Phase II Trial of Surgery followed by Risk-Directed Post-Operative Adjuvant Therapy for HPV-Related Oropharynx Squamous Cell Carcinoma:

"The *Min*imalist *T*rial (*MINT*)"

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PRINCIPAL INVESTIGATOR
Douglas Adkins, M.D.
Washington University School of Medicine
Campus Box 8056, 660 South Euclid Ave.
St Louis, MO 63110
Office Phone: 314-747-8475
dadkins@wustl.edu

Sub-Investigators	Modality
Wade Thorstad, M.D.	Radiation Oncology
Ryan Jackson, M.D.	ENT
Jason Rich, M.D.	ENT
Peter Oppelt, M.D.	Medical Oncology
Randall Paniello, M.D.	ENT
Patrik Pipkorn, M.D.	ENT
Hiram Gay, M.D.	Radiation Oncology
Esther Lu, PhD	Biostatistics
Rebecca Chernock, M.D.	Pathology
Mena Mansour	Pathology
Sid Puram, M.D., PhD	ENT
Craig Buchman, MD	ENT

Study Drugs: Cisplatin

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Phase II Trial of Surgery followed by Risk-Directed Post-Operative Adjuvant Therapy for HPV-Related Oropharynx Squamous Cell Carcinoma:

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Protocol Revision History

Initial Approval	**07/25/2018**
Amendment #1	**01/23/2019**
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Amendment #8	**02/27/2023**

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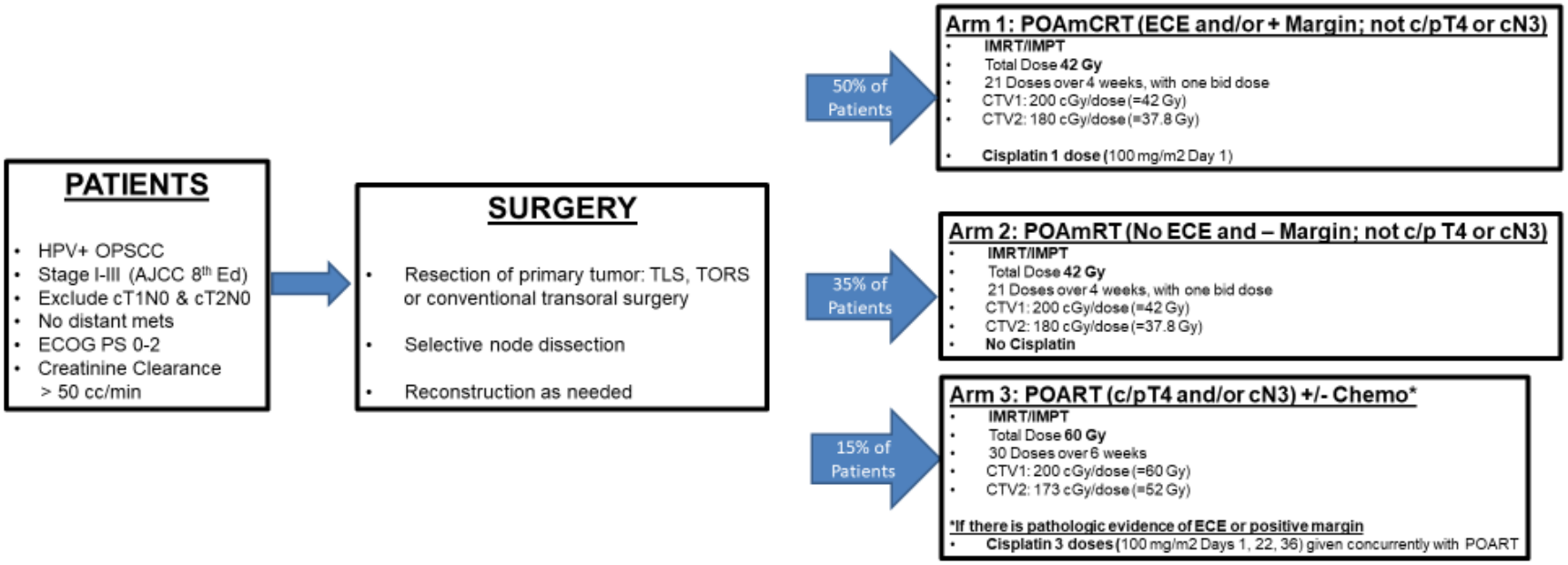
"The *Mini*malist *T*rial *(MINT)"

MINT SCHEMA



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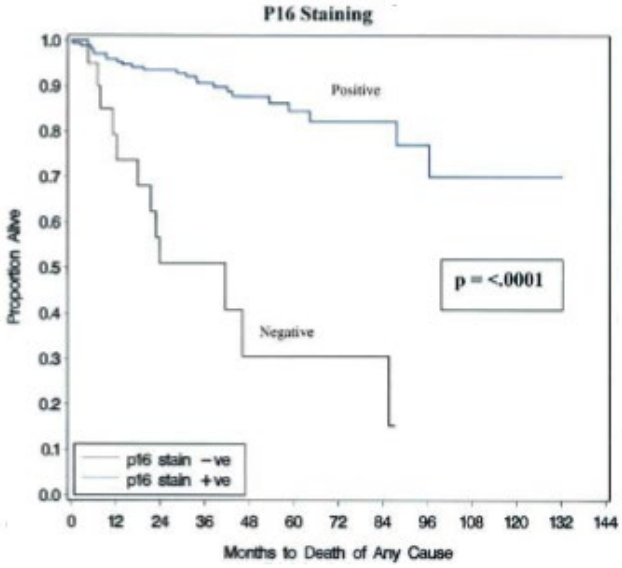
1.0 INTRODUCTION AND BACKGROUND

1.1 Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer. HNSCC originates in the squamous cell mucosa of the oropharynx (OP), oral cavity, larynx and hypopharynx. OPSCC is one of the most common subtypes of HNSCC and the incidence of OPSCC has risen significantly over the last decade.[1] Last year, 16,000 new cases of OPSCC were diagnosed in the USA. Previously, the primary cause of OPSCC was smoking; however, currently the majority of cases (>90%) are due to the Human Papilloma Virus (HPV).[2] HPV-related OPSCC is expected to comprise the majority of HNSCCs by 2030.[1]

HPV-related OPSCC has a better prognosis compared to smoking-induced HPV-unrelated disease. Only 10-15% of patients with HPV-related OPSCC develop disease relapse after initial therapy compared to 40-60% of patients with HPV-unrelated disease. Also, patients with HPV-related OPSCC are younger and healthier than patients with HPV-unrelated disease and thus deaths due to non-OPSCC causes are much lower in HPV-related OPSCC. As a result, the 5 year overall survival (OS) of patients with HPV-related OPSCC is 70-90% compared to 30% for HPV-unrelated disease (Figure)[3]:



Overall survival by p16 staining (p16+ is a surrogate marker of HPV)

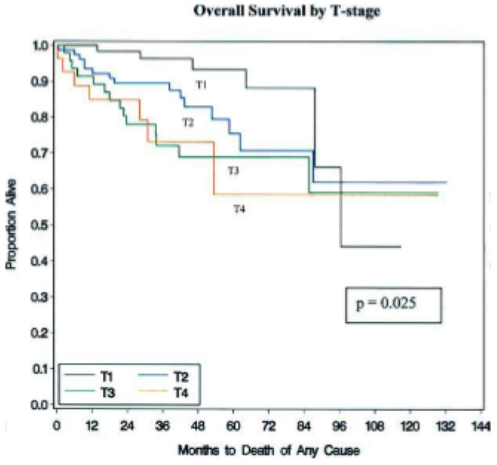
The current standard of care therapy for HPV-related and HPV-unrelated OPSCC is the same, even though the chances for cure and OS are far better with the former diagnosis. Treatment options include surgery and adjuvant radiation-based therapy or definitive chemoradiation therapy (DCRT). Both options result in intense and frequent acute toxicity and long-term morbidity that impair quality of life (QOL). The current focus for HPV-related OPSCC is to investigate less intense therapy with the goal to reduce treatment-related toxicity while maintaining the low relapse risk. The focus for HPV-unrelated disease is to investigate more intense therapy

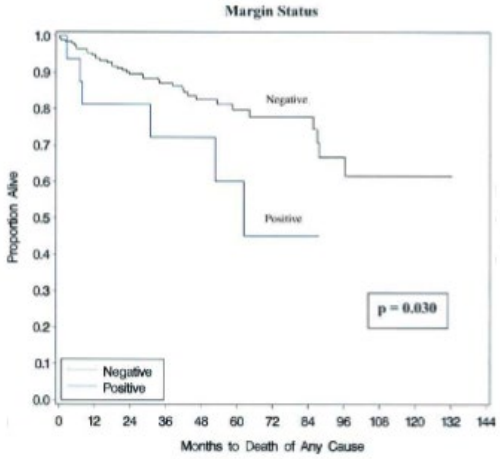
to reduce relapse risk.

