm^3, then the cisplatin will not be given that week. The next dose cisplatin will be given at full dose only if ANC has recovered to $\geq$ 1000/mm3.

If ANC remains < 1000/mm^3 for more than 7 days, all subsequent cisplatin doses will be reduced to 30 mg/m^2, and the next weekly dose only given when the ANC is > 1000/mm^3. In the event of neutropenic fever, reduce all subsequent doses of cisplatin to 30 mg/m^2 and administer only when the ANC is > 1000/mm^3.

If, on the day of scheduled treatment, the patient again experiences an ANC < 1000/mm^3 despite the first cisplatin dose reduction, the cisplatin dose for that week will again not be given.

If recovery has not occurred by the following week, or if neutropenic fever develops, there will be a second dose reduction to 20 mg/m^2 for all remaining cisplatin doses, which can be given only after recovery of the ANC to >1000/mm^3.

Any subsequent ANC < 1000/mm^3 on the day of scheduled treatment or any recurrent neutropenic fever after two dose reductions will mandate discontinuation of all remaining doses of cisplatin chemotherapy.

If hematologic recovery requires more than 3 weeks, irrespective of cisplatin dose, all subsequent cisplatin will be discontinued.

Thrombocytopenia: If on the day of cisplatin chemotherapy the platelet count is < 75,000, the dose will be held for the week. Cisplatin will be given full dose the following week if the platelets recover to ≥ 75,000/mm^3.

If the platelets remain < 75,000/mm^3 for more than 7 days, then all subsequent cisplatin doses will be reduced to 30 mg/m^2, and the next weekly dose only given when the platelet count ≥ 75,000/mm^3.

If the platelet count is again < 75,000/mm^3 on the day of scheduled treatment despite the first dose reduction, that dose of cisplatin will be held.

If recovery has not occurred by the following week, there will be a second dose reduction to 20 mg/m^2 for all remaining cisplatin doses, which can be given only after recovery of a platelet count to ≥ 75,000/mm^3.

Any subsequent platelet count < 75,000/mm^3 on the day of scheduled treatment, after two dose reductions will mandate discontinuation of all remaining cisplatin doses.

If hematologic recovery requires more than 3 weeks, irrespective of cisplatin dose, all subsequent cisplatin will be discontinued.

Neurotoxicity: If grade 2 neurotoxicity develops, hold cisplatin until toxicity improves to ≤ grade 1, then reduce all subsequent doses of cisplatin to 30mg/m^2. If the patient experiences grade 3 or greater neurotoxicity or if grade 2 neurotoxicity recurs, all remaining doses of cisplatin will be discontinued.

Renal: Cisplatin will only be administered if serum creatinine is < than 2 mg/dl. If a patient develops a rise in serum creatinine ≥ 2 mg/dL on the day of treatment, cisplatin will be discontinued for that week and held until recovery to < 2 mg/dL. All subsequent cisplatin doses will then be reduced to 30 mg/m^2. If, despite this first dose reduction, the serum creatinine is again ≥ 2 mg/dl on the day of treatment, that week's cisplatin dose will not be given, treatment will be held until renal recovery, and all subsequent cisplatin doses reduced to 20 mg/m^2. If the creatinine is again ≥ 2 mg/dl on the day of treatment despite two dose reductions, or if the serum creatinine does not improve to < 2 mg/dL in 14 days, all remaining cisplatin doses will be discontinued.

Nausea and Vomiting: Maximum supportive therapy will be given, and cisplatin will be continued at full dose for ≤ grade 2 nausea and vomiting. For grade 3 nausea and vomiting refractory to supportive therapy, cisplatin will be held until recovery to < grade 2. No dose reductions will be made.

Mucositis: Significant mucositis from both the radiation and the cisplatin is expected. However, grade 4 mucositis will prompt decision to not administer cisplatin on that day.

Ototoxicity: For clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living but that resolves prior to the next scheduled dose of cisplatin, reduce cisplatin to 30 mg/m^2. If intolerable tinnitus persists on the day of treatment or if there is new hearing loss requiring a hearing aid, discontinue cisplatin.

All other grade 3-4 non-hematological, fatigue, and alopecia adverse events: Discontinue cisplatin until toxicities have recovered to grade 1.

