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Reshaping the future of patient care

E3311

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

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Addendum #4 – 2/15
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Addendum #7 – 9/16
Addendum #8
Addendum #9

Agents	NSC#	Supply
Cisplatin	NSC# 119875	Commercial
Carboplatin	NSC# 241240	Commercial

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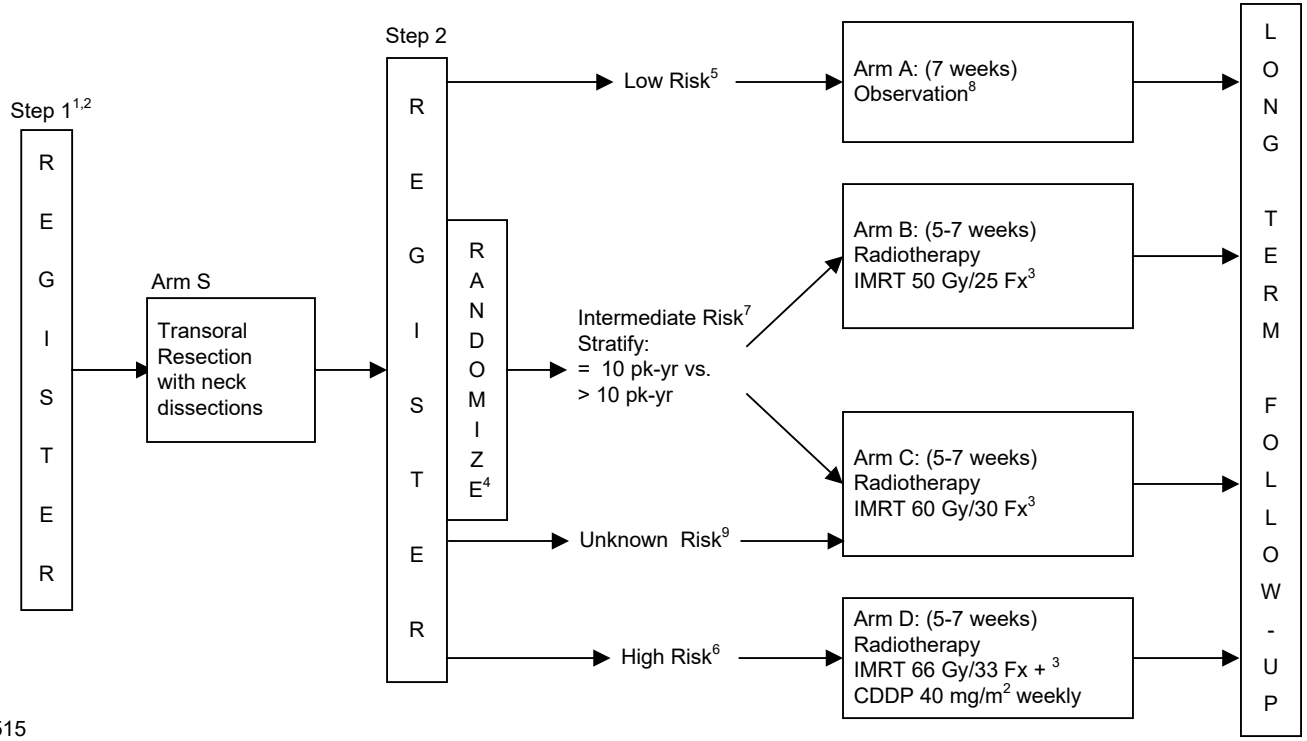
Rev. Add8

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Schema

Rev. 6/14, 2/15, 1/16



Accrual: 515

1. Resectable oropharynx carcinoma, p16$^+$ by IHC, PS 0-1
2. Credentialing of surgeon required as part of site participation, neck levels dissected and nodal yield (> nodes/neck)
3. Radiotherapy will be given with an intensity modulated radiotherapy (IMRT) technique. Standard ECOG credentialing through QARC will be required.
4. Stratify by current/former smoking history(≤ 10pk-yr vs. > 10pk-yr)
5. Low Risk: T1-T2, N0-N1 AND clear (≥ 3mm) margins, AND no ECE or PNI/LVI.
6. High Risk: Any of the following features: one or more positive margin(s) with any T stage, OR “Extensive” (> 1mm) ECE, OR ≥ 5 metastatic lymph nodes (regardless of primary tumor margin status).
7. Intermediate Risk: Any of the following features: one or more "close" (< 3mm) margin(s), OR "Minimal" (≤ 1mm) ECE, OR N2a (1 or more lymph node >3cm in diameter), OR N2b (2-4 lymph nodes positive, any diameter ≤ 6cm), OR with perineural invasion or lymphovascular invasion.
8. If = 2 events are observed among the first ten patients registered on Arm A within one year, currently enrolled and subsequently enrolled low risk patients who have not progressed will be treated with IMRT 50 Gy
9. Patients found to have N2c (bilateral nodes), OR N3 (>6cm node) disease on final pathologic analysis.

1. Introduction

1.1 Study Disease

Head and neck cancer remains a significant cause of morbidity worldwide, with approximately 400,000 new cases per year. Squamous cell carcinoma is the most common histological type, accounting for >90% of head and neck tumors. At presentation, more than half of patients present with advanced locoregional disease[1].

Ongoing advances in multidisciplinary management of this complex and multi-varied disease process are resulting in improved function, organ preservation, quality of life and survival.

Major developments include primary chemoradiotherapy (CRT) for unresectable disease with the goal of organ preservation, the addition of chemotherapy (CT) to adjuvant radiotherapy (RT) and improvement in surgical and radiation techniques[2]. A consistent result of these aggressive multi-modality approaches is improvement in local-regional control but the impact on the development of metastases is variable. Despite these advances, 50% of all patients recur either locally or at distant sites (30%)[2]. A minority of patients will undergo successful surgical salvage of recurrent disease. While single institution series evaluating intensified CRT regimens suggest a shift in failure pattern to distant metastases, better control of local disease remains paramount to improve survival of patients with HNSCC [2].

1.2 HPV Positive Oropharynx Tumors

Approximately 95% of head and neck cancers are of squamous cell histologic origin, and arise from the lip/oral cavity, nasopharynx, oropharynx, hypopharynx, and/or the larynx. Among these sub-sites, the incidence of base of tongue and tonsillar carcinomas has been increasing over the past decade, especially in individuals under the age of 45 [3] .This change has been attributed to the increasing prevalence of human papillomavirus (HPV) infection in developed countries, the practice of oral sex and increasing number of sexual partners[3]. Interestingly, patients with HPV-positive SCC have shown better overall survival and higher cure rates as compared to those with HPV-negative SCC[4]. HPV is now recognized to play a role in the pathogenesis of head and neck squamous cell carcinoma (HNSCC*)* [5]. Both molecular and epidemiologic studies demonstrate that approximately 60% of oropharynx cancers, specifically of the lingual and palatine tonsils, are HPV associated[5].

High-risk HPV genotypes (i.e. 16, 18, and 31) are known to be tumorigenic in human epithelial tissues. The E6 and E7 viral oncoproteins of high-risk HPV promote tumor progression by inactivating the *TP53* and *Rb* tumor suppressor gene products, respectively[6]. These tumors appear to be clinically and molecularly distinct from HPV-negative tumors. HPV-positive tumors are more likely to arise from the oropharynx, exhibit poor differentiation and basaloid morphologic features, and present at a lower T stage than HPV-negative primaries[5-9].

Recently, HPV-associated head and neck carcinoma, largely presenting in the oropharynx, has been identified and appears to be rapidly increasing in

incidence[8, 10]. In the US, some two-thirds of patients with OPSCC have HPV-associated tumors. Hence, in 2010 approximately 4200 squamous cancers of the oropharynx caused by tobacco and alcohol and 8400 new HPV-associated oropharynx cancer presented for treatment. HPV-associated OPSCC typically present as smaller primary tumors than those caused by substance abuse. Because HPV-associated OPSCC more frequently present in a younger population and seem particularly responsive to treatment with a better overall survival[11], attention has begun to focus reduction of treatment toxicity. In particular, attention has focused on the development of late effects from CRT (CRT) as the number of survivors have increased. While the organ-preservation CRT approach has become a standard of care[12, 13], there remain serious concerns about both short and long-term toxicity. Furthermore, the changing epidemiology of HPV-associated OPSCC has caused many to re-think this approach. Given the potential long-term sequelae of radiation therapy for a younger population, [14] an alternative treatment paradigm is needed. The clearly better prognosis of this group of patients supports re-evaluation of adjuvant treatment intensity, and in particular the prognostic and predictive role of traditional pathologic biomarkers obtained at surgery.

Results from ECOG 2399 using induction chemotherapy with carboplatin and paclitaxel followed by CRT with taxol/70Gy showed that HPV-positivity in oropharyngeal cancer patients was associated with a significantly improved overall response to 2 cycles of paclitaxel/carboplatin induction chemotherapy (82% vs. 55%, p=0.01), as well as 2-yr PFS (85% vs. 50%, p=0.05) and overall survival (94% vs. 58%p=0.004) following weekly paclitaxel/RT [16] . Although acute toxicity was acceptable with this regimen, a substantial number of OP patients have long-term consequences following CRT. In E2399, 49% of OP patients had moderate to severe swallowing impairment 3 months following treatment, and 3% were still PEG dependent after 12 months. These results have generated interest in less toxic regimens for HPV-positive patients who experience substantial treatment side effects with contemporary CRT regimens

1.3 Role of Surgery in Head and Neck Cancer

Background/Rationale:

Our central hypothesis is that transoral surgery (TOS) is feasible and effective in low- to intermediate-risk, HPV+ oropharyngeal squamous cell carcinoma (OPSCC) patients. We hypothesize that this permits pathologic-risk adjusted reduction in adjuvant therapy and radiotherapy treatment planning benefits, and may be associated with favorable functional and quality of life benefits without negatively impacting oncologic results. We will test this hypothesis in a randomized phase II design, to gather prospective data that will be essential to guide the design of a future, randomized phase III trial comparing the surgery/adjuvant therapy with standard non-surgical therapy.

The current standard of care for primary nonsurgical treatment of locally advanced HNSCC is concurrent platinum-based chemoradiotherapy (CRT), which has been shown to significantly improve overall survival (OS), progression-free survival (PFS), and/or locoreginal control compared with radiotherapy (RT) alone or the sequential administration of chemotherapy and RT[2]. In a meta-analysis of 63 trials with nearly 11,000 patients with HNSCC, the addition of chemotherapy to RT resulted in an absolute survival improvement of 6% at 5

years[15]. The results of this meta-analysis were confirmed in subsequent updated meta-analyses, the most recent of which included 93 randomized trials and 17,346 patients [16]. Cisplatin CRT (CRT) regimen is efficacious but also associated with significant toxicities and is suitable for patients with good performance status and without severe comorbidities [17]. In addition to the 3-weekly schedule, a variety of other cisplatin schedules of administration have been employed (e.g. weekly as proposed here)[18]. More recently, the combination of RT plus cetuximab, a monoclonal antibody against the epidermal growth factor receptor, was proved superior to RT alone in patients with oropharyngeal, laryngeal, and hypopharyngeal HNSCC [19, 20, 21]. The addition of cetuximab to RT was most effective in younger, good performance status, nonsmoking individuals, as tend to be present in $p16^+$ patients[22].

The last twenty years have seen many advances in the management of HNSCC. The recognition that, through combined modality therapy, many advanced cancers could be controlled without a highly morbid operation (and without compromising the chance for cure) led to the development of new treatment schedules and the incorporation of new agents in the therapeutic armamentarium. These approaches were largely predicated on the assumption that normal tissue preservation would equate to functional preservation most notably for swallow function. Unfortunately, organ preservation does not always equate to functional preservation. These apparent therapeutic gains have been accompanied by significant early and late toxicity due to CRT[23]. Chronic aspiration and dysphagia have been identified as important, but often underreported late toxicities of organ preservation regimens for HNSCC. Severe (grade 3-4) late laryngopharyngeal toxicity was reported in 43% of HNSCC survivors evaluated in a pooled analysis of 3 RTOG trials of concomitant CRT.

It is now clear that late swallowing injury is at least related to the dose of the radiotherapy and the use of concurrent chemotherapy. Both have been established as independent risk factors in several multivariate analyses[24-26]. Dose correlation studies suggest that the threshold upon which late injury to the swallowing muscles such as the constrictor muscles occur in the range of 55-60 Gy when a large volume of the muscles are exposed to these doses of radiation. In addition, recent data show that most patients who develop severe refractory dysphagia years after radiotherapy for HNSCC have been treated with doses of 70 Gy or more [27]. Hence, one strategy to reduce the risk of late swallowing injury would be to de-intensify the dose of radiation, particularly in patient populations with a favorable prognosis.