This protocol will evaluate two less intense post-operative adjuvant radiation-based therapy approaches in patients with HPV-related OPSCC who have a low (Arm 1) or very low (Arm 2) risk for disease relapse. A standard, intense post-operative CRT pathway will be reserved for patients with a high risk for disease relapse (Arm 3).

1.2 Outcomes of HPV-related OPSCC after Surgery and Adjuvant Therapy

Washington University has published a large body of data on outcomes of patients with HPV-related OPSCC treated with primary surgery and post-operative adjuvant radiation therapy (POART) or chemoradiation therapy (POACRT). In a retrospective report of 84 patients treated with transoral laser microsurgery (TLM) (median follow-up: 53 months), OS at 2 and 5 years was 94% and 88%, respectively.[4] The risk of recurrence was 7%. Most of these patients had small primary tumors (T1-2:74%). OS was adversely impacted by advanced T stage (T3-4) and positive margins. In a retrospective report of 204 patients treated with TLM, the OS at three years was 86% and the relapse risk was 13%.[3] Advanced T stage (T3-4) and positive margin were adverse prognostic factors (Figures):





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

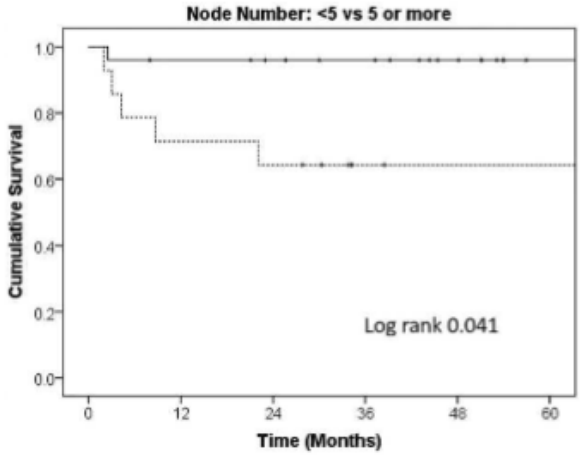


Fig. 3. Disease-free survival of surgical patients with pathological N3 disease from human papillomavirus–related oropharyngeal squamous cell carcinoma with less than five (solid line) versus five or more (dotted line) pathologically positive nodes.

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

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

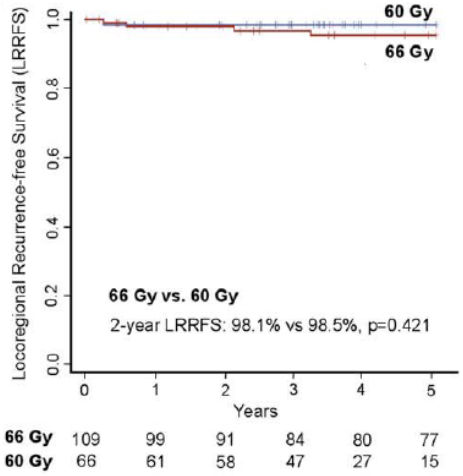
The treatment-related toxicity burden experienced by patients with HPV-related OPSCC is substantial. Adverse events (AEs) due to surgery with modern trans-oral techniques usually resolve after 3-4 weeks. Swallowing function after TLM and adjuvant therapy was good at two years in 93% of patients with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

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

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

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

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



In OPSCC patients with a clinically uninvolved contralateral neck, eliminating coverage of POART to the contralateral high level II neck and retropharyngeal nodes was associated with a minimal risk for failure in these regions and an improved PRQOL.[9]

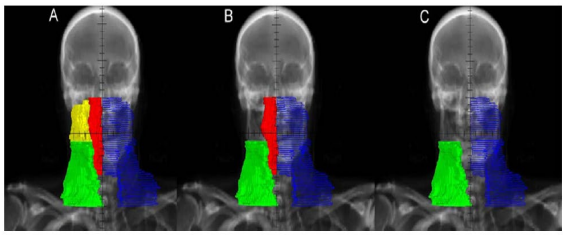


Figure 1. These anterior-posterior radiographs demonstrate clinical target volume elective lymph node volume contours from the 3 groups or generations of elective neck target-delineation guidelines: (A) generation 1, (B) generation 2, and (C) generation 3. The area in blue is the ipsilateral neck, green represents the contralateral low neck below the level at which the posterior belly of the digastric muscle crosses the internal jugular vein, yellow indicates the contralateral high level II lymph nodes, and red indicates the contralateral retropharyngeal lymph nodes.

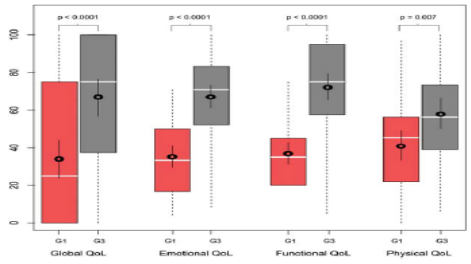


Figure 4. Box plots illustrate patient-reported quality of life (QoL) broken into 4 domains: global, emotional, functional, and physical. Red boxes indicate generation 1 (G1), and gray boxes indicate generation 3 (G3). Each box illustrates the 25th through 75th quartiles, vertical dashed lines indicate the minimum and maximum, and white horizontal bars indicate the median. Black circles indicate the mean values, and the surrounding black vertical bars indicate 95% confidence intervals. All *P* values were significant (Wilcoxon rank-sum test).

1.5 HPV-Related OPSCC is More Radiosensitive than HPV-Unrelated OPSCC

The molecular basis of the favorable outcomes of HPV-related OPSCC treated with CRT has not been clearly determined. One report did find that HPV positive HNSCC cell lines were more radiosensitive than HPV negative HNSCC cell lines.[10]

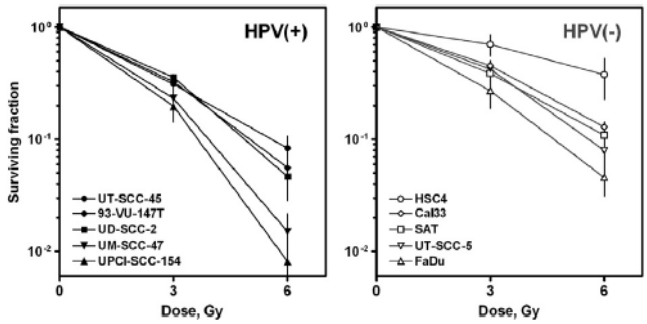


Fig. 2. Cellular radiosensitivity of HPV/p16-positive and HPV-negative HNSCC cell lines. Clonogenic survival of HPV-positive (left) and HPV-negative (right) cell lines after X-irradiation.

The increased radiosensitivity of HPV positive HNSCC cell lines was not due to increased apoptosis or cell cycle arrest in G1 a result of the effect of the E6 viral protein on *wt*p53. Impaired DNA double strand break repair capacity was found to be the likely basis for the increased radiosensitivity of HPV positive HNSCC cell lines.

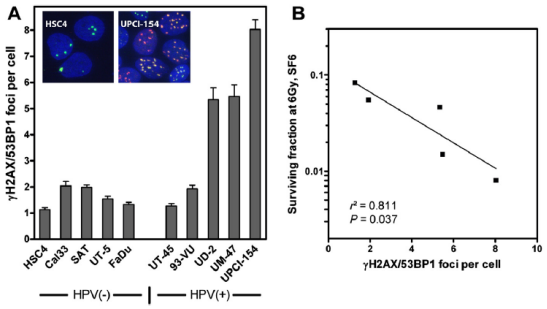


Fig. 4. DSB repair capacity in HPV/p16-positive and -negative HNSCC cell lines after X-irradiation. Cells were X-irradiated with 2 Gy and fixed after 24 h, followed by immunofluorescence staining with anti-human γH2AX and anti-human 53BP1 antibodies (see examples). Nuclei were counterstained with DAPI. (A) Quantification of residual DSBs. After correcting the numbers of residual DSBs for the respective DNA content of each cell line the number of foci measured for non-irradiated cells was subtracted. Quantification was performed for at least 150 nuclei per sample in three separate experiments by three individual researchers with very similar results. One representative experiment is shown. Data presented are mean values + SEM. (B) Association between residual DSBs and cellular radiosensitivity for HPV-positive HNSCC cell lines. Cellular radiosensitivity as measured at 6 Gy, SF6, is plotted against the number of residual DSBs at 2 Gy; data were taken from Fig. 2 and Fig. 4A. Data were fitted by linear regression analysis.