5.6 General Concomitant Medication and Supportive Care Guidelines

Adequate hydration is strongly encouraged for patients receiving cisplatin; at least 1 liter of normal saline is recommended prior to the administration of the cisplatin dose and 1 liter of normal saline is recommended after the administration of cisplatin. Additional IV fluids (1-2 liters of normal saline per day) for two consecutive days after each dose of cisplatin are recommended.

Prophylactic antiemetics prior to cisplatin administration are also strongly encouraged. At a minimum, a combination of a 5-HT3 antagonist, neurokinin inhibitor and corticosteroids is recommended.

Use of Growth Factors: Use of myeloid growth factors such as G-CSF is permitted if clinically indicated. Use of erythropoietin is not permitted.

5.7 Women of Childbearing Potential

Women of childbearing potential (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 urine pregnancy test within 7 days prior to surgery.

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 6 months following the last dose of either radiotherapy or cisplatin.

If a patient is suspected to be pregnant, radiotherapy (and cisplatin, if applicable) 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 6 months after the last dose of study treatment, the investigator must be notified in order to facilitate outcome follow-up.

5.8 Quality of Life and Functional Outcome Evaluation

5.8.1 Patient-reported Assessments to Be Performed

1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) The EORTC Quality of Life Group has developed a strategy for measuring QOL in clinical trials which consists of a questionnaire with 30 questions (41).
2. MD Anderson Dysphagia Inventory (MDADI) The MDADI is a 20 item questionnaire designed to evaluate the impact of dysphagia on quality of life in head and neck cancer patients and covers physical, functional, emotional and global domains. The Cronbach α coefficient was 0.96 for the questionnaire; the test-retest correlations on subscales ranged from 0.58 to 0.93 (42).
3. Speech Handicap Index The Speech Handicap Index is a 30 item speech-specific questionnaire, validated in head and neck cancer patients and covering speech and psychosocial domains. Internal consistency reliability using Cronbach's α for the total index and subscales were 0.95-0.98. Test-retest reliability correlation coefficients were 0.78-0.92 in the different domains (43).
4. Scale of Subjective Total Taste Acuity (SSTA) The SSTA is a 1-item scale evaluating change in taste perception and its impact on daily life (44).
5. Hearing Handicap Inventory – Adult (HHIA-S) The HHIA-S is an 11 item screener which has been validated against pure tone audiometry, with test-retest correlation coefficient of 0.84 (45).
6. Cognitive Failures Questionnaire Cancer therapy is associated with patient-reported changes in cognition, particularly multi-tasking, and has been dubbed "chemobrain." The CFQ is a 25 item questionnaire assessing self-reported failures in perception, memory, and motor function (46).
7. Neck Dissection Impairment Index (NDII) The NDII is a 10 item questionnaire designed to assess quality of life with respect to shoulder impairment. Domains include physical, functional, and social. The questionnaire is reliable (test-retest correlation 0.91 and Cronbach α coefficient 0.95 (47).
8. University of Michigan Xerostomia Index

5.8.2 Time Points at Which Assessments Will Be Performed

The battery of questionnaires will be completed at the following time points:

- prior to initiation of adjuvant therapy
- 1 month 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

Following is a calendar for administration of QOL and function questionnaires: Goal time points are specified; actual time points may vary due to patient compliance with f/u schedule, logistics, transportation issues, cost of gasoline, treatment for co-morbid illness, etc.

	Baseline (prior to initiation of adjuvant Rx)	1month after completion of adjuvant Rx	6 months after completion of adjuvant Rx	12 months after completion of adjuvant Rx	24 months after completion of adjuvant Rx
EORTC Quality of Life Questionnaire-C30	X	X	X	X	X
MD Anderson Dysphagia Inventory	X	X	X	X	X
Speech Handicap Index	X			X	
Subjective Total Taste Acuity	X	X	X	X	
Hearing Handicap Inventory - Adult	X	X		X	
Cognitive Failures Questionnaire	X	X		X	X
Neck Dissection Impairment Index	X			X	X
University of Michigan Xerostomia Index	X	X	X	X	X

5.8.3 Post-Operative Therapy Patient Experience Questionnaire

Patients will be encouraged to answer four open-ended questions at 6 months (+4 - 8 weeks) from completion of the adjuvant therapy. This is not a validated questionnaire but has been created due to the significance of patient-reported outcomes in the study design of ADEPT. This questionnaire will enable patients to report from their perspective the information which the validated QOL and function questionnaires (see section 5.8.2) do not completely capture. In addition to checking a response, they will be encouraged to add any comments that they want to make in addition to the questions asked.