Initial hypotheses that these young patients, with fewer morbidities, would tolerate treatment better and have less quality of life (QOL) impairment have been refuted; in fact, evidence suggests a greater acute QOL disadvantage in this cohort[28, 29]. Thus, attention has focused on the development of late effects from CRT as the number of survivors have increased.

While the organ-preservation CRT approach has become a standard of care [12, 13], there remain serious concerns about toxicity, both short and long-term. Furthermore, the changing epidemiology of head and neck cancer has caused many to re-think this approach. Given the potential long-term sequelae of radiation therapy for a younger population[14], an alternative treatment paradigm must be found, particularly for patients with oropharyngeal SCC. A common transoral route of exposure, incorporating minimally invasive techniques with

transoral laser CO2 microsurgery (TLM) [30] and transoral robotic surgery (TORS) [31, 32] has emerged[33]

Role of transoral surgery (TOS) for OPSCC

As HPV-associated OPSCC more frequently present in a younger population and seem particularly responsive to treatment with a better overall survival[11], attention has begun to focus on the reduction of treatment toxicity. In particular, attention has focused on the development of late effects from CRT (CRT) as the number of survivors have increased. While the organ-preservation CRT approach has become a standard of care [12, 13], there remain serious concerns about toxicity, both short and long-term. Furthermore, the changing epidemiology of head and neck cancer has caused many to re-think this approach. Given the potential long-term sequelae of radiation therapy for a younger population,[14] an alternative treatment paradigm must be developed, especially for patients with OPSCC. A common transoral route of exposure, incorporating minimally invasive techniques with transoral CO2 laser microsurgery [30] (TLM) and transoral robotic surgery (TORS) [31, 32] has emerged.[33]

TOS dramatically limits the morbidity of surgical exposure and substantially reduces the acute and late effects of resection. It is important to recognize that the morbidity of past surgeries was a function of the injury that occurred with the required transcervical neck exposure. What is not clear is to what extent resection of important swallowing structures impact on this. The experience to date with TLM and TORS would suggest that resection can be safely performed for T1-2 oropharyngeal tumors without contributing to increased late swallowing complications as measured by dependence on percutaneous gastrostomy (PEG) tube. This is a particular attractive approach as HPV-associated OPSCC typically present as smaller primary tumors than those caused by substance abuse [34, 35].

TOS for OPSCC using traditional headlight visualization, C02 laser-based TLM and more recently, robotic-assisted surgery, has been practiced at an increasing number of North American institutions. Case series suggest that excellent long-term function may be anticipated after resection. Indications, contraindications, standards of practice and outcome reporting are being defined. Surgical resection of OPSCC can be a curative single modality for appropriately selected Stage I-III tumors and for many Stage IV tumors when combined with standard adjuvant therapy. The adjuvant therapy that has been applied has been based on clinical studies evaluating adjuvant therapy for squamous cell carcinomas in multiple tumor sites [36, 39]. Clearly, patients who receive single modality transoral surgery have the functional advantage of swallowing preservation as a result of the ability to spare adjacent musculature critical to swallowing function. Whether this advantage is maintained with the addition of adjuvant radiation or chemoradiation remains unknown. Thus, the role of modern low-morbidity resection in the multidisciplinary management of Stage III-IV oropharynx cancer remains undefined.

The Head and Neck Committees of the Radiation Therapy Oncology Group and the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) have performed surgical trials in the recent past. Surgical interest in cooperative group activity remains high. For example, ECOG 4393 represented a large study evaluating surgical margins, demonstrating the ability to perform surgical/adjuvant trials. While only a handful of institutions initially pursued transoral resection, it is now

undertaken at an increasing number of academic medical centers increasing clinical investigation by qualified academically-oriented head and neck surgeons increasing the successful collection and storage of fresh, untreated tumor for scientific investigation.

Numerous retrospective single-institution reports and a few important multicenter trials have generated significant enthusiasm for these transoral approaches in the multidisciplinary approach. Indeed, many surgeons advocate its use as part of a de-intensification approach that warrants a comparative trial. In addition, while adjuvant therapy trials for oral cavity carcinoma have been published [37], little prospectively gathered data on postoperative therapy for $p16^+$ OPSCC are available.

Transoral resection of many pharyngeal and laryngeal tumors is now technically feasible and increasingly utilized. This dramatically limits the morbidity of surgical exposure and reduces substantially the acute and late effects of resection. It is important to recognize that the morbidity of past surgeries was a function of the injury that occurred with the required transcervical neck exposure. What is not clear is to what extent resection of important swallowing structures impact on this. The experience to date with TLM and TORS would suggest that resection can be safely performed in some oropharyngeal tumors, such as T1-2 tumors, without contributing to increased late swallowing complications as measured by dependence on percutaneous gastrostomy (PEG) tube. [37]

HPV-positive SCC, which often presents with a small primary tumor, is particularly amenable to such an approach because the functional deficit resulting from their removal is low. Thus, more than 7,500 of the 12,600 oropharynx cancers anticipated in 2010 are expected to be amenable to this type of transoral surgical approach, either as a single treatment modality or as part of a combined modality regimen.

Transoral resection of oropharyngeal cancers using the C02 laser or, more recently, robotic surgery, has been practiced at an increasing number of North American institutions. Furthermore, case series suggest that excellent long-term function may be anticipated after resection of early T1-T2 tumors.(ADD CITATIONS) The da Vinci surgical robot (Intuitive corp., Sunnyvale, CA) is now FDA-cleared for the resection of T1-T2 cancers of the oropharynx, and the machine is widely available. Robotic and laser transoral resection, while promising and increasingly utilized, should be investigated prospectively in order to design the most appropriate randomized phase II trial comparing this approach with CRT.

Surgical resection of oropharynx cancer is a curative therapy and can be a single modality for patients with Stage I-III tumors. For many Stage IV patients, adjuvant radiation therapy has the advantage that the radiotherapy dose is reduced (60 Gy) and may not require the addition of concurrent CT. Hence, surgical therapy has the potential to substantially diminish the application of high-dose radiation treatment as well as CRT for patients who are expected to do well. In those patients with more advanced disease, surgical resection in combination with post-operative CRT also has the potential to increase locoregional control. Clearly, patients who receive single modality transoral surgery have the functional advantage of swallowing preservation as a result of the ability to spare adjacent musculature critical to swallowing function. Whether this advantage is

maintained with the addition of adjuvant radiation or CRT remains unknown. Thus, the role of modern low-morbidity resection in the multidisciplinary management of Stage III-IV oropharynx cancer remains undefined.

The Head and Neck Committees of the Radiation Therapy Oncology Group and the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) have performed surgical trials in the recent past and surgical interest in cooperative group activity remains high. ECOG, for example, completed a large study of surgical margins, demonstrating the ability to perform surgical/adjuvant trials. While only a handful of institutions initially pursued transoral resection, it is now undertaken at an increasing number of academic medical centers. A significant additional benefit will result from increasing the numbers of qualified academically oriented surgeons in head and neck cancer clinical investigation. The last decade's emphasis on non-surgical management of head and neck cancer has resulted in impediments to the collection and storage of fresh, untreated tumor for scientific investigation. Biopsy material has been collected, but is frequently limited in volume. Even dedicated institutions continue to struggle with surgery and pathology algorithms and protocols that encourage adequate and reproducible specimen accrual. Involvement of head and neck surgical investigators in the primary treatment of this disease is critical to the development of protocols for tissue collection, processing and storage, and to the creation of large, shared tissue repositories.

Human papillomavirus-associated head and neck cancer: analysis of E2399, RTOG 0129 and ECOG 1308

Human papillomavirus has been linked to the pathogenesis of HNSCC. Approximately 50-60% of OPSCC cases are positive for HPV. HPV-positivity is associated with a better prognosis. The effect of tumor HPV status on therapeutic response and survival has been evaluated in a phase II clinical trial conducted by the ECOG (E2399) [11] as well as in the context of two phase III trials, RTOG 0129 and TROG 02.02 [40, 41].

In E2399, patients with stage III or IV oropharyngeal or laryngeal SCC were treated with induction CT followed by CRT. The impact of tumor HPV status—as determined by in situ hybridization—on survival was evaluated using proportional hazards models. Genomic DNA of HPV genotypes 16, 33, or 35 was located within tumor cell nuclei of 38 of 96 cases (40%, 95%CI 29.7- 50.1). In a total of 96 patients (out of 105 eligible) who had HPV testing performed, 58 (60%) were HPV-negative and 38 (40%) HPV-positive. In oropharyngeal primaries (n=60), the incidence of HPV positivity was 60%; in laryngeal primaries (n=36) it was only 6%. HPV-positive tumors were significantly associated with Caucasian race, fully active performance status, oropharyngeal cancers, early tumor stage, and basaloid histomorphology. Response rates after induction CT (81.6% vs. 55.2%, p=0.01) and CRT (84.2% vs. 56.9%, p=0.07) were higher in patients with HPV-positive tumors when compared to patients with HPV-negative tumors. After a median follow-up of 39.1 months, patients with HPV-positive tumors had a risk of progression that was 72% lower (HR=0.28, 95% CI: 0.07-1.0) and a risk of death that was 79% lower (HR=0.21, 95% CI: 0.06-0.74) than patients with HPV-negative tumors. The 2-year overall survival rate was 62% (±0.06) for HPV-negative patients and 95% (±0.05) for HPV-positive patients (log rank test, p-value=0.005), whereas the 2-year progression free survival rate was 50% (±0.08)

for HPV-negative patients and 86% (±0.07) for HPV-positive patients (log rank test, p-value=0.02).

RTOG 0129 was a phase III trial that compared standard and accelerated boost RT regimens, both with concurrent cisplatin. There were no differences in efficacy between the two arms. A retrospective analysis of the patients enrolled in RTOG 0129 has been published [40]. This analysis combined cases of OPSCC in both arms of the trial (n=317) and demonstrated that tumor positivity for HPV-16 was associated with HR for death of 0.36 (p =0.0001). Patients with HPV-negative OPSCC cancer had essentially identical progression-free survival as those with hypopharynx and larynx primaries, with an approximate 60% 1-year rate. Smoking history modified the risk of relapse in the RTOG 0129 analysis. OPSCC patients who were HPV-positive but smoked 20 pack-years or more had a HR for OS of 1.91 (95% CI, 1.20-3.05) over patients who were HPV positive but smoked less than 20 pack-years; patients who were HPV-negative and smoked less than 20 pack-years had a HR of 2.25 (1.44-3.50) and patients who were HPV-negative but smoked 20 pack-years or more had a HR 4.30 (2.40-7.71); and the 2-year PFS was 95%, 80%, 71% and 63%, respectively. Within the HPV-positive group, patients could be further divided by tobacco use history (in pack-years, = 10 vs. >10) and N stage (N0-2a vs. N2b-3). Patients with > 10 pack-years and N2b-3 disease make up the intermediate risk group; all others comprise the low-risk group. Looking into smoking history further, patients who were $p16^+$ and smoked >5 pack-years can be categorized as “unfavorable” or “intermediate risk”: with a 2-year PFS of 65% and a 3-year PFS of 61% using CRT in RTOG 0129. Therefore, a smoking history of 5 pack-years has been proposed as the cut-off to define favorable vs. unfavorable HPV-positive OPSCC (essentially using p16 immunoreactivity as a surrogate marker for HPV infection).

A common transoral route of exposure, incorporating minimally invasive techniques with transoral laser CO2 microsurgery [30] (TLM) and transoral robotic surgery (TORS) [31, 32] has emerged.[33] Transoral resection of many pharyngeal and laryngeal tumors is now technically feasible and increasingly utilized. This approach dramatically limits the morbidity of past transcervical surgical exposure techniques reducing the acute and late effects of resection including the impact on swallowing function. What is not clear is to what extent resection of important swallowing structures can impact functional and QOL outcome, thus necessitating prospective level I evidence to be generated. The experience to date with TLM and TORS would suggest that resection can be safely performed in some oropharyngeal tumors such as T1-2 tumors without contributing to increased late swallowing complications as measured by dependence on percutaneous gastrostomy (PEG) tube [42].

In order to gather essential oncologic and functional data for the design of a future, randomized phase III trial, this protocol aims to determine the feasibility and oncologic efficacy of prospective, multi-institutional trial of TOS for HPV-associated OPSCC, followed by risk-adjusted adjuvant therapy. In addition, we will assess the functional and quality of life outcomes following transoral resection and adjuvant therapy in patients determined to be at an “intermediate risk” for recurrence based on pathologic evaluation.