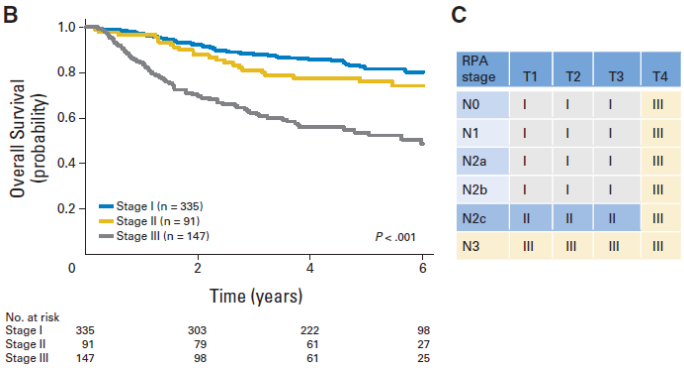
Additional pre-clinical data support the increased radiosensitivity of HPV positive OPSCC cell lines.[11] Also, HPV positive cell lines appear to retain some p53 function as shown by the ability of cisplatin or radiation to induce the p53 target gene GADD45.[12] In HPV positive cell lines, cisplatin repressed E6 expression and induced p21, p53, and BAX expression resulting in induction of apoptosis.[13]

Clinical data support that HPV-related OPSCC is more radiosensitive than HPV-unrelated OPSCC. The rate of tumor regression during week one of IMRT was greater in HPV-related OPSCC than HPV-unrelated OPSCC (33% difference in gross tumor volume [GTV] $p< 0.001$ and the average absolute change in GTV was -22.9 cc/week vs -5.9 cc/week, respectively $p< 0.001$).[14]

1.6 Selection of Appropriate Candidates with HPV-Related OPSCC for De-Intensification of CRT?

Recognition that patients with AJCC/UICC 7th edition stage III/IV HPV-related OPSCC had a substantially better prognosis than those with stage III/IV HPV-unrelated OPSCC resulted in development and implementation of a new staging system specific to HPV-related OPSCC. The new staging system correlated prognosis for each stage better than the old staging system.

Investigators at Princess Margaret Cancer Centre showed that the AJCC/UICC TNM 7th edition clinical staging system distinguished OS prognosis among the different stages of HPV-unrelated OPSCC, but it did not do so for HPV-related OPSCC.[15] Five year OS for HPV-unrelated OPSCC was 70% (stage I), 58% (stage II), 50% (stage III), and 30% (stage IV). Five year OS for HPV-related OPSCC was 88% (stage I), 78% (stage II), 71% (stage III), and 74% (stage IV). This group performed recursive partitioning analysis (RPA) on a large internal dataset and divided HPV-related OPSCC into three groups: I (59%; T1-3 N0-2b), II (16%; T1-3 N2c), and III (26%; T4 N3) with 5 year OS of 82%, 76%, and 54%, respectively.



C

RPA stage	T1	T2	T3	T4
N0	I	I	I	III
N1	I	I	I	III
N2a	I	I	I	III
N2b	I	I	I	III
N2c	II	II	II	III
N3	III	III	III	III

Weaknesses of the Princess Margaret report included data from a single institution and lack of validation in a separate cohort. The International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) report addressed these weaknesses by performing a multicenter validation study using clinical (not pathologic) staging methods.[16] T stages remained similar except that T4a and T4b were bundled into T4 based on the same OS between these T4 subsets. Clinical N stages were divided into N1 (ipsilateral neck nodes), N2 (bilateral or contralateral neck nodes), and N3 (> 6 cm neck node). The proposed ICON-S clinical classification was stage I (T1-2, N0-1), stage II (T1-2N2 or T3N0-2), stage III (T4 or N3), and stage IV (metastatic). An exploratory analysis showed that lower neck nodal involvement had a significant adverse impact on OS in stage III but no effect in stages I-II. Also, OS was similar for patients with < 5 neck nodes and ≥ 5 neck nodes, across all stages.

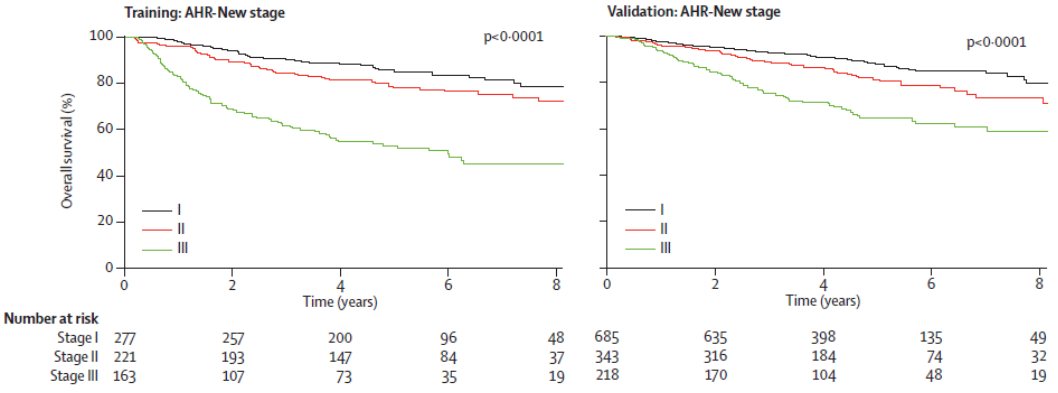


Figure 3: Kaplan-Meier estimates of overall survival in the training and validation cohorts, by stage classification

The tables below summarize the new AJCC 8th edition clinical and pathologic staging systems for HPV-related OPSCC:

TABLE 1. Clinical and Pathologic T Category for Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

T CATEGORY	T CRITERIA
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond[a]

TABLE 3. Clinical N Category Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

TABLE 5. Pathologic N Category Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

TABLE 6. Anatomic Stage and Prognostic Groups for *Clinical* TNM Grouping of Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

	N CATEGORY			
T CATEGORY	N0	N1	N2	N3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

[a]Any M1 is stage IV.

TABLE 7. Anatomic Stage and Prognostic Groups for *Pathologic* TNM Grouping of Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

	N CATEGORY		
T CATEGORY	N0	N1	N2
T0	NA	I	II
T1	I	I	II
T2	I	I	II
T3	II	II	III
T4	II	II	III

[a]Any M1 is stage IV.

The ICON-S clinical staging system determined that stages I-II HPV-related OPSCC had excellent prognoses (5 year OS > 80%) with current therapy and would be appropriate candidates for trials evaluating de-intensification of current CRT. ICON-S stages I and II represented 83% of patients in this analysis. Patients with ICON-S stage III disease (17% of all patients) had a poorer prognosis (5 year OS 60%), and would not be appropriate candidates for trials evaluating de-intensification of current therapy.

1.7 Current Trials of De-intensification Therapy in HPV-related OPSCC

Nine trials evaluating strategies to de-intensify CRT in patients with HPV-related

OPSCC are either ongoing or recently completed with results awaiting maturation of data. Five of these trials use the surgical platform and four use the definitive radiation platform. The lowest dose of once daily radiation being investigated in all current trials of de-intensification is 50 Gy, with one exception. The Mayo Clinic trials are evaluating 30-36 Gy RT; however, RT is delivered in an accelerated scheme, which is known to be more toxic than once daily radiation schemes. Note that risk stratification factors vary in each of these trials, making comparisons challenging.

Surgery Trials: ECOG 3311 is a phase III trial that treats post-operative patients who have intermediate risk (IR) features with POART 50 vs 60 Gy to the primary tumor site and bilateral neck nodes. Chemotherapy is not given to these patients. The PATHOS trial also compares POART 50 Gy vs 60 Gy in patients with IR disease. The DART phase III trial (Mayo Cinic) compares arm 1: 30 Gy in 150 cGy bid x 12 doses (IR) or 36 Gy in 180 cGy bid x 12 doses (HR: ECE) + docetaxel 2 doses vs arm 2: 60 GY in 200 cGy doses, both with weekly cisplatin x 7. The SIRS phase II trial (Mt Sinai) uses POART 50 Gy, but is limited to patients with T1-2 IR disease. MC 1273 phase II trial (Mayo Clinic) used POART 36 Gy (180 cGY bid) + docetaxel (2 doses).

Definitive Radiation Trials: NRG HN002 is a phase III trial that compares definitive RT 60 Gy in 6 weeks + weekly cisplatin x 6 vs accelerated definitive RT 60 Gy in 5 weeks (6 doses per week). This trial does not include patients with T4, N2c or N3 disease, or patients with > 10 pack-year history of smoking. RTOG 1016 is a phase III trial comparing accelerated definitive RT 70 Gy over 6 weeks (with 2 fractions one day per week) + HDB cisplatin x 2 vs cetuximab x 8. ECOG 1308 was a phase II trial in which all patients were treated with induction chemotherapy followed by definitive RT 54 Gy + cetuximab (if complete response to induction chemotherapy) or RT 69.3 Gy + cetuximab (if not complete response to induction chemotherapy). A single arm phase II trial (University of California) treated patients with two cycles of induction paclitaxel and carboplatin followed by either 54 Gy IMRT + paclitaxel (CR or PR) or 60 Gy IMRT + paclitaxel (< PR).[17]

The results of these trials (except ECOG 1308 and the University of California trials) are not available yet, as many are still accruing and none have mature follow-up.

1.8 Rationale for 42 Gy IMRT + Chemotherapy for HPV-related OPSCC

Normal Tissue Complication Probability (NTCP) due to radiation therapy is an important concept related to the likelihood and severity of acute and long term toxicity in an attempt to cure malignancy with a radiation therapy approach. When other modalities are used, NTCP can be extended to account for the overall complication probability due to the sum of all treatment modalities involved. It is anecdotally evident that lower dose and/or lower volume of radiation correlate with less toxicity, but it was not until the advent of 3D radiation therapy technology that

NTCP could be quantified. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) study[18] summarized the latest understanding of organ specific dose/volume/outcome data.