5.8.4 Objective Measures of Functional Outcomes

Modified barium swallow studies are allowed to be performed by speech pathology as per standard clinical practice within 1 year of completion of therapy, but these are optional.

5.9 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.

- Death
- Documented and confirmed disease recurrence/progression during adjuvant therapy
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of radiation or chemotherapy
- 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.

5.10 Duration of Follow-up

Patients will be followed for a minimum of 2 years, but will also be followed beyond this if available, and reported on at 5 years, to document rare late recurrences or second primaries. Patients removed from study for unacceptable adverse events will be followed clinically until resolution or stabilization of the adverse event.

As of Amendment 8 – 10/22/2019, patients will no longer be followed beyond 2 years.

Follow up examination will include:

- Appointments will be scheduled at 1 and 3 months post-completion of adjuvant therapy, then every 3-4 months for year 1 and, every 4-6 months for year 2. After year 2, we will collect survival data through internal sources.
- General H&P, full head and neck examination, laryngo-pharyngoscopy (mirror and/or fiberoptic and/or direct procedure), imaging and laboratory evaluations as indicated by clinical findings.
- Whole body PET at 6 months (± 6 weeks) after completion of adjuvant therapy, contingent on patient compliance with follow-up schedule. PET is recommended but head and neck CT/MRI and chest imaging can also be performed if whole body PET cannot be performed due to logistic reasons such as insurance, compliance, etc.

- Neck and Chest imaging at 12 months (± 6 weeks) after completion of treatment and then semi-annually (± 6 weeks) for year 2, contingent on patient compliance with follow-up schedule. Chest-CT or CT/PET will be strongly preferred for the first 2 years, although a chest X-ray will be acceptable depending on patient compliance and insurance.

5.10.1 Determination of recurrent disease

Any possible signs of disease recurrence will be carefully evaluated. All lesions suspected for recurrent disease at the primary site, the neck or distant sites will undergo histological evaluation with biopsy or cytology. Histological confirmation of recurrence does not require central review.

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 Formulation

Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

6.1.3 Mechanism of Action

The dominant mode of action of cisplatin appears to be the inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents. Additional information can be found in the package insert.

6.1.4 Supplier

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

6.1.5 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 loss of potency. Mannitol 12.5 to 25 gm may be added per institutional guidelines.

6.1.6 Storage and Stability

The dry, unopened vials should be stored at room temperature (15° -25° C). The unopened container should be protected from light and stored in the carton until contents are used. The vials and injection should not be refrigerated. Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

6.1.7 Administration

Patients will receive cisplatin via IV infusion over 60 minutes. Adequate hydration must be maintained during and after administration as described in the treatment section. All patients should be premedicated with antiemetics.

7.0 REGULATORY AND REPORTING REQUIREMENTS

7.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (v4.03: June 14, 2010) will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 (v4.03: June 14, 2010) can be downloaded from the website below.
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

7.2 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 (in this guidance document, 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.

7.3 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies 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.

7.4 Serious Noncompliance

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

7.5 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.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. HRPO approval is not required for protocol exceptions occurring at secondary sites.

7.6 Reporting to the Human Research Protection Office (HRPO) and the Quality Assurance and Safety Monitoring Committee (QASMC) 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.

7.7 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 7.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via e-mail if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's 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 of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines.

7.8 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites (as described in Section 7.6) within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

7.9 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment.