We base our study design on the successfully completed, ECOG 1308 trial of $p16^+$ OPSCC patients treated with induction chemotherapy, followed by risk-adjusted, reduced RT dose [54Gy for complete response (CR) after induction

therapy versus 69.3Gy for all others]. In the current E3311 study, a surgical "CR" would be obtained by R0 resection using transoral surgery and neck dissection, including "intermediate" risk factors such as N2 status, close margins and microscopic ECE in good prognosis, $p16^{+}$ disease, to permit de-intensification with lower RT dose (50GY or 60GY) without chemotherapy.

We will test our hypothesis that upfront surgery permits treatment de-intensification through selection of risk-adjusted adjuvant therapy based on pathologic biomarkers used to define an "intermediate risk" cohort (defined below). This proposal will seek to differentiate a cohort of patients following post-transoral resection defined by the absence of high risk features, including a positive margin (defined as carcinoma at the cut-specimen edge), 5 or more positive lymph nodes or ECE. Patients with no pathologic risk factors constituting a low risk cohort will be observed. For the remaining intermediate risk patients, we propose that the primary tumor bed with indications for irradiation such as perineural invasion or lymphovascular invasion but negative margin can be effectively treated to either 50 Gy or 60 Gy. This represents an experimental reduction of approximately 13% from the lowest dose range that has been administered for the postoperative cohort of patients (57.6 Gy). The necessity for postoperative radiotherapy (PORT) following surgery to a tumor bed that fails to demonstrate any adverse pathologic features is a controversial practice, rooted historically in the use of transcervical neck exposures and the early and seminal observations of Fletcher [43] that was intended to also address the risk of tumor surgical seeding. The risk of local-regional relapse without adjuvant PORT for transcervical surgery would appear to be on the order of 10% [36]. In the setting of a transoral approach where no cervical fascial planes are disrupted, the evidence to date suggests that the risk of local relapse with either TLM or TORS is approximately 5% [44, 42]

In summary, the suggestion is that cases of HPV-associated OPSCC have a more favorable prognosis in part due the natural biology of the cancer and possibly more radiosensitivity. In vitro analyses have demonstrated evidence to support that HPV infection can associated with increased intrinsic chemo-radiosensitivity [45, 46]; though it is recognized that there is no consensus on this issue. Nevertheless, there is compelling evidence both from the perspective of cancer cytotoxicity and normal tissue functional preservation (see above) to reduce the dose of postoperative radiotherapy in HPV-positive OPSCC to doses on the order of 55 Gy or less.

Pathologic risk factors and prognosis in HPV+ OPSCC

This proposal will seek to differentiate low-risk and intermediate-risk post-TOS

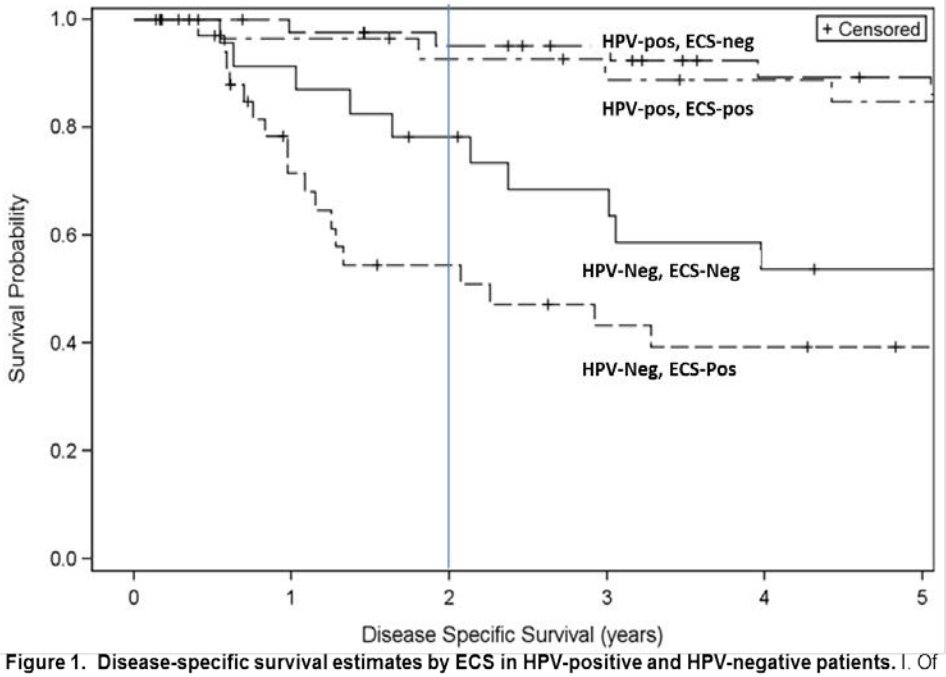


Figure 1. Disease-specific survival estimates by ECS in HPV-positive and HPV-negative patients. I. Of the 137 patients, 75 (54.7%) were HPV-positive and 62 (45.3%) were HPV-negative. Of 75 HPV-positive patients at the University of Pittsburgh with cervical lymph node metastases, 60% (45/75) had ECS and 40% (30/75) did not have ECS. HPV-positive patients with ECS did not have worse DSS (Figure 1) compared to HPV-positive patients without ECS. The 2-year DSS was similar for HPV-positive patients with and without ECS (95.1% [95% confidence interval (CI): 81.8%, 98.8%] and 92.7% [95% CI: 73.9%, 98.1%], respectively). The 5-year DSS was also similar for HPV-positive patients with and without ECS (89.3% [95% CI: 73.8%, 95.9%] and 84.8% [95% CI: 64.4%, 94.0%], respectively). 2 year DSS is marked by the vertical line.

patients defined by the absence of high-risk features that include a positive margin (defined as carcinoma at the cut-specimen edge), extensive/gross ECE (defined as greater than the 1mm cutoff) or the presence of ≥5 LN [47]. We propose that the primary tumor bed/neck that has intermediate-risk indications for irradiation (perineural invasion or lymphovascular invasion but negative margin) can be effectively treated to either 50 Gy or 60 Gy. In the neck, N2a-N2b disease consisting of 5 or fewer positive nodes [47]), or with microscopic (<1mm) ECE [48, 49] also demonstrate outstanding prognosis and data do not current support the use of chemotherapy in prospective trials, given that the survival of HPV+ OPSCC approximates 85-90%. Recent, large retrospective analyses of the prognostic role of ECE has indicated that in a subset of HPV+ patients with microscopic ECE survival is excellent (85-90% 2 year PFS, see Figure 1), and may be spared treatment intensification using high dose cisplatin, However, this emerging data must be validated prospectively, including establishment of consistency in pathologic measurement.

1.4 Postoperative radiotherapy (PORT) with or without cisplatin chemotherapy

Current postoperative radiotherapy (PORT) doses derive from a series of seminal investigations conducted at MD Anderson Cancer Center [39, 50]. The cumulative experiences from these randomized trials demonstrated that for SCC of all anatomic sites in the head and neck (32% of subjects with SCC of the oral cavity), the recommended PORT dose can be pathologically guided with high

rates of local-regional disease control. While various risk stratification schema have been evaluated, the presence of a positive margin (not defined) and nodal ECE warrant at least 63 Gy [51]. In the presence of any pathologic risk factors identified in the tumor specimen, an increased risk of local relapse was statistically identified if < 54 Gy was administered compared to 57.6 Gy [39] (63% vs. 92%, *p*=.02). While the optimal postoperative dose for ECE and positive margins has not been established, several institutional reports have used doses typically in the range of 65-66 Gy or greater [37, 38].

There is also indirect supportive evidence that a lower PORT dose may be sufficient when irradiating the pathologically involved neck. Investigators from the Netherlands (University Medical Center Groningen) demonstrated in a large retrospective review of over 800 patients (52% of subjects with SCC of the oral cavity) that postoperative irradiation of the pathologically involved cervical neck to only 56 Gy was associated with 85-93% 5-year regional control rates depending on whether only a single or multiple nodes were involved (Vergeer et al, *personal communication*).

Neither of these clinical experiences distinguished the local or regional control rates by HPV status and potentially may have represented a predominantly HPV-negative study population based on the predominantly oral cavity SCC patients treated. Nevertheless, it demonstrates that high rates of cancer control may be seen in the pathologically involved site. For these reasons, the optimal postoperative radiotherapy dose for the HPV-positive OPSCC patient remains undefined.

As such, this proposal will seek to differentiate a cohort of patients following post-transoral resection defined by the absence of high risk features, including a positive margin (defined as carcinoma at the cut-specimen edge), 4 or more positive lymph nodes or ECE. Patients with no pathologic risk factors constituting a low risk cohort will be observed. For the remaining intermediate risk patients, we propose that the primary tumor bed with indications for irradiation such as perineural invasion or lymphovascular invasion but negative margin can be effectively treated to 50 Gy. This represents an experimental reduction of approximately 13% from the lowest dose range that has been administered for the low risk postoperative cohort of patients (57.6 Gy).

The necessity for PORT following surgery to a tumor bed that fails to demonstrate any adverse pathologic features is a controversial practice, rooted historically in the use of transcervical neck exposures and the early and seminal observations of Fletcher [43] that was intended to also address the risk of tumor surgical seeding. The risk of local-regional relapse without adjuvant PORT for transcervical surgery would need to be on the order of 10%. In the setting of a transoral approach where no cervical fascial planes are disrupted, the evidence to date suggests that the risk of local relapse with either TLM or TORS for T1/T2 primary OPSCC is approximately 5% [44].

While concurrent CT, typically cisplatin, has been administered for the high-risk patient cohort following surgery, it is clear that the use of chemotherapy can also unnecessarily increase the risk of late swallowing complications [23-26]. Retrospective cohorts of TORS followed by RT have reported on the risk of swallowing complications, but whether reduced dosage (50 Gy vs 60 Gy) should be used in desiging the prospective, randomized phase III trial in comparison to

CRT is now yet known. This proposal hypothesizes that reduced dose RT may provide comparable 2-year PFS rates with the potential for reduced, late normal tissue injury.

1.5 Role of IMRT and Lower Dose RT in Oropharynx Squamous Cell Carcinoma

A significant long-term toxicity in the irradiated oropharynx cancer patient is xerostomia caused by radiation delivered to the major salivary glands. Technologic advancements that now permit conformal fields using intensity modulated radiotherapy [IMRT] initially applied dose-constraints to reduce the volume of parotid gland parenchyma exposed to high radiation doses. However, the salivary glands continue to receive lower radiation doses that can still result in long-term xerostomia, albeit of lower severity, despite the use of IMRT. This can still result in significant impairment based on patient reported quality of life measures.

Dysphagia is the primary functional complication encountered after radiotherapy for oropharyngeal cancer. Impaired laryngopharyngeal physiology that results from neuromuscular fibrosis, independent of xerostomia, contributes to radiation-induced dysphagia. Even in the era of IMRT for oropharynx cancer, authors report rates of aspiration ≥1-year of 6% to 31% and g-tube dependence of 6% to 8%.[25, 52, 53]…Recent studies have demonstrated significant associations between swallowing outcomes and dose-volume coverage to key structures after IMRT including the anterior oral cavity, superior pharyngeal musculature, and inferior larynx/CP inlet. Dose-volume correlations have been observed for late objective endpoints of swallowing dysfunction such as nutritional dependence on a gastrostomy tube, measures of swallowing efficiency, aspiration, and swallowing-related QOL. [52, 54, 55] Pharyngeal dose to superior as well as inferior constrictor musculature is consistently found to relate to a variety of swallowing measures in numerous studies. Threshold pharyngeal doses as low as 50 Gy to the inferior constrictors (V_{50}) [54] and as high as 65 Gy to the [52, 55] superior constrictors have been significantly associated with aspiration, stricture, and swallowing efficiency. In addition, mean pharyngeal dose is associated with [55] QOL scores. As such, there exists supportive evidence that reductions in the prescribed RT dose to the pharynx and neck offer the potential to reduce the risk of both objective and patient-reported evidence of late RT-induced swallowing dysfunction. Based on these data, a dose threshold of at least 55 Gy to the superior pharyngeal musculature is felt to portend dysphagia. Moreover, IMRT has not historically used dose-limiting constraints with the primary goal of preserving swallowing function. These data also suggest early guidelines for dose-constraints to dysphagia-specific organs-at-risk using IMRT that may further improve long-term functioning after treatment for HNSCC.