Based on QUANTEC, there is much to be gained by reducing radiation therapy dose to 42 Gy for HPV related OPSCC. The organs related to swallowing function include the pharyngeal constrictors, larynx, and esophagus. For the pharyngeal constrictors, a mean radiation dose of less than 50 Gy reduces the risk of symptomatic dysphagia and aspiration to less than 20%. For the larynx, a mean dose of < 50 Gy reduces the risk of aspiration to less than 30%, and the risk of laryngeal edema is less than 20% with a mean dose of less than 44 Gy. For the esophagus, if the volume receiving 50 Gy is less than 40%, the risk of grade 2 or above toxicity is no more than 30%. The increase in NTCP with dose has an exponential component. Therefore at doses above 50 Gy, the risk of damage increases exponentially with rising dose. However, the reduction in NTCP also has an exponential component, meaning that a dose of 42 Gy would significantly reduce normal tissue risk relative to 50 Gy in the QUANTEC data above, and relative to the 60 Gy standard dose for OPSCC in the postoperative setting.

Like HPV-related OPSCC, anal canal SCC is also caused by HPV. Anal SCC is treated non-operatively with CRT. Radiation therapy and concurrent chemotherapy (5-FU and Mitomycin C) is the standard of care treatment for non-metastatic anal canal SCC. The treatment plan for T2N0 disease is 42 Gy elective nodal and 50.4 Gy anal tumor planning target volumes (PTV) in 28 fractions and for T3-4N0-3 disease is 45 Gy elective nodal, 50.4 Gy for $\leq$ 3 cm or 54 Gy for > 3 cm metastatic nodal and 54 Gy anal tumor in 30 fractions. Use of IMRT reduced acute GI and GU mucosal toxicity compared to non-conformal radiation.[19]

In anal SCC, mitomycin C and 5-FU are the standard chemotherapy agents given with RT. In OPSCC, cisplatin is the standard agent given with RT. Mitomycin C has not been tested in HPV-related OPSCC. However, cisplatin and 5-FU was compared to mitomycin C and 5-FU with RT in anal SCC[20]. The OS was not different between the two regimens. The rates of distant metastasis were not significantly different between the two groups (15% with mitomycin C and 19% with cisplatin). In anal SCC, the total dose of cisplatin given during RT is 150 mg/m^2; whereas, in HPV-related OPSCC, the total dose of cisplatin given during RT is 300 mg/m^2.

The studies of CRT in anal SCC showed that a radiation dose of only 42 Gy and a total cisplatin dose of only 150 mg/m^2 were effective in eliminating <u>microscopic</u> disease in most patients. Is it possible that a dose of only 42 Gy would also eliminate microscopic disease in patients with HPV-related OPSCC?

The optimal platform to test this question is in patients who undergo surgery to resect all gross disease at the primary tumor site and neck nodes. Many of these patients still have microscopic disease at the primary tumor site or in neck nodes

and thus all patients are treated with adjuvant therapy to reduce the risk of disease recurrence. The standard radiation dose used in this setting is 60 Gy, and most of these patients also receive concurrent cisplatin 100 mg/m^2/dose for up to three doses. Based on studies in anal SCC, 42 Gy of RT should eliminate microscopic disease in most patients with OPSCC who have undergone complete resection of all gross disease. Studies in anal SCC used a total cisplatin dose of 150 mg/m^2; however, these patients were managed non-operatively and thus all patients had gross disease when CRT was initiated. For this reason, a total dose of cisplatin lower than 150 mg/m^2 seems reasonable to explore in patients with OPSCC who have undergone complete resection of all gross disease. In HNSCC, 5-FU has not been shown to add benefit to RT.

De-intensification of adjuvant therapy by reduction in radiation dose from 60 Gy to 42 Gy and in the total cisplatin dose from 300 to 100 mg/m^2 should result in a substantial reduction in acute toxicity and improvement in QOL, but this is only acceptable if there is not an increased risk of disease relapse.

1.9 "The *MINT* Trial"

The overarching goal of the *MINT* trial is to reduce treatment-related toxicity while maintaining efficacy. Patients with HPV-related OPSCC will undergo resection of the primary tumor site and involved/at risk regional neck nodes. Based on the clinical and pathologic staging and the details of the pathology report, patients will be assigned to one of three adjuvant treatments:

- **Arm 1** (extracapsular extension (ECE) or positive margin but not clinical or pathologic T4 or clinical N3 disease) will be treated with POAmCRT (42 Gy RT + cisplatin 1 dose)
- **Arm 2** (no ECE, no positive margins, and not clinical or pathologic T4 or clinical N3 disease) will be treated with POAmRT (42 Gy RT, no cisplatin)
- **Arm 3** (clinical or pathologic T4 or clinical N3 disease) will be treated with POART (60 Gy RT). If there is pathologic evidence of ECE or positive margin, 3 cycles of cisplatin will be given concurrently with POART (60Gy).

Intermediate risk patients will be assigned to Arm 1 where they will be treated with de-intensified CRT: 42 Gy of RT (vs 60 Gy) and cisplatin 1 dose (vs 3). Reduction in treatment-related toxicity is expected in Arm 1.

Low risk patients will be assigned to Arm 2 where they will be treated with de-intensified RT: 42 Gy (vs 60 Gy) and no cisplatin at all. Reduction in treatment-related toxicity is expected in Arm 2.

High risk patients will be assigned to Arm 3 where they will be treated with standard intensive therapy, so reduction in treatment-related toxicity is not expected in this group.

Mucosal damage is the key mediator of most of the acute toxicity for POART and POACRT. The primary endpoint for the *MINT* trial is weight loss, a reliable, easily measured and practical surrogate marker of mucosal toxicity. **Historical data showed that the percent weight loss during POACRT in patients with HPV-related OPSCC was 7.39%. The primary hypothesis of this trial is that the percent weight loss of patients in Arm 1 during POAmCRT will be 3.7% (50% reduction).**

Secondary endpoints of mucosal toxicity to be determined include the proportion of patients who had PEG tubes placed, who experienced a doubling of the serum creatinine from baseline (a surrogate of dehydration and/or cisplatin toxicity), and who remained on narcotics at 6 weeks after POAmCRT. The secondary hypothesis for this trial is the proportion of patients with the composite endpoint of PEG tube placement/doubling of the serum creatinine/requirement for narcotics at 6 weeks after POAmCRT will be reduced from the historical control of 72.6% to 36.3% (50% reduction). Similar endpoints will be monitored for Arm 2, although the number of patients in this arm is expected to be small based on historical data. As such, we will not develop formal hypothesis testing for Arm 2, but will report the toxicity data in descriptive form.

Patients (and clinicians) will not accept an increased risk of disease recurrence even with a significant reduction in toxicity with de-intensified therapy.[21] To address this concern, we will establish rates of disease recurrence for Arm 1 that will be unacceptable. Our historical control data showed that the absolute risk of disease recurrence in patients with the characteristics of Arm 1 was 10% and that 89% of these recurrence events occurred by 24 months after completion of therapy. The upper threshold for disease recurrence in Arm 1 will be 20% by 24 months after completion of therapy. In Arms 2 and 3, we will report the proportion of patients with disease recurrence, but will not develop formal hypotheses testing because Arm 2 patients will be too few in number and Arm 3 patients will receive standard POACRT.

2.0 STUDY ENDPOINTS AND OBJECTIVES

2.1 Primary Objective

1. To determine the percent weight loss in patients during POAmCRT (Arm 1) starting at Day 1 and ending on the last day of RT.

2.2 Secondary Objectives

1. To evaluate the narcotics administration of patients 6 weeks after POAmCRT (Arm 1).
2. To determine the disease recurrence rate at 24 months post-treatment in each arm.

3. To determine progression free survival (PFS) and overall survival (OS) for each arm.
4. To evaluate the proportion of PEG tube placements in each arm.
5. To determine the serum creatinine changes in patients receiving POAmCRT (Arm 1).

2.3 Exploratory Objectives

1. To document the measures of Quality of Life (QOL) at baseline, during treatment, and through one year after completion of treatment in each arm.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

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

3.2 Exclusion Criteria

1. cT1N0 or cT2N0 staging.
2. Prior curative therapy for HNSCC.
3. Patient must not have known distant metastatic disease at presentation.
4. History of prior invasive malignancy diagnosed within 2 years prior to study enrollment; exceptions are malignancies with a low risk of metastasis or death (e.g., expected 5-year OS > 90%) that were treated with an expected curative outcome, such as squamous cell carcinoma of the skin, in-situ carcinoma of

the cervix uteri, non-melanomatous skin cancer, carcinoma in situ of the breast, or incidental histological finding of prostate cancer (TNM stage of T1a or T1b).
5. Receiving any other investigational agents.
6. Uncontrolled serious inter-current illness or serious psychiatric illness/social situations that would limit compliance with study requirements.
7. Pregnant and/or breastfeeding. A negative serum or urine pregnancy test is required at screening for all female patients of childbearing potential.