Deaths	
Any reportable death while on study or within 30 days of study	Immediately, within 24 hours, to PI and the IRB
Any reportable death while off study	Immediately, within 24 hours, to PI and the IRB
Adverse Events/Unanticipated Problems	
Any reportable adverse events as described in Sections 7.1 and 7.2 (other than death)	Immediately, within 24 hours to PI and within 10 working days to the IRB
All adverse events regardless of grade and attribution should be submitted cumulatively	Include in DSM report
Noncompliance and Serious Noncompliance	
All noncompliance and serious noncompliance as described in Sections 7.3 and 7.4	Immediately, within 24 hours, to PI and within 10 working days to the IRB

8.0 STUDY CALENDAR

For all time points from completion of therapy: goal time points are specified; actual time points may vary due to patient compliance with f/u schedule, logistics, transportation issue, cost of gasoline, treatment for co-morbid illness, etc.

	Prior to registration	Within 6-8 wks of surgery**	Weekly during RT/CRT	At 1 mo. post-RT/CRT	At 3 mos. post-RT/CRT	Every 3-4 months up to 12 mos. and every 4-6 mos. between 12 and 24 mos. post-adjuvant completion	At 6 & 12 mos. post- RT/CRT	At 24 mos. post-RT/CRT
Pre-treatment biopsy*								
Surgeon's exam to confirm site and clinical stage*								
USG Neck or CT, or CT/PET or MRI of H&N*							X [At 12 mos. (± 6 weeks) and then semi-annually (± 6 weeks) for the year 2 or if suspicion of recurrence]	
Chest imaging (X-ray or CT or CT/PET) (also see Section 5.10)*							X [At 12 mos. (± 6 weeks) and then semi-annually (± 6 weeks) for the year 2	
Whole body PET*							X (6 mos)§	
Radiation oncology consult (also see Section 4.4)*								
Medical oncology consult (also see Section 4.4)*								
Surgery [TLM/TORS + neck dissection(s)]	X							
Pathology assessment at participating center & tissue banking (separate institutional consent)*								
Central pathology assessment		X						
Informed consent after surgery & path assessment	X							
Demographics		X						
Comorbidity		X						
Height and weight (height only w/in 6 wks of surgery)		X	X	X	X	X	X	X
Performance status		X	X	X	X		X	
Randomization		X						
Adjuvant therapy (RT/CRT)		X						
QOL/Function Assessments (per QOL metrics in Section 5.8.1)		X		X			X	X
Focused H & P by surgeon				X (6-12 weeks)		X	X	X
Focused H&P by radiation oncologist or medical oncologist			X (± 2 days)	X (± 2 weeks)	X (± 4 weeks)			
Image-guided or direct biopsy		If suspicion of recurrence						
Pregnancy test (if applicable)	X*	X						
CBC w/diff & Absolute Granulocyte count	X*	X	X***	X (± 2 weeks)***				

Basic metabolic panel	X*	X	X***	X (± 2 weeks)***				
Bilirubin, AST or ALT	X*	X	X***					
Serum creatinine or Creatinine Clearance		X	X***					
Adverse event evaluation			X	X	X			
Dental evaluation if necessary		X						
Modified barium swallow if done≠		X					X (6 mo)	X
Baseline Audiometry if done		X						

*Interventions that are generally performed as part of the initial work-up prior to primary surgical resection and are not interventions related to the trial. Each of these interventions individually or collectively is not required for enrolment, e.g., imaging may include any, but not all of the following modalities; CT or MRI or PET-CT.

**The goal will be 6 weeks from surgery; however complications/logistical delays for a minority of patients are inevitable. An outer range for the interventions including initiation of adjuvant treatment will be 8 weeks after surgery.

***These lab investigations will be done only if the patient gets randomized to chemoradiation arm.

§ Timing is contingent on patient compliance with follow-up schedule. Head and neck CT/MRI and chest imaging can be done instead of PET due to logistic reasons (see section 5.10).