Given the favorable prognosis that has been well described for the HPV-associated OPSCC patient, we hypothesize that the prescribed RT dose may be safely reduced following transoral surgical resection and pathologic risk stratification for the risk of relapse. On the other hand, patients with traditional high-risk pathologic features would be treated with current CRT to 66 Gy. Similarly, low-risk patients could be observed. For the intermediate-risk patient, we hypothesize that the prescribed dose may be safely reduced from a standard intermediate-risk prescription of 60 Gy to 50 Gy without compromise in local-

regional control rates. Moreover, we expect a reduction in the development of both objective and patient-reported measures of late RT toxicities.

Radiotherapy dose reduction has been studied in the recently completed E1308. This study prospectively examined the oncologic efficacy of reducing the RT dose to 55 Gy following a complete clinical response to induction CT. No pathologic evaluation of the primary site was required. The long-term results of this remain pending. Thus, the current hypothesis is predicated on transoral resection leaving a comparable, if not favorable, microscopic burden of residual cancer cells.

Theoretical mathematical modeling of radiation response and cancer control in human solid tumors has been extensively reported and is based on the modeling of reported local-regional control rates. Withers et al has evaluated the published literature and concluded that a dose of 50 Gy is associated with a 90% control rate for subclinical microscopic cancer. Evaluation of the clinical data has permitted mathematical modeling of the biologic effect of fractionated RT demonstrating that it may be modeled with linear quadratic equation, with most solid human tumors requiring an average of 3 Gy (D_0) to reduce the surviving cells to 37% which reflects the intrinsic biology of the cell to the radiation and its repair response. Modeling suggests that a cytoreduction of 10^{-10} is required to achieve a 90% probability tumor control rate summarized by the D_{10} parameter that represents the relative dose that would be required to sterilize a tumor with 90% probability of tumor control. The D_{10} can be represented by:

$D_{10} = 2.3 \times D_0$, where 2.3 is the natural logarithm of 10.

Thus, the dose required would be:

$$D_{10} = 2.3 \times D0 = 2.3 \times 3 = 6.9 \text{ Gy}.$$

The probability of achieving tumor control is influenced by the number of tumor cells present. While this is largely unknown and likely varies from patient to patient, it has been estimated that 10^9 cells may be present in a typical 4 cm tumor mass. Thus, the estimated modeled dose required would be:

$$10 \times 6.9 \text{ Gy} = 69 \text{ Gy}.$$

For a tumor cytoreduced to microscopic burden, it is estimated that there may be 10^7 or less residual cancer cells. Thus, it has been estimated that the radiation dose required to obtain a 90% likelihood of cure is:

$$D_8 = 8 \times 6.9 \text{ Gy} = 55.2 \text{ Gy}$$

This dose is consistent with the minimum dose (57.6 Gy) that has been found to be required in patients with pathologic evidence of risk for recurrence (intermediate-risk group).

This proposal will randomize patients to an experimental arm of 50 Gy based on the hypothesis that HPV-associated cells will be more radiosensitive modeled by a decrease in the D_0 of approximately 10% (2.7 Gy instead of 3 Gy)

1.6 Correlative Studies Background

1.6.1 *TP53* Mutation and Prognosis

TP53 mutation is frequent in HPV-negative HNSCC while it is rare in HPV-positive HNSCC. However, it is suggested that HPV-positive patients with mutated *TP53* have a poorer prognosis when compared to HPV-positive patients with wild type *TP53* (Licitra, C, JCO, 2006). In addition, the location of mutations within *TP53* can manifest as an abnormally truncated protein (nonsense mutation), disruption of DNA binding capacities (missense mutation), or without functional consequence (silent mutation). Poeta ML, et al. found that 53.3% of SCCHN patients had *TP53* mutations; functionally non-disruptive 33%, disruptive 20%, and wild type 47% (41). The patients with any *p53* mutations associated with the worse overall survival compared to wild-type *TP53* (HR to death, 1.4; 95% confidence interval 1.1-1.8, p=0.009) while the association was stronger with functionally disruptive *TP53* mutation (HR 1.7; 1.3-2.4, p<0.001). Therefore, we hypothesize that the patients with HPV-positive and functionally disruptive *TP53* mutations will have shorter time to disease progression and overall survival compared to patients with wild type *TP53*. In addition to *TP53*, a panel of 200 common cancer-related genes will be sequenced in one assay which may yield novel prognostic and/or predictive biomarkers.

1.6.2 Quantification of EGFR Expression by Automated Image Analysis Technique AQUA

Epidermal growth factor receptor (EGFR) is known to be overexpressed and prognostic in HNSCC (29,30). Also, there is evidence that higher expression of EGFR is associated with poor outcome in HPV-positive patients (Kumar, B. JCO, 2008)(18). However, quantification of EGFR receptors using conventional immunochemical staining is unreliable due to poor inter- and intraobserver reproducibility, limited quantification range of peroxidase staining and difficulty delineating signals within cellular compartments. These limitations can be partly alleviated by automated quantitative analysis (AQUA) technology (33). Using AQUA, protein expression has been shown to provide reproducible analysis of target signal expression in fixed tissues on a continuous and more quantitative scale while preserving spatial information such as subcellular localization. The use of this technology has been successfully applied to several protein targets for biomarker identification in other solid tumors, including measurement of EGFR in head and neck cancers (33). We hypothesize that higher expression of EGFR will associate with poor prognosis in HPV-positive patients when compared to the HPV-positive patients with lower expression of EGFR because of the survival signal mediated by the EGFR pathway induced by radiation.

1.6.3 Excision Repair Cross-complementation Group 1 (ERCC1) Single Nucleotide Polymorphism (SNP) and XPF Protein Expression in HNSCC

Excision repair cross-complementation group 1 (ERCC1) is a rate-limiting enzyme in the nucleotide excision repair pathway that removes cisplatin-induced DNA adducts (24,25). Recent studies have shown that ERCC1 SNP (Thr259Thr) and high ERCC1 protein expression in tumors are associated with poor survival in HNSCC (26-28). When patients with stage I or II were treated with radiation therapy alone, the patients with ERCC1 SNP resulting in Thr259Thr (4.1%) compared to Thr259Lys (25.5%) or Lys259Lys (70.4%) had shorter time to progression (11.6 vs. 87.6 or 85.2 months) and median survival (27.9 vs. 89.9 or 88.3 months) (28). Furthermore, low ERCC1 protein expression in the tumors was seen in 27-29% of the patients and associated with higher response rate and lower risk of death when the patients were treated with cisplatin-based induction chemotherapy or cisplatin-based concurrent CRT (26,27). Therefore, we hypothesize that the patients with ERCC1 SNP Thr259Thr will have shorter time to progression and survival compared to the patients with Thr259Lys or Lys259Lys because of radiation resistance associated with Thr259Thr. We also hypothesize that the patients with lower expression of ERCC1 protein in their tumors will have higher response to cisplatin-based chemoradiotherapy, and longer time to progression and survival.

1.6.4 Correlation of radiologic markers with pathologic nodal status

Preoperative CT/MRI scans will be analyzed for nodal stage and prediction of ECE, and correlated with final pathologic nodal stage, presence and extent of ECE (< or >1mm).

1.6.5 HPV DNA measurement and alteration in serum and saliva

HPV DNA and seropositivity to HPV antigens will also be measured quatitatively and qualitatively, before and after surgical and adjuvant treatment to measure stability and predictive ability over time in a prospective treated population. Baseline and posttreatment cytokines are potentially predictive of outcome. Furthermore, the association between serologic markers (detected in blood at baseline and two other timepoints, including cytokines, chemokines, growth factors, and angiogenic factors in blood and treatment efficacy will also be examined.

DNA from buffy coat or PBMCs will be analyzed for quantitative and qualitative alterations in HPV DNA. These analyses will be performed under the direction of Robert L. Ferris, MD, PhD.

1.6.6 Oral or serum HPV DNA level may correlate with PFS

Given the ability to detect HPV DNA in salivary and serum specimens, we will perform an exploratory correlation between pre-treatment and post-treatment (1- and 2- year) HPV DNA, using QRT-PCR for HPV E6/E7. The data will be used to determine the feasibility and potential

value of incorporating this potential biomarker into the future randomized phase III trial.

1.6.7 Tumor antigen specific cellular immunity

We and others have characterized the antigen specific cellular immune response to OPSCC, including HPV-, EGFR- and other antigens. PBL from pretreatment and post treatment patients will be correlated with disease recurrence, DFS, and OS.

1.6.8 Quantification of HPV DNA and serology in serum and saliva

Presence of HPV DNA and seropositivity has been reported in healthy individuals HPV/p16+ OPSCC patients, in approximately 60-70% of patients' serum and saliva. We collect blood and saliva from all patients for prediction of clinical response based on quantitative or qualitative alterations in these biomarkers in each specimen type after therapy and correlated with clinical outcome/response and Arm of adjuvant therapy.

1.7 Clinical Functional Outcomes

Clinical outcomes are those readily tracked by the clinical assessment team and trialist, most of which reflect assessment utilized in routine clinical practice. These include patient weight (and weight loss), ECOG performance status, tracheostomy tube status (present/absent), and enteral feeding tube status (present/absent). In addition, the [49, 64]Performance Status Scale – Head and Neck (PSS-HN) will be measured. This instrument consists of 3 items rated by the research associate, requiring less than 5 minutes and no patient effort, and measuring speech, swallowing and diet. Classically, H&N cancer patients have a high burden of comorbidity, related in part to risk behaviours of smoking and alcohol use. While comorbidity is expected to be lower in HPV-related cancers, Charlson comorbidity index will be collected by chart extraction once at baseline to characterize the study cohort and assess comparability of the 4 treatment arms.

1.8 Functional Swallowing Outcomes

Swallowing is a complex biomechanical process involving 5 cranial nerves and over 25 muscles in the upper aerodigestive tract. Swallowing impairments can occur as the result of surgery alone, radiotherapy or CRT. Although there are many ways to report swallowing outcomes, the MBS study remains the only measure that defines physiology and is predictive of adverse health effects (i.e., pneumonia). Although patient-reported outcomes provide an important, complementary perspective of swallowing abilities, they do not accurately reflect swallowing competency. Much of our knowledge of aspiration and physiologic impairment comes from data of laryngeal preservation trials that aggregate functional outcomes from multiple sites of HNSCC and show aspiration rates up to 40% in unselected cohorts, and in up to 80% of symptomatic patients when laryngopharyngeal function is impaired. These data based on findings from MBS studies confirm that when physiology is impaired, patients have high rates of aspiration, much of which is undetected by patient report because of a lack of sensory awareness. Hence, silent aspiration has been reported in excess of 50% of patients who [14, 50, 51, 53, 65, 66] aspirate. Data specific to patients

with oropharyngeal primary tumors continue to demonstrate a high burden of dysphagia. In a population-based analysis of over [52, 67] 8,000 HNSCC, patients with cancers of the oropharynx had the second-highest prevalence of dysphagia. In addition, 31% of patients demonstrated elevated occurrences of aspiration relative to baseline >1 year after treatment, and 22% developed pneumonia in a trial of chemoIMRT that was designed to protect dysphagia-organs-at-risk using dose-constraints for oropharyngeal cancer[46, 61]. Furthermore, aspiration based on MBS findings was significantly predictive of pneumonia in this trial of chemoIMRT for oropharyngeal cancer (p=0.017, Se 80%, Sp 60%), and silent aspiration was evident on MBS studies in 63% of patients who developed pneumonia. In addition, pharyngeal residue on MBS studies was significantly associated with the development of pneumonia after [53] chemoIMRT (p<0.01) [68]. These results offer compelling support for the examination of swallowing physiology (i.e., “airway protection” and “pharyngeal transit”) as these health-related endpoints cannot be obtained by PROs. Thus, we propose to evaluate swallowing using MBS studies as the primary objective functional measure of this trial.

1.9 Patient-Reported Outcomes

Patient-reported outcomes will include head-and-neck specific symptoms (MDASI-HN), cancer and head and neck-specific quality of life (FACT-H&N), swallowing perception and performance (MDADI), voice outcomes (VHI-10), overall health status (EQ-5D) and a cost questionnaire. Additionally, ability to return to employment will be assessed using a return to work instrument in use by the Radiation Therapy and Oncology Group (RTOG). Head and neck-specific symptoms include issues of dry mouth, mucositis and mucosal sensitivity, shoulder and neck discomfort, and skin changes as well as swallowing and voice-related problems. It is well documented that head and neck cancer patients experience a profound, acute decrement in the level of general physical functioning and general cancer-specific QOL as a result of both surgery and adjuvant RT/CRT. Data regarding the late effects of treatment on disease-specific function is more limited; however, available studies indicate that a significant percentage of patients fail to return to baseline functioning. Patient-perception of swallowing performance has been shown to be associated with long-term swallowing related quality of life, and to remain depressed from baseline levels after treatment for [54, 69]oropharyngeal cancers. Voice-related changes that include alterations in resonance, pitch variation, loudness, and quality (i.e., hoarseness, raspiness, etc) more commonly result from treatments that affect the oropharynx, compared with articulatory changes that result from management of oral cavity cancers.