3.3 Inclusion of Women and Minorities

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

4.0 REGISTRATION PROCEDURES

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

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

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

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

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

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

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

4.3 Assignment of UPN

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

5.0 TREATMENT PLAN AND SCHEDULED ASSESSMENTS

Patients with HPV-related OPSCC will undergo resection of the primary tumor site and involved/at risk regional neck nodes. Based on the clinical and pathologic staging and the details of the pathology report, patients will be assigned to one of three adjuvant treatments. Arm 1 (ECE or positive margin but not clinical or pathologic T4 or clinical N3 disease) will be treated with POAmCRT (42 Gy RT + cisplatin 1 dose). Arm 2 (no ECE, no positive margins, and not clinical or pathologic T4 or clinical N3 disease) will be treated with POAmRT (42 Gy RT, no cisplatin). Arm 3 (clinical or pathologic T4 or clinical N3 disease) will be treated with POART (60 Gy RT). If there is pathologic evidence of ECE or positive margin, 3 cycles of cisplatin will be given concurrently with POART (60Gy).

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

5.1 Baseline Assessment

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

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

5.2 Standard of Care Surgery

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

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

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

5.3 Interim Assessment

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

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

5.4 Postoperative Adjuvant Chemotherapy

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

The dose of cisplatin will be given on the same day as one of the initial 5 doses of POART (refer to Section 5.5 for RT dosing).

Recommended procedures for cisplatin therapy are as follows:

1. Antiemetic premedication prior to cisplatin: palonosetron 0.25 mg IVPB, dexamethasone 10 mg IVPB and aprepitant 150 mg IVPB.
2. Hydration consisting of 1L IVF NS (10 meq KCL/L + 8 meq $MgSO_4$/L) over 60 minutes before and after cisplatin on the day of dosing. 2L IVF NS over 60 minutes on each of the two days following cisplatin dosing.
3. Administration of cisplatin (100 mg/m^2 IVPB over 60 minutes) on one day only during one of the first 5 doses of radiation.
4. Physical examination will be performed on the day of cisplatin administration and on day 22 (+/- 2) and 36 (+/- 2) after starting radiation therapy.
5. Weight (kg) will be collected weekly during radiation.
6. Documentation of ECOG performance status will be done on the day of cisplatin administration and on days 22 (+/- 2) and 36 (+/- 2) after starting radiation therapy.
7. Documentation of patient symptoms using NCI-CTCAE version 4.0 will be done on the day of cisplatin administration and on days 22 (+/- 2) and 36 (+/- 2) after starting radiation therapy.
8. CBC, BMP and magnesium on the day of cisplatin administration and on days 22 (+/- 2) and 36 (+/- 2) after starting radiation therapy.
9. Patient to complete QOL questionnaire prior to starting radiation (-7/+0) and during the fourth week of radiation (radiation doses 16-21) and 36 (+/- 2) days after starting radiation therapy.
10. OPTIONAL: Patient to receive speech and swallowing assessments prior to starting radiation* and during the fourth week of radiation (radiation doses 16-21) and 2 weeks after completing radiation therapy. *Modified barium swallow not needed within one week prior to starting radiation.

5.4.2 ARM 2: No Cisplatin. 21 doses of RT only.

Refer to Section 5.5 for RT dosing instructions.

1. Physical examination and weight (kg) will be performed on the first day of radiation therapy and on days 22 (+/- 2) and 36 (+/- 2) after starting radiation therapy.
2. Weight (kg) will be collected weekly during radiation.

3. Documentation of ECOG performance status will be done on the first day of radiation therapy and on days 22 (+/- 2) and 36 (+/- 2) after starting radiation therapy.
4. Documentation of patient symptoms using NCI-CTCAE version 4.0 will be done on the first day of radiation therapy and on days 22 (+/- 2) and 36 (+/- 2) after starting radiation therapy.
5. CBC, BMP and magnesium on the first day of radiation therapy and on days 22 (+/- 2) and 36 (+/- 2) after starting radiation therapy.
6. Patient to complete QOL questionnaire prior to starting radiation (-7/+0) and during the fourth week of radiation (radiation doses 16-21), and 36 (+/- 2) days after starting radiation therapy.
7. OPTIONAL: Patient to receive speech and swallowing assessments prior to starting radiation* and during the fourth week of radiation (radiation doses 16-21) and 36 days after starting radiation therapy. *Modified barium swallow not needed within one week prior to starting radiation.

5.4.3 ARM 3 ONLY – Thirty doses of RT (+ 3 doses of Cisplatin if positive margins or ECE)

If the patient has positive margins or ECE, they will receive Cisplatin with the 30 doses of RT. The first dose of cisplatin will be given on one of the days during the initial 5 days of POART, the second cisplatin dose on the day of radiation dose 16 (+/- 5 days), and the third cisplatin dose on the day of radiation dose 26 (+/- 5 days).

Recommended procedures for Arm 3 are as follows:

1. Physical examination will be performed on each day of cisplatin administration (radiation dose 1, 16 (+/- 5) and 26 (+/- 5)).
2. Documentation of ECOG performance status will be done on each day of cisplatin administration (radiation dose 1, 16 (+/- 5) and 26 (+/- 5)).
3. Documentation of patient symptoms using NCI-CTCAE version 4.0 will be done on each day of cisplatin administration (radiation dose 1, 16 (+/- 5) and 26 (+/- 5)).
4. Patient to complete QOL questionnaire prior (-7/+0) to starting radiation, during the fourth week of radiation (radiation doses 16-20) and during the last week of radiation (radiation doses 26-30).
5. OPTIONAL: Patient to receive speech and swallowing assessment prior (within one week) to starting radiation*, during the fourth week of radiation (radiation doses 16-20) and during the last week of radiation (radiation doses 26-30). *Modified barium swallow not needed within one week prior to starting radiation.

Recommended procedures for cisplatin therapy (on Arm 3) are as follows:

1. Antiemetics premedication prior to each dose of cisplatin: palonosetron

0.25 mg IVPB, dexamethasone 10 mg IVPB and aprepitant 150 mg IVPB.
2. Hydration consisting of 1L IVF NS (10 meq KCL/L + 8 meq $MgSO_4$/L) over 60 minutes before and after cisplatin on the day of dosing. 2L IVF NS over 60 minutes on each of the two days following cisplatin dosing.
3. Administration of cisplatin (100 mg/m^2 IVPB over 60 minutes) on days 1, 22 (+/- 5), and 36 (+/- 5).
4. Weight (kg) will be collected weekly during radiation.
5. CBC, BMP and magnesium on each day of cisplatin administration (radiation dose 1, 16 (+/- 5) and 26 (+/- 5)).

5.5 POART

It is recommended that radiation therapy begin within 28 to 49 days (and no later than 56 days) after the surgical resection. Intensity modulated radiation therapy (IMRT) or intensity modulated proton therapy (IMPT) is to be used exclusively for this study. IMRT or IMPT will be delivered once per day Monday through Friday per routine clinical practice in Arm 3. In Arms 1 and 2, one BID treatment will be given during the course of therapy. If patient logistics prohibit the one BID treatment, once daily treatments throughout will be acceptable. The total dose to the postoperative tumor bed will be:

- Arm 1: 4200 cGy in 21 fractions of 200 cGy each over 4 weeks
- Arm 2: 4200 cGy in 21 fractions of 200 cGy each over 4 weeks
- Arm 3: 6000 cGY in 30 fractions of 200 cGy each over 6 weeks

Additional regions in the ipsilateral and contralateral neck at risk for microscopic disease in the cervical lymph nodes will receive:

- Arm 1: 3780 cGy in 21 fractions of 180 cGy each
- Arm 2: 3780 cGy in 21 fractions of 180 cGy each
- Arm 3: 5200 cGy in 30 fractions of 173 cGy each

5.5.1 CT Simulation

As per routine practice, computed tomography (CT) will be the primary image platform for targeting and treatment planning. Prior to the scan, the patient will be given IV contrast according to institutional protocols (provided the patient has normal renal function and no allergies to contrast). The patient will be positioned supine on the CT simulator table (head toward the gantry). The head will be placed on standard or customized headrest so as to have the neck slightly extended. Alternatively, a custom head/shoulder mold may be used for immobilization. An immobilization mask will then be fashioned. A CT dataset will be acquired from the top of the head through 5 cm below the clavicular heads with no more than 5 mm axial slices. Three localization marks will be drawn and wired on the patient's immobilization mask at the angle of the mandible bilaterally and midline. These marks will serve to establish an internal reference from which an isocenter is placed

midline, midplane, at the level of the angle of the mandible.

5.5.2 Virtual Simulation and Contouring

The CT scan will be exported to a commercially available virtual simulation software package. Guidelines for delineating each lymph node level will be based on the international consensus for delineation of head and neck lymph nodes (http://www.rtog.org/hnatlas/main.html). These guidelines were derived in part from Washington University School of Medicine institutional data and are consistent with routine clinical practice at Washington University.