≠ Modified Barium Swallow in patients with T3-T4 tumors which receive radiation to the pharynx (optional, for trial purpose)

9.0 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, after surgery & pathologic analysis
Registration Form	After consent, Prior to randomization
On Study Pathology Registration & Eligibility Checklist Randomization and Treatment Assignment	After central pathology confirmation
Surgery Form	After Registration and Eligibility confirmation
Adjuvant Treatment Record	Due within 4 weeks after completion of adjuvant treatment
Follow-up Form*	Per study calendar (see section 8.0)
EORTC QLQ-C30 MDADI Speech Handicap Index Subjective Total Taste Acuity Hearing Handicap Inventory – Adult Cognitive Failures Questionnaire Neck Dissection Impairment Index U Mich Xerostomia Questionnaire	Prior to adjuvant therapy initiation and 1 month, 6 months, 12 months, and 24 months after completion of adjuvant therapy according to the QOL metrics (Section 5.8.2)*
Adverse Events Form	At the time of any toxicity
SAE Reporting Form	At the time of any SAE

*Goal time points are specified; actual time points may vary due to patient compliance with f/u schedule, logistics, transportation issues, cost of gasoline, treatment for co-morbid illness, etc.

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

10.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Data and Safety Monitoring Committee (DSMC) will meet to review toxicity data at least every 6 months following the activation of the first secondary site. The report will be prepared by the statistician with assistance from the study team and will be submitted to the Quality Assurance and Safety Monitoring Committee (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 including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site, and accrual by arm
- 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 at all participating sites and separated by arm
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

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.

A DSMC will consist of no fewer than 3 members including 2 clinical investigators (none of whom is involved in this trial) and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at http://www.siteman.wustl.edu/uploadedFiles/Research_Programs/Clinical_Research_Resources/Protocol_Review_and_Monitoring_Committee/QASMCQualityAssurcance.pdf

10.1 Early Stopping Rules

A. Greater than 15% rate of loco-regional recurrence events in the POART only arm.
B. Greater than 10% rate of local recurrence in the T1 or T2 patients (who do not receive RT targeted to the primary site).
C. For POACRT, >50%, and for POART, > 30% severe acute toxicity rates in the form of ≥ Grade III [(CTCAE) version 4.0 (v4.03: June 14, 2010)] dysphagia or xerostomia,

up to 100 days post completion of adjuvant therapy. We will perform the first check when 40 patients are 6 months post-completion of therapy.

D. A 3% treatment-related mortality (TRM) in either arm, POART or POACRT.

The study statistician has developed check points that regularly assess frequency of events (recurrences, severe acute toxicity) in the above categories (A,B,C) and the probability that such rates would, or would not be due to chance. The stopping rules were based on the trial size, recurrence rate and median time to recurrence, and toxicity rates, allowing the study to be suspended if the recurrence rate or the severe toxicity rate is unacceptable.

11.0 AUDITING

Since Washington University is the coordinating center, each site will be audited annually by Siteman Cancer Center personnel (QASMC) unless the outside institution has an auditing mechanism in place and can provide a report. The outside sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Additional details regarding the Auditing Policies and procedures can be found at http://www.siteman.wustl.edu/uploadedFiles/Research_Programs/Clinical_Research_Resources/Protocol_Review_and_Monitoring_Committee/QASMCQualityAssurcance.pdf

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Endpoints

The study's primary endpoints will be (1) disease-free survival and (2), locoregional control. Disease-free survival (DFS) is defined as the time from surgery to the date of death or recurrence of disease. Locoregional failure will include local recurrence at the primary oropharyngeal site and regional recurrence in the neck nodal basins. Local recurrence will be defined as biopsy proven tumor in the immediate vicinity (i.e. within 2 cm) of the original primary. Regional recurrence will be defined as development of histologically proved metastases in cervical lymph nodes.

The secondary oncological endpoints will be distant metastasis rates and disease specific survival. After completion of treatment, biopsy or imaging-detected recurrent disease at sites away from the original primary and cervical zone will constitute a distant metastasis.

Disease-specific survival (DSS) is defined as the time from surgery to death from recurrent oropharyngeal cancer or treatment-related death.

The secondary toxicity endpoints are the incidence of adverse events as defined by CTCAE 4.0 (see above under Section 7.0 "Regulatory and reporting requirements").

The secondary quality of life endpoints will include the EORTC-QLQ-C30, which has a total score, one general QOL and one “within the last week” subscale, as well as a single general health item and a single overall QOL item. The MDADI has 1 global dysphagia item, physical, function and emotional subscales and one summary scale, which is the sum of the 3 subscales rescaled to 0-100. The SHI has one global speech handicap item and a summary score, which is a sum of the remaining 29 items on a 0-120 scale. The SSTA has a single 5-point item. The HHI-A has 12 sensory and 13 emotional items, which are summed separately for form 2 summary subscores. The CFQ has 3 subscales describing perception, memory and motor function. The NDII has 3 subscales describing physical, functional and social components of neck dissection and a total score, which is the sum of the three subscale scores rescaled to 1-100. The UMXI has a single, total score, which is the sum of the 8 items rescaled to 0-100.