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2. Objectives

2.1 Primary Objective

2.1.1 Accrual, risk distribution, and surgical quality will be used to determine the feasibility of a prospective multi-institutional study of transoral surgery for HPV+ oropharynx cancer followed by risk-adjusted adjuvant therapy.

2.1.2 To assess the oncologic efficacy following transoral resection and adjuvant therapy in patients determined to be at “intermediate risk” after surgical excision, the 2-year PFS rate will be examined.

2.2 Secondary Objectives

2.2.1 To estimate the patient distribution with various histologic risk features.

2.2.2 To assess and compare early and late toxicities associated with TOS and the different doses of adjuvant PORT.

2.2.3 To evaluate swallowing function before and after TOS and risk-adjusted adjuvant therapy.

2.2.4 To evaluate QOL, swallowing perception and performance, voice outcomes, and head and neck symptoms.

2.3 Laboratory Research Objectives:

2.3.1 To correlate tumor *TP53* mutation and other associated mutation profile with pathologic findings, with PFS and other outcome parameters in patients with resectable HPV-associated OPSCC after the above treatments.

2.3.2 To evaluate radiation resistance markers, including ERCC1 single nucleotide polymorphism and protein expression, and correlate them with treatment efficacy.

2.3.3 To investigate the usefulness of biomarkers in predicting progression-free survival and biomarkers, including tumor ERCC1, EGFR, plasma cytokine/chemokines, cellular immunity to HPV, and oral HPV DNA

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____
Patient's Initials (L, F, M) _____
Physician Signature and Date _____

Rev. 9/16 **NOTE:** All questions regarding eligibility should be directed to the study chair.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Registration to Surgery (Arm S)

_____ 3.1.1 Age >/= 18 years.

_____ 3.1.2 ECOG performance status of 0 or 1.

Rev. 2/15 _____ 3.1.3 Patients must register to Step 1 prior to surgery.

_____ 3.1.4 Patients must have newly diagnosed, histologically or cytologically confirmed squamous cell carcinoma or undifferentiated carcinoma of the oropharynx. Patients must have been determined to have resectable oropharyngeal disease. Patients with primary tumor or nodal metastasis fixed to the carotid artery, skull base or cervical spine are not eligible

Rev. 2/15 Rev. 9/16 _____ 3.1.5 Patients must have AJCC TNM tumor stage III, IV a, or IV b (with no evidence of distant metastases) as determined by imaging studies (performed < 30 days prior to registration) and complete neck exam, from the skull base to the clavicles. The following imaging is required: CT scan with IV contrast or MRI.

AJCC TNM tumor stage III, IV a, or IV b?

Stage _____ Date scans performed_____

CT scan with IV contrast or MRI?

The primary tumor should be cT1 or T2 and cervical nodes cN1, N2a, or N2b based on clinical or radiographic criteria.

Rev. 6/14 Rev. 2/15 _____ 3.1.6 Patients must have biopsy-proven p16+ oropharynx cancer; the histologic evidence of invasive squamous cell carcinoma may have been obtained from the primary tumor or metastatic lymph node. It is required that patients have a positive p16 IHC (as surrogate for HPV) status from either the primary tumor or metastatic lymph node.

_____ 3.1.7 Carcinoma of the oropharynx associated with HPV as determined by p16 protein expression using immunohistochemistry (IHC) performed by a CLIA approved laboratory. Using p16 antibody obtained from Roche mtm laboratories AG (CINtec, clone E6H4) is recommended.

Confirmed $p16^+$ disease? Yes _____ No ____

_____ 3.1.8 No prior radiation above the clavicles.

_____ 3.1.9 Patients with a history of a curatively treated malignancy must be disease-free for at least two years except for carcinoma in situ of cervix, melanoma in-situ (if fully resected), and/or non-melanomatous skin cancer.

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History of curatively treated malignancy?

Yes_____ No_____

If yes, disease-free for at least two years?

Yes_____ No_____

Rev. 9/16 _____ 3.1.10 Patients with the following within the last 6 months prior to registration must be evaluated by a cardiologist and/or neurologist prior to entry into the study.

Congestive heart failure > NYHA Class II?

Yes _____ No _____ Date _____

CVA/TIA? Yes _____ No _____ Date _____

Unstable angina? Yes _____ No _____ Date _____

Myocardial infarction? (with or without ST elevation)

Yes _____ No _____ Date _____

_____ 3.1.11 Patients must not have evidence of extensive or "matted/fixed" pathologic adenopathy on preoperative imaging.

_____ 3.1.12 Patients must have acceptable renal and hepatic function within 4 weeks prior to registration as defined below:

- Absolute neutrophil count ≥1,500/mm^3

  Yes_____ No_____

  ANC_____ Date of Test_____
- Platelets ≥ 100,000/mm^3

  Yes_____ No_____

  Platelets_____ Date of Test_____
- Total bilirubin ≤ the upper limit of normal (ULN)

  Yes_____ No_____

  Total bilirubin_____ Institutional ULN _____

  Date of Test _____

- Calculated creatinine clearance must be > 60 ml/min using the Cockcroft-Gault formula :

  (140-age)*wt(kg)/([Cr]*72).

  For women the calculation may be multiplied by 0.85

  Creatinine clearance _____ Date of Test_____

_____ 3.1.13 Women must not be pregnant or breast-feeding due to the teratogenicity of chemotherapy. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.14 Patient must not have an intercurrent illness likely to interfere with protocol therapy or prevent surgical resection.

Intercurrent illness? Yes_____ No_____

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_____ 3.1.15 Patients must not have uncontrolled diabetes, uncontrolled infection despite antibiotics or uncontrolled hypertension within 30 days prior to registration.

- Uncontrolled diabetes?

  Yes_____ No_____ Date _____
- Uncontrolled infection?

  Yes _____ No _____ Date _____
- Uncontrolled hypertension?

  Yes _____ No _____ Date _____

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_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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

_____ 3.2.1 Histopathologic assessment of surgical pathology must include examination for perineural invasion (PNI) and lymphovascular invasion (LVI) and reported as absent or present. The absence or presence of extracapsular extension (ECE) requires gross and microscopic assessment and is defined to be:

- absent (negative or nodal metastasis with smooth/rounded leading edge confined to thickened capsule/pseudocapsule),

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- present - minimal (tumor extends ≤ 1 mm beyond the lymph node capsule), or
- present - extensive (Gross, tumor extends >1 mm beyond the lymph node capsule (includes soft tissue metastasis)

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_____ 3.2.2 Patient must be stratified/classified into one of the following risk categories:

The highest risk feature assessed pathologically will determine the patient's category/treatment arm assignment.

- Low Risk: T1-T2, N0-N1 AND clear (≥ 3mm) margins, AND no ECE or PNI/LVI.
- High Risk: Any of the following features: one or more positive margin(s) with any T stage, OR “Extensive” (> 1mm) ECE, OR ≥ 5 metastatic lymph nodes (regardless of primary tumor margin status).
- Intermediate Risk: Any of the following features: one or more “close” (< 3mm) margin(s), OR “Minimal” (≤ 1mm) ECE, OR N2a (1 or more lymph node > 3cm in diameter), OR N2b (2-4 lymph nodes positive, any diameter ≤ 6cm), OR with perineural invasion or lymphovascular invasion.
- Unknown Risk: Patients found to have N2C or N3 disease on final pathologic analysis are at unknown risk for recurrence, but are not candidates for deintensified adjuvant therapy in this trial. These patients will be treated on Arm C.

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- **Patients not categorized into the appropriate risk category will be considered ineligible for the study.**

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_____ 3.2.3 Patient must be registered/randomized to Step 2 within a maximum of 7 weeks following surgery.

_____ 3.2.4 Women of childbearing potential and sexually active males are strongly advised to use an accepted and effective method of contraception

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Registration and Randomization Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization

- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Requirements for E3311 site registration:

- IRB approval (local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Downloading Site Registration Documents

Site registration forms may be downloaded from the E3311 protocol page located on the CTSU members' website.

- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol #E3311
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org/ (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.

2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.

Or

B. Signed HHS OMB No. 0990-0263 (replaces Form 310).

Or

C. IRB Approval Letter

4. Surgeon Certification Form (See Section 4.1.5.6).

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**
- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

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Patients must not start protocol treatment, including surgery, prior to registration.

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Surgery should take place within 3 weeks, and not more than 4 weeks after registration to Arm S.

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If more than one surgery is performed as part of the Arm S resection, all surgeries must be completed within 4 weeks of registration to Arm S.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Registration To Surgery (Arm S)

The following information will be requested

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name (Institution CTEP ID)

4.1.2.2 Investigator's name (NCI number)

4.1.2.3 Cooperative Group Credit

4.1.2.4 Credit Investigator

4.1.2.5 Protocol specific contact information

4.1.3 Patient Identification

4.1.3.1 Patient's initials (first and last)

4.1.3.2 Patient's Hospital ID and/or Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Gender

4.1.3.3.2 Birth date

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.1.3.3.7 Country of residence

4.1.4 Eligibility Verification

Patients must meet all the eligibility requirements listed in Section 3.1.

4.1.5 Additional Requirements

4.1.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

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4.1.5.2 Patients unable to read/write in English fluently will complete patient-reported/QOL instruments in their own language if/when validated translations are available. They will be coded as ineligible for analysis of patient-reported instruments unavailable in their language.

4.1.5.3 Submission of pathology materials for diagnostic review and classification is mandatory. Submission guidelines outlined in Section 11.

4.1.5.4 Biological materials are to be submitted as indicated in Section 11.

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4.1.5.5 Data collection for this study will be done exclusively through the Medidata Rave clinical data management

system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at http://www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.1.5.6 Surgeon Credentialing

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Surgeon credentialing in transoral oncologic surgery will be required for participation in this study. Only transoral oropharynx cancer resections are applicable; oral cavity and larynx surgeries are not applicable, even if transoral in approach. Surgeons must be proficient at the proper open technique for OPSCC resection.

Surgeons performing robotic or laser procedures must be credentialed for those procedures at their respective institution, providing evidence of sufficient training and active credentialing by their Hospital medical staff privileging board(s).

Surgeons must have performed at least 20 transoral OPSCC resections using any oncologic technique (at least 5 transoral cancer resection cases) in the immediately preceding year.

The most recent 10 consecutive cases must be submitted (de-identified) with accompanying operative notes and pathology reports. The submitted 10 cases (above) will undergo review by the E3311 PI and the surgical quality assurance members. Ultimately the PI has responsibility for final approval of all surgical investigators.

Surgeons interested in participating in the trial must have an active CTEP ID number. Surgeons who do not have a CTEP ID number must first register with the Pharmaceutical Management Branch, Cancer Therapy Evaluation Program (PMB, CTEP) at https://eapps-ctep.nci.nih.gov/iam/. For additional information on obtaining a CTEP ID number and joining ECOG-ACRIN, go to www.ecog.org/general/newmember_indiv.html. If you have any questions, please contact ecog.membership@jimmy.harvard.edu.

Access to the Medidata Rave "E3311/RTOG1221 Surgical Credentialing Database" will be granted when IRB approval is obtained. A Head and Neck Surgeon Credentialing Questionnaire must be completed as part of the initial credentialing process. The questionnaire will be completed directly in Rave. Please see Appendix VII to reference a copy of the Surgeon Credentialing Questionnaire.

To register a surgeon and to complete the credentialing questionnaire, the responsible CRA must send an email to HNsurgicalcredentialing@jimmy.harvard.edu with the following information:

Surgeon First and Last Name
Surgeon CTEP ID number
Institution Site name
CTEP Site ID number
Surgeon's fax number
Surgeon's telephone number
Surgeon's email address

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A confirmation email will be sent to the CRA when the Head and Neck Surgeon Credentialing Questionniare is ready for their completion.

CREDENTIALING DURING THE CONDUCT OF THE TRIAL: Active surgeon credentialing will be in force until the first 5 cases per surgeon are accrued. If no grossly positive margins are encountered, an additional 5 case may be accrued by that surgical investigator. Positive

margins are not permitted to exceed 10% of accrued patients per surgeon – thus a single case with grossly positive margins is acceptable per 10 cases per surgeon. In the event that a single surgeon accrued two cases out of 10 consecutive cases with grossly positive margins (yielding a rate > 10% for positive margins), that surgeon will be placed on hold, and may become reactivated as an accruing surgeon through the submission of an additional 5 consecutive cases with clear margins. This process will be in effect for each accruing surgeon for the duration of the trial. If a surgeon is not reactivated due to recurrent positive margins, the previously accrued cases will be included in the study but no further cases are allowed to be enrolled. If an active surgeon accrues zero patients for 18 months, they will be required to repeat the credentialing process.