Arms 1 and 2: An example case of a T3N2BM0 (AJCC 7th edition), stage IVA tonsil cancer is outlined in the table below. Current treatment guidelines for this case including dose levels are represented with CTV1 and CTV2.

CTV1	CTV2
[GTVp + GTVn] + 1.0 to 1.5 cm minimum concentric margin excluding bone and air with aid of preop imaging with/without fusion	IN (II-V) + BRPLN + CN (IIb-IV) Exclusive of CTV1.
Dose 42 Gy/21 fx	Dose 37.8 Gy/21 fx

Key: GTVp = GTV primary tumor; GTVn = GTV nodal tumor; IN = ipsilateral neck; CN = contralateral neck; roman numbers relate to the level system of naming lymph node regions; BRPLN = bilateral retropharyngeal lymph nodes).

Arm 3: An example case of a T4N2M0 (AJCC 7th edition), stage IVA tonsil cancer is outlined in the table below. Current treatment guidelines for this case including dose levels are represented with CTV1 and CTV2.

CTV1	CTV2
[GTVp + GTVn] + 1.0 to 1.5 cm minimum concentric margin excluding bone and air with aid of preop imaging with/without fusion	IN (II-V) + BRPLN + CN (IIb-IV) Exclusive of CTV1.
Dose 60 Gy/30 fx	Dose 52 Gy/30 fx

Key: GTVp = GTV primary tumor; GTVn = GTV nodal tumor; IN = ipsilateral neck; CN = contralateral neck; roman numbers relate to the level system of naming lymph node regions; BRPLN = bilateral retropharyngeal lymph nodes).

Normal structure and treatment volume contours will be delineated in a manner consistent with routine clinical practice.

5.5.3 IMRT and/or IMPT Optimization

The image and contour data will be exported to the Varian Eclipse platform where IMRT or IMPT optimization will be performed.

5.5.4 Treatment Field Arrangement

The Varian System employs up to ten co-planar fields with static or dynamic multileaf collimation. The treatment planning system calculates the optimized collimator leaf delivery pattern that most closely approximates the prescribed constraints and prescription goals.

5.5.5 Dose, Energy and Prescription Parameters

Arms 1 and 2: External beam radiation with 6 MV photons will be delivered in 200 cGy daily fractions (Monday through Friday), 21 fractions over 4 weeks to a total dose of 4200 cGy.

Prescription Coverage Goals
99% of clinical treatment volumes should receive at least 95% of the respective prescription dose (i.e. 99% of PTV 4200 should be covered by 3990 cGy and 99% of PTV 3780 covered by 3591 cGy).

No more than 5% of the volume “Skin” should receive more than the prescription dose (42 Gy) and hotspots must be within the PTV.

Arm 3: External beam radiation with 6 MV photons will be delivered in 200 cGy daily fractions (Monday through Friday), 30 fractions over 6 weeks to a total dose of 6000 cGy.

Prescription Coverage Goals
99% of clinical treatment volumes should receive at least 93% of the respective prescription dose (i.e. 99% of PTV 6000 should be covered by 5700 cGy, and 99% of PTV 5200 covered by 4940 cGy).

No more than 5% of the volume “Skin” should receive more than the prescription dose (60 Gy) and hotspots must be within the PTV.

5.5.6 Normal Structure Dose Limit Guidelines

Arms 1 and 2: Dose limit guidelines for normal structures are as follows:

Structure	Volume	Dose Guideline (Gy)	Dose Mean (Gy)
Critical Structures			
Spinal Cord + 8 mm	1 cc	42	
Spinal Cord	0.1 cc	40	

Brainstem	1%	40	
	0.1 cc	40	
Brain	1%	40	
	5 cc	45	
Optic nerve*	1%	40	
	0.1 cc	42	
Optic chiasm	1%	40	
	0.1 cc	42	
Eye*			45
Normal Structures			
Retina*	1%	40	25
Lens*			2
Oral cavity			35
Larynx			42
Mandible	5%	45	
Skin	5%	45	
Partial esoph	2 cc	40	
Middle Ear*			45
Parotid glands*	20 cc	20	26

*Paired structures. Dose constraints apply to one such structure and are equivalent for the contralateral side.

Priority for Above Dose Constraints

1. Critical Structures
2. PTV Prescription Goals
3. Salivary Glands
4. Other Structures

Arm 3: Dose limit guidelines for normal structures are as follows:

Structure	**Volume**	**Dose Guideline (Gy)**	**Dose Mean (Gy)**
Critical Structures			
Spinal Cord + 8 mm	1 cc	50	
Spinal Cord	0.1 cc	45	
Brainstem	1%	60	
	0.1 cc	60	
Brain	1%	60	
	5 cc	65	
Optic nerve*	1%	60	
	0.1 cc	60	
Optic chiasm	1%	60	
	0.1 cc	60	
Eye*			45
Normal Structures			
Retina*	1%	50	35
Lens*			2
Oral cavity			35

Larynx			45
Mandible	5%	73.5	
Skin	5%	70	
Partial esoph	2 cc	54	
Middle Ear*			45
Parotid glands*	20 cc	20	26

*Paired structures. Dose constraints apply to one such structure and are equivalent for the contralateral side.

Priority for Above Dose Constraints

1. Critical Structures
2. PTV Prescription Goals
3. Salivary Glands
4. Other Structures

5.5.7 Treatment Plan Evaluation

The plan will be reviewed by the treating physician prior to treatment in order to ensure that all parameters have been met. Isodose curves and dose volume histograms (DVH) will be analyzed.

Arms 1 and 2: Criteria for plan evaluation will include:

- Isodose Curves:
  The 95% isodose line must be generally conformal to the PTV with visually acceptable tumor coverage and visually acceptable critical structure avoidance.
  The 110% isodose line must not include any critical structure volumes.
  The 4200 cGy isodose line must not encroach on the “Spinal cord + 5 mm”.
  The 2600 cGy isodose line should spare parotid glands when possible.

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

Arm 3: Criteria for plan evaluation will include:

- Isodose Curves:
  The 95% isodose line must be generally conformal to the PTV with visually acceptable tumor coverage and visually acceptable critical structure avoidance.
  The 110% isodose line must not include any critical structure volumes.

The 4200 cGy isodose line must not encroach on the “Spinal cord + 5 mm”.
The 2600 cGy isodose line should spare parotid glands when possible.

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

5.5.8 Daily Radiation Treatment

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

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

5.5.9 Quality Assurance

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

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

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

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

5.6 Follow-Up Assessments after Adjuvant Therapy

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

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

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

5.6.1 Six Week (+/- 1 week) Assessment

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

5.6.2 Four Month (+/- 2 weeks) Assessment

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

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

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

5.6.4 Annual Assessments Subsequently

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

5.7 Evaluations for Toxicity and Disease Relapse

All patients who receive any study treatment (starting point of "study treatment" is first dose of post-operative RT) are evaluable for toxicity. Patients are evaluated from first day of study treatment until five years after the conclusion of treatment, or death.

All patients who undergo surgery are evaluable for disease relapse.

5.8 General Concomitant Medication and Supportive Care Guidelines

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

5.9 Women of Childbearing Potential

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

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

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

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

5.10 Duration of Therapy

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

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

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

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

6.0 PHARMACEUTICAL INFORMATION

6.1 Cisplatin (CDDP, Platinol-AQ®)

6.1.1 Cisplatin Description

Molecular formula: PtCl2H6N2
Molecular weight: 300.1.

6.1.2 Clinical Pharmacology

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

6.1.3 Supplier

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

6.1.4 Dosage Form and Preparation

The stability of cisplatin in solution is dependent upon the chloride ion concentration present in the diluent. Cisplatin should be diluted into an IV solution containing NaCL at a minimum chloride ion concentration of 0.040

mol/L (0.2% NaCL). Needles, syringes, catheters and IV administrations sets containing aluminum must be avoided during preparation and administration due to cisplatin-aluminum reaction causing precipitation and loss of potency. Mannitol 12.5 to 25 gm may be added per institutional guidelines.

6.1.5 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. Do not refrigerate. Cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

6.1.6 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. It is recommended that all patients should be premedicated with antiemetics.

7.0 DOSE MODIFICATIONS

At each of the scheduled visits noted in the study calendar, an assessment of adverse events (AEs) will be made by the treating physician with toxicity grading using the NCI CTCAE version 4. Patients without AEs will continue on study treatment as planned. Patients who develop grade 1-2 or selected grade 3 (nausea/vomiting/fatigue) AEs will be supported symptomatically and encouraged to continue on study treatment as planned. Modifications in their therapy may be necessary and will be detailed below. Management of specific AEs is noted below.

7.1 Cisplatin Dose Modifications (Arm 3 only)

7.1.1 Ototoxicity

Grade 3-4 hearing loss/tinnitus is an indication to consider discontinuation of the drug.