12.2 Study Design

A multicenter, randomized, two-armed prospective trial has been planned with equal allocation of patients to each arm stratified by T stage and smoking history (see above under Section 5.3 "Treatment randomization"). Power calculations are based on non-inferiority analyses of the two primary endpoints. The definitive analysis will be performed when each of the study patients has been followed for a minimum of two years. One interim analysis will be performed midway through the recruitment period and at the end of it. An interim report will be issued once all data is collected on the last accrued patient two years from closure of enrolment and a further report at 3 years from closure. Patients who do not consent to randomization or who refuse participation in the arm to which they are randomized prior to receiving any treatment on study will be followed in a separate, observational cohort.

12.3 Sample Size and Power Estimation

12.3.1 Primary Endpoints

Sample size calculation for the planning of a prospective non-inferiority trial with a time-to-event endpoint was performed by the Siteman Cancer Center Biostatistics Core, assuming power=0.8 and a family-wise type I error rate =0.05 (48). Based on our preliminary data from 112 patients with p16+ oropharynx cancer and ECS, for a margin of 5% clinically allowable difference in the disease-free survival of patients receiving CRT versus adjuvant RT alone, a total of approximately 496 patients would be required, with equal numbers in both arms. The 2 year DFS estimate in adjuvant RT alone group was 92.7% versus 94.7% in the group receiving adjuvant CRT.

The same data indicate an expected locoregional failure rate of 0/65 with chemoRT (0% with 95% confidence interval (0.37%, 4.5%)) and 2/66 with RT alone (3% with 95% confidence interval (0.37%, 10.5%)). The proposed sample size will provide power=.80 at a 0.025 significance level to reject the null hypothesis of inferiority of locoregional failure rate with RT alone. The assumptions of the power calculation are that a Z-test will be used with a noninferiority margin of 5%, a baseline failure rate of 1% with chemoRT and a maximum failure rate of 3.2% with RT alone. The power calculation for DFS was carried out using Jung et al (48) methodology. The power calculation for locoregional control rate was carried out using SAS 9.3 proc power. The sample size and power calculations above apply to patients randomized to treatment, but would also have formed the basis for a purely non-randomized observational cohort design, driven by the same hypothesis.

12.3.2 Secondary Oncologic and Toxicity Endpoints

Disease specific survival will be described by estimation of median DSS and DSS rates at 2 years with 95% confidence intervals. This endpoint is primarily descriptive, and no power calculation has been performed.

Approximately 50 tests for difference of proportion are anticipated when comparing rates of complications and adverse events. Expected frequencies in the two study arms are not well documented, and many of these events are rare. At a minimum, the proposed sample will provide power ≥ .80 to detect a difference of 19% using a Hochberg step-up method to limit the familywise type I error rate to .05.

12.3.3 Secondary Quality of Life Endpoints

Mean or median quality of life will be compared in the two study arms to determine whether the observed difference is larger than noise (total variance, including within-patient and between-patient variance). Patient-specific and clinical significance of observed differences will be a matter for discussion at the end of the study; that is, the study does not intend to determine a minimal important difference (MID) (49). The study does use current empirical guidelines for the EORTC-QLQ-30 global score (50)with the understanding that both the magnitude and variance of scores vary considerably from patient to patient, from one time point to another and by such factors as disease condition, age and comorbidity. MIDs are undefined for patients similar to those to be included in this study, although SHI scores > 7 are considered to indicate significant worsening function. For the remaining scales, a change of 1 standard deviation can be considered a perceptible difference; that is, a change of 20.0 for the subscales of the MDADI, 15.0-20.0 for the subscales of the HHI-A, 2.8-4.1 for the items of the NDII and ~24.4 in the UMXI. The proposed sample will have ≥ .80 power at a multiplicity corrected α=.001 to detect a difference of 3 points in the EORTC-QLQ-30 global score. It will have > .95 power

at the same significance level to detect the "small" 7 point difference documented by Cocks et al (50).