4.1.5.7 Site Participation in Modified Barium Swallow (MBS) Studies

The Modified Barium Swallow (MBS) Credentialing Checklist must be completed by the institution before patients can be registered to E3311. Once the form is completed please fax this to the ECOG-ACRIN Operations Office - Boston at (617) 632-2990, Attention: E3311 Data Manager. You will receive an email from the ECOG-ACRIN Data Manager confirming the receipt of the checklist. A contact from MD Anderson will then email you with instructions and reminders for video uploads.

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If a site agrees to participate in the study, MBS videos completed by the site will be uploaded to the Box® Cloud-based storage account maintained by MD Anderson Cancer Center. It will be the responsibility of the site to upload the videos to this cloud account. For sites that agree to participate in the study a designated contact will need to be identified on the MBS Credentialing Checklist. This contact will be given access to the MD Anderson Box® Cloud-based storage account to upload MBS videos to the cloud. Please contact E3311_MBS@jimmy.harvard.edu for questions regarding access and questions for Box® Cloud-based storage.

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The MBS studies are optional, however, they will be required at baseline and after treatment for patients from sites that have declared participation in the MBS studies, and strongly encouraged from other institutions that use the MBS study as standard-of-care for patients with swallowing dysfunction.

Please refer to Appendix VI for details of study participation. Please refer to Section 10.1.6 and Appendix IX for details regarding MBS video upload.

4.1.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E3311 Forms Completion Guidelines.

4.2 Registration/Randomization To Step 2 (Arms A, B, C, and D)

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Treatment should start within ten working days after registration to Step 2.

The following information will be requested

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2.2 Investigator's name (NCI number)

4.2.2.3 Cooperative Group Credit

4.2.2.4 Credit Investigator

4.2.2.5 Protocol specific contact information

4.2.3 Patient Identification

4.2.3.1 Patient's initials (first and last)

4.2.3.2 Patient's Hospital ID and/or Social Security number

4.2.3.3 Patient demographics

4.2.3.3.1 Gender

4.2.3.3.2 Birth date

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit ZIP code

4.2.3.3.6 Method of payment

4.2.3.3.7 Country of residence

4.2.4 Stratification and Classification Factors

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4.2.4.1 Classification Factors

- The highest risk feature assessed pathologically will determine the patient's category/treatment arm assignment.
  - Low Risk: T1-T2, N0-N1, with clear (≥ 3mm) margins, and without any ECE or PNI/LVI.

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  - High Risk: Any T stage with positive margin(s), meaning tumor at the specimen edge, not superceded by an additional, tumor free margin, OR "Extensive" (> 1mm) ECE, OR ≥ 5 metastatic

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lymph nodes, regardless of primary tumor margin status.

- Intermediate Risk: Any T stage with one or more "close" (<3mm) margin(s) OR "Minimal" (≤ 1mm) ECE, OR 1 or more lymph node >3cm in diameter (N2a neck disease), OR 2-4 lymph nodes positive, any diameter ≤ 6cm (N2b neck disease (regardless of primary tumor margin status)], OR with perineural invasion or lymphovascular invasion.
- Unknown Risk: Pathologic N2c (bilateral nodes), OR Pathologic N3 (> 6cm node)

4.2.4.2 Stratification Factors - Intermediate Risk

- Smoking Status: ≤ 10pk-yr vs. >10pk-yr

4.2.5 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

4.2.6 Additional Requirements

4.2.6.1 Participation in the Quality of Life Studies

4.2.6.2 Biological materials are to be submitted as indicated in Section 11

4.2.6.3 Patients with oropharynx squamous cell cancer are at a nutritional risk at baseline, and this risk will increase during chemo-radiotherapy. Patients who are at nutritional risk at baseline will be considered for prophylactic feeding tube placement prior to the initiation of radiation therapy. Given the importance of preservation of physiology, patients who maintain adequate adequate oral nutrition at baseline will be closely monitored by the clinical team throughout the treatment regimen to ensure optimal nutrition.

4.2.6.4 Data collection for this study will be done exclusively in Medidata Rave. Prior to beginning data entry in Rave, study staff must be registered in Medidata and complete the required training modules. Study staff will receive an invitation to join the study in Rave after evidence of IRB approval is submitted to RSS.

4.2.7 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E3311 Forms Completion Guidelines.

5. Treatment Plan

5.1 Primary Surgical Therapy (Arm S)

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Patients will be assessed clinically with a complete head and neck exam and radiographically with imaging studies. The tumor should be >1cm from the midline. The attending surgeon will determine the ultimate preoperative disease stage for trial accrual/eligibility.

Swallowing evaluation including MBS will be performed prior to starting therapy in all patients from sites that declared participation in the MBS studies. In addition, patient-reported outcome measures will be administered before starting therapy.

Any transoral approach intended to obtain negative margins of p16+ Stage III/IV (T1-T2N0-N2) oropharynx SCC

Neck dissection (Levels II-IV) to be performed during resection of the primary tumor or within 4 weeks of the study entry. If more than one surgery is performed as part of the Arm S resection, all surgeries must be completed within 4 weeks of registration to Arm S.

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5.1.1 Surgical Credentialing/Quality Control

Surgeons must be credentialed prior to enrolling patients on the trial. Adequate experience in at least one of the three categories of transoral surgery (TLM, TORS and non-laser/non-robotic transoral resections) must be demonstrated to ensure quality control. Only transoral oropharynx cancer resections are applicable; oral cavity and larynx surgeries are not applicable, even if transoral in approach. For each category of transoral surgery this experience will be confirmed, as follows:

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- Each participating surgeon must document that he/she has performed a minimum number of 20 cases of transoral excision for OPSCC as the primary surgeon;
- Each participating surgeon must document that he/she has performed at least 10 transoral resections of OPC in the past 12 months;
- The Principal Investigator will review each surgeon's submitted pathology report and operative notes for 10 OPSCC cases excised using a modality specific technique for which credentialing is being sought;

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- Responses to a surgeon questionnaire;

Surgical technique (for both TLM and TORS) will be standardized. Transoral resection of the oropharyngeal tumor will be performed at the discretion of the attending head and neck surgeon. The type of resection chosen should provide complete removal of the primary lesion with negative gross margins; this is not subject to quality assurance review; documentation of margins by frozen section at surgery is required. For en bloc resections, the gross margins will be assessed by palpation. If it is clear that a margin is close or positive -

the specimen will be inked and frozen section margins will be taken from the surgical specimen. 3- 5 mm of mobile soft tissue, then the surgeon will do a wide re-resection of that margin. The specimens will then be inked by the surgeon, avoiding ink on the main specimen in areas of a close or positive margin (which has undergone re-resection) will be done by the surgeon. Standard terminology will rely on a deep margin and four quadrants: anterior, posterior, medial, lateral. However, specific issues and approaches should vary by subsite, as detailed below.

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Surgery should be performed within 3 weeks after registration onto the study and not more than 4 weeks after study registration. If more than one surgery is performed as part of the Arm S resection, all surgeries must be completed within 4 weeks of registration to Arm S.

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Reconstruction of surgical defects should be performed using conventional techniques at the discretion of the surgeon, most often with primary closure or healing by secondary intention. In general, patients with T1 and T2 OPC do not require microvascular reconstruction flaps, therefore patients requiring free flaps will be replaced with another patient and listed as a minor protocol deviation. Secondary intention healing is recommended when appropriate but should not be pursued at the expense of obtaining wide, tumor-free margins. Reconstructive closure with local flaps is at the discretion of the surgeon.

For tonsillar carcinoma, the extent of en bloc-resection must include a tongue base margin, soft palate margin, complete constrictor margin, a complete anterior tonsillar pillar margin and a complete posterior tonsillar pillar margin.). Simple “tonsillectomy” should not be performed.. The surgeon should aim to achieve resection of tumor and surrounding structures, with an attempt made to achieve a 1 cm gross visual mucosal margin, with a minimum of 3 mm microscopic margins. For tonsillar fossa cancers,the exception to this will be the superior constrictor, which represents the deep margin which will necessarily obviate a stipulated microscopic margin but must be histologically negative . However, the constrictor margin must have a gross margin of 5 mm of mobile tissue. Therefore, given the three-dimensional complexity of the superior constrictor, margin status will be assessed as a binary endpoint: as clear or positive. These stipulations are subject to quality assurance review.

For tongue-base carcinoma, a standard en bloc resection is preferred to include, wide mucosal margins, resection of the underlying muscle, as well as the inferior portions of the tonsillar pillars (anterior and posterior). The surgeon should aim to achieve an en-bloc resection of tumor and surrounding structures, with an attempt made to achieve a minimum of 1 cm gross visual margins with ≥ 3mm microscopic margins. These are recommendations subject to quality assurance review.

For lesions with glossotonsillar sulcus involvement, the same principles of four-quadrant margin assessment will apply, with appropriate deep margin constituting the base of tongue (BOT) and/or

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constrictor muscle and/or parapharyngeal fat as the deep margin. Of note, cancers which involve extrisinic muscles of the tongue (e.g. hyoglossus muscle),as evident by preoperative imaging, are excluded since they are T4a cancers.

Surgeon credentialing and standardization of technique will be consistent between the two proposed transoral surgical trials, the current one coordinated by ECOG-ACRIN and the other by RTOG.

5.1.2 Surgical technique

5.1.2.1 Evaluation for Surgery

5.1.2.2 Access for Transoral Endoscopic Head and Neck Surgery.

The attending surgeon will perform such preoperative assessments as necessary to determine the likelihood of transoral exposure for tumor resection, including ASA classification, Mallepatti classification, dentition, difficulty with c-spine extension, etc. In the judgement of the operating surgeon, the oropharynx should be sufficiently exposed intraoperatively to proceed with enrollment on this trial.

5.1.2.3 Surgical Staging will be performed by the attending surgeon, based on clinical and radiographic criteria as well as endoscopic examination and measurements (see AJCC T-stage criteria in Appendix III).

5.1.3 Primary tumor resection. Transoral resection of the oropharyngeal tumor will be performed at the discretion of the attending head and neck surgeon. The type of resection chosen should provide complete removal of the primary lesion with negative gross margins. The type of instruments utilized and surgical technique are not subject to quality assurance review. Documentation of margins by frozen section at surgery is required. Standard terminology will rely on at least a deep margin and four quadrants: anterior, posterior, medial and lateral. However, specific issues and approaches should vary by subsite, as detailed below.

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5.1.3.1 Surgery should be performed within 3 weeks after randomization, and no more than 4 weeks after randomization. Reconstruction of surgical defects should be performed using conventional techniques at the discretion of the surgeon. Primary closure is recommended when appropriate but should not be pursued at the expense of obtaining wide, tumor free margins. Reconstructive closure is at the discretion of the surgeon. Need for microvascular (free flap) reconstruction is an exclusion criterion

5.1.3.2 For tonsillar carcinoma, a transoral lateral pharyngectomy should be performed to include resection of the underlying superior constrictor muscle, as well as the tonsillar pillars (anterior and posterior) and cranial and caudal margins.

The surgeon should aim to achieve resection of tumor and surrounding structures, with an attempt made to achieve a 1cm gross visual margin, with a minimum of 3 mm microscopic margins. For tonsil and tonsillar fossa cancers, the superior constrictor represents the deep margin. These stipulations are subject to quality assurance review.

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5.1.3.3 For tongue-base carcinoma, a standard en bloc resection is preferred to include resection of the underlying superior constrictor muscle, as well as the tonsillar pillars (anterior and posterior) and cranial and caudal margins. The surgeon should aim to achieve an en-bloc resection of tumor and surrounding structures, with an attempt made to achieve a minimum of 1 cm gross visual margins with 3 mm microscopic margins. These are recommendations subject to quality assurance review. The tongue base musculature represents the deep margin, to be sent separately for margin analysis.

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5.1.3.4 For hybrid lesions, the same principles of four-quadrant margin assessment will apply, with appropriate deep margin constituting the base of tongue and/or constrictor parapharyngeal fat as the deep margin.

5.1.3.5 A positive margin is defined as carcinoma in situ or invasive carcinoma at the margin of resection, which is not superceded by additional tissue (a new separate margin) found to be histopathologically free of disease. If a new separate margin is obtained adjacent to a specimen or margin containing CIS or invasive SCC is deemed pathologically negative, the patient will be considered to have “close” margins.