7.1.2 Kidney Impairment

Calculated Creatinine Clearance	**Percent Dose to Give**
≥ 50 mL/min	100%

< 50 mL/min	0% (withhold treatment for this dose and repeat serum creatinine weekly after additional hydration), then for next chemotherapy dose:	
	If CrCl was already < 50 mL/min and is now:	**The percent dose to give is:**
	> 40 but < 50	50%
	< 40	0%

Please note that dose reduction percentage is calculated by taking off from the original dose and not the previous dose.

7.1.3 Neutropenia/Thrombocytopenia

Nadir of last course	**ANC/Platelets (Day 1 of each cycle)**		
	ANC < 500 Plts < 60,000	ANC 500-749 Plts 60,000-99,000	ANC ≥ 750 Plts ≥ 99,000
ANC > 500 Plts > 30,000	Hold cisplatin	50% cisplatin	100% cisplatin
ANC < 500 Plts < 30,000	Hold cisplatin	Hold cisplatin	50% cisplatin

7.1.4 Other Grade 2-4 Non-Hematologic AEs

At the discretion of the treating physician, clinical judgement may be used to hold doses of cisplatin if current or interim toxicities are felt to significantly increase the risk of serious toxicity with administration of that dose of cisplatin.

7.2 Radiation Dose Modifications

There are no planned dose modifications or delays for radiation therapy. Delays are allowed at the discretion of the treating physician.

8.0 CORRELATIVE STUDIES

8.1 Tumor Acquisition Protocol

All patients will be strongly encouraged to participate on this companion protocol (HRPO #201102323) for future correlative studies. Tumor samples will be collected in the operating room by trained research personnel, processed and stored according to established protocols.

Correlative studies may be conducted to further determine potential molecular markers of risk in HPV-positive oropharyngeal cancer. These studies may include DNA sequencing for mutational analysis and copy number variations. HPV viral load and integration versus episomal status may also be assessed.

Additionally, gene expression studies, including expression of viral genes, may be conducted on all samples and correlated with other tumor characteristics and outcomes. Future studies may also include the creation of PDX models as well as immunohistochemistry.

8.2 Quality of Life Assessments

QOL will be assessed using the FACT-H&N (Appendix 3), MD Anderson Dysphagia Inventory (Appendix 4), University of Michigan Xerostomia Index (Appendix 5), Scale of Subjective Total Taste Acuity (Appendix 6), and Neck Dissection Impairment Index (Appendix 7) at the following time points:

- Baseline (before the start of any treatment)
- Interim assessment (14-42 days post-surgery)
- Day 1 of radiation (-7/+0 days)
- Day 22 after the start of radiation (Arm 1 & 2 +/- 2 days; Arm 3 +/- 5 days)
- Day 36 after the start of radiation (Arm 1 & 2 +/- 2 days; Arm 3 +/- 5 days)
- 6 weeks after the completion of adjuvant therapy (+/- 1 week)
- 4 months after the completion of adjuvant therapy (+/- 2 weeks)
- 6 months after the completion of adjuvant therapy (+/- 6 weeks)
- 12 months after the completion of adjuvant therapy (+/- 6 weeks)
- 24 months after the completion of adjuvant therapy (+/- 6 weeks)

9.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 9.2.

9.1 Definitions

9.1.1 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 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

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

9.1.2 Serious Adverse Event (SAE)

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

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

9.1.3 Unexpected Adverse Experience

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

9.1.4 Life-Threatening Adverse Experience

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

9.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.6 Noncompliance

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

9.1.7 Serious Noncompliance

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

9.1.8 Protocol Exceptions

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

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

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

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

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

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

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

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

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

9.4 Timeframe for Reporting Required Events

Adverse events will be tracked through the 6 weeks post-end of adjuvant therapy visit. For the purposes of this protocol, adverse events related to the standard of care surgery will not be collected and documented on CRFs.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design

This is a three-arm non-randomized Phase II trial. All the enrolled patients will undergo resection of the primary tumor site and involved/at risk regional neck nodes. Patients will be assigned to one of three adjuvant treatments based on the clinical and pathologic staging and the details of the pathology report. 90%, 5%, and 5% of the patients are expected to be in Arm 1, 2, and 3, respectively. The overarching goal is to reduce treatment-related toxicity while maintaining efficacy. Weight loss is a reliable, easily measured and practical surrogate marker of mucosal toxicity. Therefore, the primary objective is to determine the percent weight loss of patients during POAmCRT in Arm 1. The secondary objectives are to evaluate the proportion of PEG tube placements, determine the serum creatinine changes in patients receiving POAmCRT, evaluate the narcotics administration of patients 6 weeks after POAmCRT, document the measures of Quality of Life (QOL) at baseline/during treatment/one year after completion of treatment on all arms, determine the disease recurrence free survival (RFS) at 24 months post-treatment in each arm, and determine progression free survival (PFS) and overall survival (OS).

10.2 Sample Size Calculation

The primary endpoint is percent weight loss from Day 1 of treatment to last day of RT. The sample size calculation is based on the primary endpoint only. Our historical data showed that the mean and standard deviation of percent weight loss during POACRT in patients with HPV-related OPSCC are 7.39% and 5.46%, respectively. The primary hypothesis of this trial is that the percent weight loss of patients in Arm 1 during POAmCRT will be 3.7% (50% reduction). Twenty patients

will have 80% power to detect the percent weight loss difference if assuming the standard deviation of 5.46% using a two-sided one-group t test at the type I error of 5%. We will enroll 24 patients in Arm 1 accounting for 15% drop-out[22]. We estimate that 14 patients will be enrolled in Arm 2 and 6 patients will be enrolled in Arm 3 for a total of 40 patients.

In December 2019, we reached the 40 patient enrollment mark. However, Arm 1 had enrolled only 13 of the target of 20 patients at that time. In June 2020, we plan to increase enrollment to reach 7 additional patients on Arm 1, or 20 additional patients onto any arm, whichever comes first.

10.3 Accrual

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

10.4 Statistical Analyses

10.4.1 Patient Disposition

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

10.4.2 Protocol Deviations

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

10.4.3 Demographics and Baseline Characteristics

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

10.4.4 Endpoint Analysis

The primary endpoint is percent weight loss. Weight (kg) will be collected weekly during radiation within each arm. The percent weight loss from the baseline is calculated at any post-baseline. The generalized estimating equation (GEE) model with identity link function will be used to analyze this percent weight loss data, in which the correlation among the repeated measures from the same patient need be considered. The autoregressive

of first order as working correlation structure will be used. The GEE model includes baseline weight and time points. The p-value is estimated to assess whether the percentages of weight loss across all time points are different. Least square means for percent weight loss at each time point and mean differences between any time points will be estimated, and their standard errors will be calculated within the use of GEE sandwich method when accounting for within-patient correlation.

The secondary endpoints include proportion of PEG tube placements for all enrolled patients, the serum creatinine changes in patients receiving POAmCRT, proportion of the narcotics administration of patients 6 weeks after POAmCRT,and RFS. Proportions of PEG tube placements for all enrolled patients and the narcotics administration of patients 6 weeks after POAmCRT and their associated 95% confidence intervals will be calculated assuming a binomial distribution[23]. The serum creatinine is measured at the baseline and six weeks after POAmCRT. The paired t-test will be considered to test the change.

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

PFS will be calculated from the date of surgery to the date of progression, death of any cause, or last known date alive. OS will be calculated from the date of surgery to the date of death or last known date alive. PFS and OS will be evaluated using Kaplan Myer.

The exploratory endpoint includes the measures of Quality of Life (QOL). QOL are measured at baseline/during treatment/one year after completion of treatment on all arms. Similarly, the GEE model will be used to analyze the longitudinal QOL data.

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

11.0 DATA SUBMISSION SCHEDULE

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

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Surgery Form	Time of surgery
QOLs Forms	Baseline Interim assessment Day 1 of RT (-7/+0) Day 22 after start of RT (Arm 1 & 2 +/- 2 days; Arm 3 +/- 5 days) Day 36 after start of RT (Arm 1 & 2 +/- 2 days; Arm 3 +/- 5 days) 6 weeks after completion of adjuvant therapy 4 months after completion of adjuvant therapy 6 months after completion of adjuvant therapy 12 months after completion of adjuvant therapy 24 months after completion of adjuvant therapy
Toxicity Form	Continuous
Weight Form	Baseline, weekly during treatment, and at each follow-up visit
Treatment Summary Form	Completion of treatment
Follow Up Form Narcotics Form PEG Form	6 weeks, 4 months, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, and 48 months after the completion of adjuvant therapy
RECIST Form	Baseline, 6 weeks after completion of adjuvant therapy, and 6 months after completion of adjuvant therapy

12.0 DATA AND SAFETY MONITORING

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

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

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual

- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

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.