12.3.4 Patient Accrual

Six centers are currently participating in the study. Each center is anticipated to enroll about 20 - 25 patients per year. This enrollment rate would complete accrual in approximately three to four years, with a further two year minimum follow up from completion of last patient enrolment. Any loss of anticipated accrual due to smaller than expected numbers of patients with extracapsular spread will be compensated for by recruitment of additional study sites, once we have a fully approved protocol. These new sites will be unanimously agreed upon by the foundational member institutions of the study.

12.3.5 Drop Offs

Patients who do not start adjuvant therapy for whatever reason will be followed, but not entered into the analysis of adjuvant therapy- randomized groups.

12.4 Analysis

12.4.1 Analysis Population

All patients who receive a randomized assignment will be included in the intent-to-treat analysis, regardless of the treatment received. Randomized and observational cohorts will be analyzed jointly with stratification by cohort to adjust for systematic differences between patients choosing and those refusing randomization. Additional exploratory analyses also may be carried out within each cohort.

12.4.2 Analysis Plan

The statistical analysis will commence after the final enrolled patient has reached the minimum two-year follow-up.

12.4.3 Analysis Plan for Primary Endpoints

The primary analysis of disease free survival, including patients from both cohorts, will be carried out using Kaplan-Meier models and p-values calculated by log-rank test. Additional Cox proportional hazards models may be created to estimate hazard ratios by study arm and to allow for covariate adjustment.

Locoregional control failure rates will be compared using a chi-square test with normal approximation. Fisher's exact test may be used if failure frequencies are too low to allow a valid chi-square test.

To correct for testing two primary endpoints, non-inferiority of DFS and locoregional control failure rate, a Hochberg step-up method will be used (51). Both endpoints will be tested without multiplicity correction. Following this step, the decision criteria are: if the larger p-value is $< .05$, then the study would conclude that non-inferiority has been shown. If the larger p-value is $\geq .05$ and the smaller one is $< .025$ (that is, $\alpha/2$), then the study would conclude that non-inferiority has been shown. If the larger p-value $\geq .05$ and the smaller one is $\geq .025$, then the study would fail to show non-inferiority.

12.4.4 Analysis Plan for Interim Analysis

A Lan–DeMets alpha spending function with the O'Brien–Fleming stopping boundary will be applied to the interim analysis of primary and secondary endpoints (52). If the stopping boundary is not crossed, patients will continue to receive the group assignments until the final analysis. Analyses of primary and secondary endpoints are performed in the intention-to-treat population.

12.4.5 Analysis Plan for Secondary Endpoints

Chi-square tests will be used to compare distant metastasis rates and Kaplan-Meier models to compare disease specific survival by study arm. Additional Cox proportional hazards models may be created to estimate hazard ratios by study arm and to allow for covariate adjustment.

Chi-square or Fisher's Exact tests will be used with Hochberg step-up multiplicity correction to test for differences in rates of complications and adverse events.

Tables and histograms will be used to explore change in the subscales and summary scales at each time point and over time. Multiplicity corrected tests for trend (such as the non-parametric Jonckheere-Terpstra test) will be used to compare patients with and without chemotherapy at single time points. Spearman's rank correlation or, where there are a large number of tied scores, Kendall's tau-b will be used to explore correlation (redundancy) between QOL (sub)scales prior to modeling. Generalized estimating equations (GEE) will be used to model the probability of each (sub)scale score by study arm at each of 6 time points (study entry 1, 3, 6, 12 and 24 months).

13.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Each participating institution must have the following documents on file at Washington University prior to first subject enrollment:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of Federal Wide Assurance, signed FDA Form 1572, and signed and dated CVs of all participating investigators.
- Documentation of training in protection of human subjects by all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The Principal Investigator is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. There will be one current version of the protocol document at any given time and each participating institution will utilize that document. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 2 weeks of obtaining Washington University IRB approval with acknowledgement of receipt requested. Secondary sites are to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt, and confirmation of submission must be forwarded to the appropriate contact person on the Washington University study team at the time of submission. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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