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5.1.4 Margin excision and histopathologic assessment.

Intraoperatively, the surgeon must send 4 quadrant margins plus deep margin (recommend 3 mm diameter at minimum), submitting the oriented specimen to the pathologist. A positive margin found on final pathologic analysis after negative frozen sections will be classified as a “close” negative margin resection (R0) and entered in the RT randomization (Arms B-C) if additional histopathologically benign tissue surrounding and deep to the region of concern is removed and analyzed pathologically.

Recommendation for standard practice (permanent section histopathology). It is recommended to perform photodocumentation of the specimen by the pathologist after these procedures, using high resolution digital photography with annotation. If the surgeon obtains additional margins from the patient, the “new margins” should refer back to the geometric orientation of the resected tumor specimen. A statement by the pathologist in the final surgical pathology report should point out that this “new” margin represents the final margin of resection in addition to its histologic status.

5.1.4.1 An adequate resection is defined as clear resection margins with at least enough clearance from gross tumor to obtain clear frozen section and permanent margins (defined as at least 3 mm grossly)

5.1.4.2 The details of resection margins should be included in the operative dictation. The margins may be assessed on the resected specimen or alternatively from the surgical bed with proper orientation.

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5.1.4.3 A “clear margin” is defined as a distance from the invasive tumor front that is ≥ 3 mm from the resected margin. If the surgeon obtains additional margins from the patient, the “new” margins should refer back to the geometric orientation of the resected tumor specimen. A statement by the pathologist in the final surgical pathology report should point out that this “new” margin represents the final margin of resection in addition to its histologic status.

5.1.4.4 A “close margin” is defined as a distance from the invasive tumor front that is < 3 mm from the resected margin

5.1.5 Neck Dissection

5.1.5.1 A formal selective or modified radical neck dissection, level II-IV, will be performed in all cases. Numbering and/or nomenclature outlined in the “Neck Dissection Guide” will be used. Resection of levels II-IV are required, with levels I and/or V electively dissected at the discretion of the attending surgeon. The neck dissection should be oriented or separately partitioned in order to identify levels of lymph nodes encompassed in the dissection.

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5.1.5.2 Extent of neck dissection

Patients will undergo ipsilateral selective or modified radical neck dissection of levels II-IV for lateralized lesions of the tongue-base, tonsillar region and/or glossopharyngeal sulcus. Midline lesions are discouraged from accrual to this trial. For patients with SCC of the base of tongue that approaches within 1 cm of the midline, a contralateral neck dissection should be performed, also of levels II-IV. For ipsilateral and contralateral lymphadenectomy, level I-b and V may be electively dissected at the discretion of the attending surgeon, but is not required.

5.1.5.3 A minimum of 20 lymph nodes per dissected side of the neck is required and is subject to quality assurance review. Removal of < 20 but > 15 lymph nodes will be considered a minor protocol deviation and recorded.

5.1.5.4 For patients with SCC of the base of tongue where the tumor is within 1 cm of the midline, a contralateral neck dissection should be performed, also of levels II-IV. For

ipsilateral and contralateral lymphadenectomy, level I and/or V may be electively dissected at the discretion of the attending surgeon, but is not required. For lateralized base of tongue cancers not within 1 cm of midline, the contralateral neck treatment is at the discretion of the treating surgeon. The neck dissection should be oriented or separately partitioned in order to identify levels of lymph nodes encompassed in the neck dissection specimen.

5.1.5.5 Adequacy of Nodal Harvest: Histopathologic assessment of 20 nodes is required for all neck dissection specimens. Realizing that there is some anatomic variation from patient to patient, an absolute minimum of 15 nodes is required. More specifically, specimens of < 20 but > 15 lymph nodes would be an acceptable protocol violation.

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5.1.5.6 Pathologic assessment of extracapsular extension (ECE): Lymph nodes ≤ 2 cm in greatest dimension are considered adequately assessed with one section. Multiple lymph nodes ≤ 2 cm in greatest dimension may be submitted in a single cassette. Lymph nodes > 2 cm in greatest dimension require multiple sections (and possibly multiple cassettes); specifically, one section per 1 cm should be submitted. Sections should include the edge of the lymph node that interfaces with surrounding fibroadipose tissue.

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5.1.5.7 Ligation of arterial blood supply of the primary oropharyngeal tumor is required to avoid major postoperative pharyngeal hemorrhage.[78, 79]

- At a minimum, it is recommended that the surgeon ligate the ipsilateral lingual and facial arteries. At the surgeon's discretion and judgment, ligation of other arteries, such as the ascending pharyngeal and superior thyroid, may be considered.
- If the external carotid arterial trunk itself is ligated, the surgeon must ligate the vessel at an adequate distance from the carotid bulb to avoid injury to the internal carotid artery. Care should be taken to avoid injuring the internal carotid artery if ligating the ascending pharyngeal artery, since its takeoff may occur posteriorly putting the ICA at risk.
- The attending surgeon is directed to perform this portion of the procedure him/herself.
- The arteries should be ligated but not divided.
- The case report form will now require the documentation, taken from the operative report, confirming that arterial ligation was performed and delineating which vessels were ligated.
- Please contact the study chair, Dr. Ferris, with any questions or to clarify.

Failure to perform arterial ligation, and provide written documentation of this critical aspect of the surgery, will constitute a reportable deviation which will be forwarded to the Credentialing Committee and subject to peer-review and appropriate action. Such action may include suspension of the surgeon's credentials for involvement in the trial, thus preventing further accrual to the trial.

5.1.6 Surgical Quality Assurance Reviews

5.1.6.1 The study chair, Robert L. Ferris, MD, PhD, and designated Surgical Quality Assurance co-Chairs will review surgical preoperative eligibility criteria and operative reports for both the transoral endoscopic resection as well as the neck dissection(s) (i.e., the Operative and Surgical Pathology reports for the initial evaluation of lymph nodes and the surgical resection).

5.1.6.2 Dr. Ferris will perform a Quality Assurance Review after complete data for the first 15 cases enrolled has been received at ECOG-ACRIN Headquarters. Dr. Ferris will perform the next review after complete data for the next 15 cases enrolled has been received at ECOG-ACRIN Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at ECOG-ACRIN Headquarters, whichever occurs first.

5.1.6.3 Goals of Surgical Quality Assurance

- To assure eligibility and correct surgical staging of patients;
- To assure safety of patients undergoing resection
- To assure adequate resection of primary tumor and neck dissection

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5.1.6.4 Surgical Protocol Compliance Criteria

Deviations Minor:

- "Close" margin, (< 3mm)
- suboptimal neck dissection (< 20 nodes removed)

Deviations Unacceptable: Those deviations that affect patient safety/outcome, which will result in an institution being suspended from further participation in the study, such as:

- Positive Margin rate exceeding 20% (assessed every 5 cases accrued)
- Inadequate nodal dissection (< 15 nodes removed)

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- Postoperative bleeding requiring return to the operating room for control, exceeding 20% of submitted patients (assessed every 5 patients accrued)

5.1.7 Pathologic Analysis of Surgical Specimens

Within RTOG / ECOG-ACRIN centers, a designated surgical pathologist will be responsible for quality control of surgical pathology material processing, evaluation and reporting at their respective institution.

Histopathologic Assessment: Histopathologic assessment of surgical pathology frozen and permanent sections must include examination and reporting of the following parameters:

- Perineural invasion (PNI) and lymphovascular invasion (LVI) Absent, or Present
- Extracapsular extension (ECE) requires gross and microscopic assessment
  - *absent* (negative or nodal metastasis with smooth/rounded leading edge confined to thickened capsule/pseudocapsule),
  - *present - minimal* (tumor extends ≤1 mm beyond the lymph node capsule), or
  - *present - extensive* (tumor extends >1 mm beyond the lymph node capsule (includes soft tissue metastasis)

p16 Immunohistochemistry (must be performed in a CLIA-certified laboratory); p16 antibody obtained from Roche mtm laboratories AG (CINtec® clone E6H4™) is recommended.

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- *negative* (cytoplasmic immunoreactivity noted in < 70% of tumor cells), and
- *positive* (cytoplasmic immunoreactivity noted in ≥ 70% of tumor cells).

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Pathology materials are required to be submitted for central review as outlined in Section 11.

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5.1.8 Post-operative Management

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Treatment should start within ten working days after registration to Step 2.

The highest risk feature assessed pathologically will determine the patient's category/treatment arm assignment.

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5.1.8.1 Definition of Low-Risk Patient Cohort and Management: Arm A (7 weeks)

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Low-risk stratification will require the presence of both primary site and neck dissection low-risk pathologic features, and pathologic stages T1N0, T1N1, T2N0, and T2N1, with no ECS and clear margins (≥ 3mm). This category will include the absence of close margins (< 3mm), perineural invasion and lymphovascular invasion in the primary site surgical specimen. Low-risk neck

dissection pathologic features include no more than N1 nodal disease without extracapsular extension.

The adjuvant management plan for low-risk HPV-associated OPSCC patients treated with transoral surgery and neck dissection will be prospective observation.

Summary of acceptable pathologic stage for "low risk" Arm A:

T1-2N0-1, with clear (≥ 3mm) margins, and without any ECE or PNI/LVI.

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5.1.8.2 Definition of High-Risk Patient Cohort and Management: Arm D (5-7 weeks)

High-risk stratification will be applied when the presence of primary site or neck dissection high-risk pathologic features are identified. High-risk primary site pathologic features will include a positive surgical margin or the presence of "extensive" (> 1mm) ECE (i.e. *present – beyond minimal*). Within the context of this protocol, only patients with tumor that extends > 1 mm beyond the lymph node capsule (including soft tissue metastasis) will be considered for concurrent cisplatin.

Patients with extensive N2b neck disease (≥ 5 metastatic lymph nodes) regardless of primary tumor margin status will also be considered high-risk.

Summary of acceptable pathologic stage for "high risk" Arm D:

- **Any one of the following features constitutes "high risk" status and will assign the patient to Arm D.**
- **Any T stage with positive margin(s), meaning tumor at the specimen edge that is not superceded by an additional, tumor free margin**
- **"Extensive" (> 1mm) ECE**
- **≥ 5 metastatic lymph nodes) regardless of primary tumor margin status.**
- **Please contact the PI, Dr. Ferris with any questions or to clarify.**

The adjuvant management plan for high risk HPV-associated oropharyngeal carcinoma patients treated with transoral surgery and neck dissection will be concurrent postoperative CRT to 66 Gy in 33 daily fractions. Concurrent cisplatin will be administered at a dose of 40 mg/m^2 on days 1, 8, 15, 22, 29, 36, 43.

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5.1.8.3 Definition of Intermediate-Risk Patient Cohort and Management: Arms B-C (5-7 weeks)

Intermediate-risk stratification will be applied when the presence of primary site or neck dissection intermediate-risk pathologic features are identified. **Any one of the pathologic features below will constitute "intermediate risk" and assign the patient to the randomized RT dose arms B or C.**

Summary of acceptable pathologic stage for "intermediate risk" Arms B or C – randomized RT dose:

- **Any one of these features constitutes "intermediate risk" status and will assign the patient to Arm B or C.**
- **Any T stage with one or more "close" (<3mm) margin(s)**
- **"Minimal" (≤ 1mm) ECE**
- **1 or more lymph node >3cm in diameter (N2a neck disease).**

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- **2-4 lymph nodes positive, any diameter ≤ 6cm (N2b neck disease), regardless of primary tumor margin status.**
- **perineural invasion**
- **lymphovascular invasion**
- **Please contact the PI, Dr. Ferris with any questions or to clarify.**

The adjuvant management plan for intermediate risk HPV-associated OPSCC patients treated with transoral surgery and neck dissection will be postoperative RT alone. Patients will be randomized to either 60 Gy or 50 Gy fractionated daily over 30 or 25 fractions, respectively. For all patients, bilateral cervical nodal chains and the primary site will be irradiated. For selected patients randomized to 60 Gy, the ipsilateral nodal regions involved with carcinoma and the primary surgical site will receive a 10 Gy boost to a total of 60 Gy

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5.1.8.4 Definition of Unknown-Risk Patient Cohort and Management: Arm C (5-7 weeks)

Patients found to have N2C or N3 disease on final pathologic analysis are at unknown risk for recurrence, but are not candidates for deintensified adjuvant therapy in this trial. These patients will be treated on Arm C.

5.1.9 Postoperative Radiation Therapy

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5.1.9.1 Credentialing

Institutions not previously credentialed for use of IMRT in NCTN trials must irradiate IROC Houston's head and neck phantom. Contact IROC Houston

(http://irochouston.mdanderson.org) for information about their phantoms.