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14.0 STUDY CALENDARS

14.1 Baseline and Treatment Calendar

	Baseline[4]	Surgery	Interim Assessment (14 to 42 days post-surgery)	Post-operative Adjuvant Chemotherapy/Radiation		
				D1	D22[12]	D36[12]
Informed consent	X					
Laryngoscopy[1]	X					
PE w/ECOG PS	X		X	X	X	X
Weight	X			X[8]----------X[8]		
Comorbidity index	X		X			
CBC	X		X	X	X	X
CMP + magnesium	X					
BMP + magnesium			X	X	X	X
PT/PTT	X		X			
Pregnancy test[2]	X					
Neck CT w/contrast	X					
FDG-PET/CT	X					
QOLs[3]	X		X	X[13]	X	X
OPTIONAL: Speech & Swallow Study[10]	X		X	X[11]	X	X[9]
Surgery[5]		X[5]				
Rad Tx Planning			X			
IMRT or IMPT[6]				X----------X[9]		
Arms 1 & 3: Cisplatin[7]				X[7]	X[9]	X[9]
AE assessment	X		X	X	X	X
Documentation of narcotic usage				X	X	X

1. Assessment of primary tumor site will be done by laryngoscopy performed in the office or operating room.
2. In women of childbearing potential only.
3. FACT H&N, M.D. Anderson Dysphagia Inventory, University of Michigan Xerostomia Index, Scale of Subjective Total Taste Acuity, and Neck Dissection Impairment Index.
4. Baseline assessments must take place no more than 35 days prior to enrollment, with the exception of PET scans (within 42 days).
5. See Section 5.2.
6. Arms 1 and 2: Once daily M-F, with one BID treatment each week for 4200 cGy in 21 fractions. Arm 3: Once daily M-F for 6000 cGy in 30 fractions
7. To be given during initial 5 doses of POART. See Section 5.4.1 for fluids and premedications. On Arm 3, cisplatin will only be given to patients with pathologic evidence of positive margins or ECE (see section 1.9).

8. Collect weight weekly during Radiation.
9. Arm 3 only.
10. Modified barium swallow and the Performance Status Scale for Head and Neck Cancer (PSS-HN) questionnaire.
11. Modified barium swallow NOT needed on this day.
12. Arm 1 & 2 +/- 2 days; Arm 3 +/- 5 days
13. -7/+0 days

14.2 Follow-up Calendar

	Short Term Follow-up		Long-Term Follow-Up							
			Months post-end of CRT[3]							
	6 weeks post-end of tx (+/- 1 week)	4 months post end of tx (+/- 2 weeks)	6	12	18	24	30	36	48	Annually Thereafter5
PE w/ECOG PS + Weight	X	X	X	X	X	X	X	X	X	X
BMP	X									
Neck CT w/contrast	X		X	X	X	X		X		
Chest CT w/contrast[2]			X	X	X	X		X		
QOLs	X	X	X	X		X				
OPTIONAL: Speech & Swallow Assessment	X	X	X	X[4]		X[4]				
Documentation of narcotic usage	X	X	X	X	X	X	X	X	X	
Documentation of PEG tube usage	X	X	X	X	X	X	X	X	X	
AE assessment	X									

1. FACT H&N, M.D. Anderson Dysphagia Inventory, University of Michigan Xerostomia Index, Scale of Subjective Total Taste Acuity, and Neck Dissection Impairment Index.
2. Chest x-ray (PA and Lateral) may be substituted for chest CT if it is unable to be obtained (i.e. insurance issues)
3. +/- 6 week window
4. Modified barium swallow not required
5. For 5 years (total of 10 years of follow-up)

APPENDIX 1: ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX 2: Comorbidity Index

http://otooutcomes.wustl.edu/Research/Research-Focus/Cancer/Comorbidity-Calculator

If a patient has Grade 2 events in more than one system, their overall score will be Grade 3

APPENDIX 3: FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

APPENDIX 4: M.D. Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of these statements may apply to you.

Please read each statement and mark the response which best reflects your experience IN THE PAST WEEK.

	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
My swallowing ability limits my day to day activities.	O	O	O	O	O
I am embarrassed by my eating habits.	O	O	O	O	O
People have difficulty cooking for me.	O	O	O	O	O
Swallowing is more difficult at the end of the day.	O	O	O	O	O
I do not feel self-conscious when I eat.	O	O	O	O	O
I am upset by my swallowing problem.	O	O	O	O	O
Swallowing takes great effort.	O	O	O	O	O
I do not go out because of my swallowing problem.	O	O	O	O	O
My swallowing difficulty has caused me to lose income.	O	O	O	O	O
It takes me longer to eat because of my swallowing problem.	O	O	O	O	O
People ask me, “Why can’t you eat that?”	O	O	O	O	O
Other people are irritated by my eating problem.	O	O	O	O	O
I cough when I try to drink liquids.	O	O	O	O	O
My swallowing problems limit my social and personal life.	O	O	O	O	O
I feel free to go out to eat with my friends, neighbors, and relatives.	O	O	O	O	O
I limit my food intake because of my swallowing difficulty.	O	O	O	O	O
I cannot maintain my weight because of my swallowing problem.	O	O	O	O	O
I have low self-esteem because of my swallowing problem.	O	O	O	O	O
I feel that I am swallowing a huge amount of food.	O	O	O	O	O
I feel excluded because of my eating habits.	O	O	O	O	O

APPENDIX 5: University of Michigan Xerostomia Index

Please mark the appropriate answer.

1. Rate your difficulty in talking due to dryness

0	1	2	3	4	5	6	7	8	9	10
NO Dry Mouth										Extreme Dry Mouth

2. Rate your difficulty in chewing due to dryness

0	1	2	3	4	5	6	7	8	9	10
NO Dry Mouth										Extreme Dry Mouth

3. Rate your difficulty in swallowing solid food due to dryness

0	1	2	3	4	5	6	7	8	9	10
NO Dry Mouth										Extreme Dry Mouth

4. Rate the frequency of your sleeping problems due to dryness

0	1	2	3	4	5	6	7	8	9	10
NO Dry Mouth										Extreme Dry Mouth

5. Rate your mouth or throat dryness when eating food

0	1	2	3	4	5	6	7	8	9	10
NO Dry Mouth										Extreme Dry Mouth

6. Rate your mouth or throat dryness while not eating

0	1	2	3	4	5	6	7	8	9	10
NO Dry Mouth										Extreme Dry Mouth

7. Rate the frequency of sipping liquids to aid swallowing food

0	1	2	3	4	5	6	7	8	9	10
NO Dry Mouth										Extreme Dry Mouth

8. Rate the frequency of sipping liquids for oral comfort when not eating

0	1	2	3	4	5	6	7	8	9	10
NO Dry Mouth										Extreme Dry Mouth

APPENDIX 6: Scale of Subjective Total Taste Acuity

Please circle the appropriate answer **(Only ONE answer).**

Symptom	Grade
Same taste acuity as before treatment	0
Mild loss of taste acuity, but not inconvenient in daily life	1
Moderate loss of taste acuity, and sometimes inconvenient in daily life	2
Severe loss of taste acuity, and frequently inconvenient in daily life	3
Almost complete or complete loss of taste acuity	4

APPENDIX 7: Neck Dissection Impairment Index

As a result of the cancer **TREATMENT OF YOUR NECK**, how much have you been bothered by the following over the past **4 WEEKS**? **Please mark the appropriate answer.**

	Not At All	A Little Bit	A Moderate Amount	Quite A Bit	A Lot
1. Are you bothered by neck or shoulder pain or discomfort?					
2. Are you bothered by neck or shoulder stiffness?					
3. Are you bothered by difficulty with self-care activities because of you neck or shoulder (for example, combing hair, dressing, bathing, etc?)					
4. Have you been limited in your ability to lift light objects because of your shoulder or neck?					
5. Have you been limited in your ability to lift heavy objects because of your shoulder or neck?					
6. Have you been limited in your ability to reach above for objects because of your shoulder or neck (for example, from shelves, tables or counters)? 7. Are you bothered by your overall activity level because of your shoulder or neck?					
8. Has the treatment of your neck affected your participation in social activities?					
9. Have you been limited in your ability to do leisure or recreational activities because of your neck or shoulder?					
10. Have you been limited in your ability to do work (including work at home) because of neck or shoulder discomfort or pain?					

APPENDIX 8: Performance Status Scale for Head & Neck Cancer Patients – PSS-HN

NORMALCY OF DIET /__/__/__/

100	Full diet (no restrictions)
90	Full diet (liquid assist)
80	All meat
70	Raw carrots, celery
60	Dry bread and crackers
50	Soft chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)
40	Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)
30	Pureed foods (in blender)
20	Warm liquids
10	Cold liquids
0	Non-oral feeding (tube fed)

PUBLIC EATING /__/__/__/

100	No restriction of place, food or companion (eats out at any opportunity)
75	No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods (e.g., liquids)
50	Eats only in presence of selected persons in selected places
25	Eats only at home in presence of selected persons
0	Always eats alone
999	Inpatient

UNDERSTANDABILITY OF SPEECH /__/__/__/

100	Always understandable
75	Understandable most of the time; occasional repetition necessary
50	Usually understandable; face-to-face contact necessary
25	Difficult to understand
0	Never understandable; may use written communication

List MA, Ritter-Sterr C, Lansky SB. A Performance Status Scale for Head and Neck Cancer Patients. Cancer. 66:564-569, 1990