Patients will be considered unevaluable if required credentialing has not been completed.

5.1.9.2 Equipment

5.1.9.2.1 Modality: Accelerator x-ray beams with nominal energy of at least 4 MV shall be used. Linear accelerators must be capable of delivering treatment using multi-leaf collimation.

5.1.9.2.2 Intensity Modulated Radiation Therapy (IMRT) is mandatory for this study. Guidelines developed by the NCI for the use of IMRT in clinical trials should be followed. (See IROC website, http://www.irocri.qarc.org).

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5.1.9.2.3 Calibration: All therapy units used for this protocol shall have their calibrations verified by the IROC Houston QA Center (RPC).

5.1.9.2.4 CT Simulation: CT simulation will be required in all patients. A thermoplast mask shall be used for patient immobilization (shoulders along with head strongly encouraged, although an alternative method of ensuring reproducible shoulder position is acceptable) for both CT-simulation and for each daily treatment. IV contrast is required in all patients (unless renal function prohibits contrast). Slice thickness of ≤ 3mm is required. The patient should be simulated and immobilized with the neck in a hyper-neck extended position as best tolerated by the patient that will be reproducible on a daily basis. Surface delineation of surgical scars with radio-opaque markers will also be required at the time of CT simulation.

5.1.9.2.5 Image Fusion: Additional images of the patient in the treatment position such as with MRI and 18-fluorodeoxyglucose PET will be permitted to facilitate the treatment planning process. However, the primary image set for the treatment planning will be the CT image set.

5.1.10 Organs at Risk (OAR) Delineation

In general, the OARs that require delineation are dictated by the superior and inferior extent of the planning target volumes. For example, if the superior extent of the target volume extends to the level of the C1 vertebral body, the brainstem at this level will need to be delineated.

5.1.10.1 OARs that are required for delineation include the following if they lie within the superior and inferior extent of the planning target volumes**:**

- spinal cord
- brainstem
- right and left middle and inner ears
- right and left globe of the eye
- right and left lacrimal gland
- right and left optic nerves
- optic chiasm
- right and left lens
- superior constrictor muscle
- middle constrictor muscle
- inferior constrictor muscle
- cricopharyngeus muscle
- esophagus
- endolarynx: This volume will consist of the tissues medial and contained within the laryngeal cartilage and will include the endolaryngeal structures from the level of the tip of the suprahyoid epiglottis to the inferior extent of the cricoid cartilage that does not overlap with any adjacent PTV. This OAR will be gapped from the adjacent PTV by 5-15 mm. Where the adjacent PTV is to be prescribed 50 Gy, the endolarynx will be gaped from the PTV by 5 mm. Where the adjacent PTV is to be prescribed 60 Gy, the endolarynx will be gapped from the PTV by 10 mm. Where the adjacent PTV is to be prescribed 66 Gy, the endolarynx will be gapped from the PTV by 15 mm.
- right and left parotid glands
- right and left submandibular glands
- skin
- midline oral avoidance (MOA): This midline avoidance structure will include the portion of the oral cavity and oropharynx that is not included in the planning target volume. The avoidance structure will be delineated such that there is a gap between the avoidance structure and the adjacent PTV that may range from 5-

15 mm. Where the adjacent PTV is to be prescribed 50 Gy, the MOA will be gaped from the PTV by 5 mm. Where the adjacent PTV is to be prescribed 60 Gy, the MOA will be gapped from the PTV by 10 mm. Where the adjacent PTV is to be prescribed 66 Gy, the MOA will be gapped from the PTV by 15 mm

- mandible

5.1.10.2 Additional OARs that may be contoured but not required include

- right and left temporal-mandibular joint
- right and left thyroid gland
- right and left brachial plexus
- laryngeal cartilage
- hyoid bone
- thyroid gland

5.1.10.3 Planning OARs

For critical neurologic OARs such as the brainstem, spinal cord, chiasm and optic nerves a systematic margin of 2 mm may be added to generate additional planning OAR volumes (PRVs).

To avoid the potential under-dosing of the CTV-N50 or CTV-N60 volumes where they overlap with the deep parotid lobes, a planning parotid volume may be delineated that represents the non-overlap portion of the parotid glands. This planning OAR will be referred to as “parotid-PTV”.

5.1.11 Target Volume Delineation

5.1.11.1 Target Volumes Definitions: The definition of volumes will be in accordance with ICRU Reports #50 and #62. Target volume nomenclature shall include the following:

- Clinical Target Volume (CTV) is defined as all areas that may have subclinical carcinoma based on assessment of the preoperative imaging, intraoperative findings by the surgeon and the final pathologic evaluation. Where there is potential discordant findings especially between the final pathology and the intraoperative findings typically with regards to the extent of the primary tumor, communication between the radiation oncologist and the surgeon is required for a consensus to be reached regarding the original extent of the primary carcinoma.

  Planning Target Volume (PTV) will provide a margin around the CTVs to compensate for variabilities in daily treatment set up, patient positioning, and internal organ motion. A minimum of 3 mm and a maximum of 5 mm

around the CTVs is required in all directions to define each respective PTV (i.e. PTV-P60, PTV-N60, PTV-N50). The extent of the PTV margin is influenced by the set-up reproducibility at each institution.

Where there is a concern of gross tumor identified postoperatively and where further surgery is not possible, the radiotherapy treatment plan may be modified to include delineation of a gross tumor volume (GTV).

- Gross Tumor Volume (GTV) is defined as all known areas of gross disease determined from CT, MRI, clinical information, and endoscopic findings. Grossly involved lymph nodes are defined as any lymph node ≥1cm or nodes with a necrotic center or that have abnormal FDG uptake on PET. It is strongly encouraged that the radiation oncologist outlines the radiographic extent of the primary tumor and neck nodes along with neuro-radiologist. Whenever possible, it is recommended that diagnostic images be fused to the planning CT scan image dataset to more accurately determine the GTV. The gross tumor at the primary site will designated as GTV-P, and clinically involved gross lymph nodes are designated GTV-N.

5.1.11.2 Guidelines for Target Volume Delineation

- CTV-P60: CTV-P60 will represent the primary **invasive tumor base**. As the surgery will be transoral, the need to comprehensively treat the surrounding normal tissues that would otherwise be at risk for tumor seeding is not a major consideration. The primary factor influencing the delineation of the CTV-P60 volume should be influenced by the intra-operative assessment of the invasive base of the tumor. These findings should be compared to the preoperative imaging to reconcile any discrepancy. CTV-P60 should **not** include the preoperative intra-luminal extent of the primary tumor that did not invade the oropharyngeal mucosa. This volume shall include a 3-5 mm margin of uncertainty around the estimated extent of the invasive tumor base that is deemed at risk.
- CTV-N60: CTV-N60 will represent the dissected cervical nodal volume found to have nodal metastases. This nodal volume will include the peripheral extent of the sternocleidomastoid muscle laterally and medially, will include a portion of the levator scapulae and the scalene muscles.
- CTV-N50: CTV-N50 will represent the either dissected cervical nodal volumes found not to have nodal

metastases or the undissected contralateral cervical neck when it is treated. This nodal volume will include the peripheral extent of the sternocleidomastoid muscle laterally and medially, will include a portion of the levator scapulae and the scalene muscles. Anteriorly, the posterior aspect of the submandibular gland and the medial pterygoid muscle will be the anterior boundary of level II nodal region.

a. For the ipsilateral dissected neck, CTV-N50 should be extended to nodal volumes adjacent to pathologically involved nodal volumes. For example, if the neck dissection reveals nodal metastases in level II, the adjacent level I and level V should be included in CTV-N50. This nodal volume will include the peripheral extent of the sternocleidomastoid muscle laterally and medially, will include a portion of the levator scapulae and the scalene muscles.

b. Indications for inclusion of the lateral retropharyngeal lymph nodes include the presence of ipsilateral level II nodal metastases or primary tumor extension to involve the posterior pharyngeal mucosa or suspected to be at risk due to involvement of the posterior tonsil pillar mucosa. The ipsilateral lateral retropharyngeal lymph nodes lie medial to the internal carotid artery and are predominantly located at the level of C1 vertebral body and occasionally at the C2 vertebral body level. The medial retropharyngeal lymph nodes are not to be delineated.

c. The contralateral retropharyngeal lymph nodes will be delineated as part of CTV-N50 when there is clinical/pathologic findings of ipsilateral retropharyngeal lymph node metastases.

d. For the contralateral undissected neck, CTV-N50, the nodal volume should include the contralateral level II, III and IV nodal regions beginning at the level of the posterior digastric muscle. This nodal volume will include the peripheral extent of the sternocleidomastoid muscle laterally and medially, will include a portion of the levator scapulae and the scalene muscles.

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e. Ipsilateral neck will be permitted, ie. omitting the contralateral CTV-N50 when the mucosal invasive base of the tumor is > 1 cm from the midline mucosa as judged at the time of the surgery. For base of tongue cancers, the primary tumor adverse pathologic features including the positive surgical margins should not be present on the medial tumor

specimen. For base of tongue cancers, the primary tumor should also not demonstrate a deep invading tumor front at the time of the surgery. The distance from the midline mucosa will require documentation including the mucosal surface that is involved when the contralateral CTV-N50 is omitted. Omitting the contralateral neck CTV-N50 is not permitted for N2c tumors and where clinical/pathologic findings of ipsilateral retropharyngeal lymph node metastases.

- CTV-P66: CTV-P66 will represent the region in the primary tumor bed deemed to be at risk due to the presence of a positive involved surgical margin. Typically, this will be at the deep surgical resection margin and thus will not be significantly extending into the pharyngeal lumen.
- CTV-N66: CTV-N66 will represent the region in the dissected neck found to have grade 4 ECE. This volume should include sternocleidomastoid muscle in the nodal levels found with ECE *present - beyond minimal* (tumor extends > 1 mm beyond the lymph node capsule (includes soft tissue metastasis).
- CTV-P70 or CTV-N70: CTV-P70 or CTV-N70 will represent postoperative gross tumor that requires treatment to 70 Gy.

5.1.12 IMRT Prescription and Treatment Planning

5.1.12.1 The prescription dose will be administered with a cone-down prescription with daily doses of 2 Gy. No simultaneous in-field boost / dose-painting will be permitted. Treatment will be delivered once daily, 5 fractions per week. Treatment breaks, if necessary, should not exceed 5 treatment days and the reason(s) for the break must be clearly recorded in the treatment record. Any treatment break(s) exceeding two (2) treatment days for reasons other than toxicity/illness will be considered a protocol deviation. The reason for the missed treatment or treatments must be clearly indicated in the copy of the patients treatment record submitted to IROC Rhode Island.

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- PTV-N50: will be prescribed 50 Gy in 25 daily fractions
- PTV-P60 or PTV-N60: will be prescribed 60 Gy in 30 daily fractions
- PTV-P66 or PTV-N66: will be prescribed 66 Gy in 33 daily fractions
- PTV-P70 or PTV-N70: will be prescribed 70 Gy in 35 daily fractions

As a cone-down IMRT technique will be used, a dose-summary that represents all the phases of IMRT treatment

planning shall be generated. For example, if the maximum PTV prescription for a patient is to PTV-P66, then the first phase will deliver 50 Gy to both the primary and unilateral (see section 5.1.11.2.e) or bilateral cervical nodal volumes followed by a second phase to the primary surgical bed for an additional 10 Gy and a third phase to the just the boost volume at the site of the positive surgical margin for an additional 6 Gy.

5.1.12.2 Tissue Heterogeneity: The dose calculation shall take into account the effect of tissue heterogeneities. The method used for tissue heterogeneity calculations shall be reported. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

5.1.12.3 No specific beam arrangements will be specified. Commonly, a co-planar beam arrangement is used.

5.1.12.4 Treatment Planning Objectives: The treatment plan(s) used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTVs and critical normal structures. Inverse optimization algorithms will be used to achieve at least 95% of the volume of the specified PTVs is covered by the prescribed isodose surface while meeting the dose limitations to the delineated OARs.

Priority	Structure Name	Treatment Planning Objective				
		Coverage	Volume	OAR Maximum Dose Constraint(Gy)	OAR Partial Volume Dose Constraint	
					Volume	Dose (Gy)
1	PTVs	D95= prescription dose				
1	spinal cord		1 cc	45 Gy		
1	brainstem		1 cc	54 Gy		
1	R and L optic nerve		0.1 cc	45 Gy		
1	optic chiasm		0.1 cc	45 Gy		
2	R and L optic nerve PRV		0.1 cc	50 Gy		
2	R or L parotids				50%	< 20 Gy
2	R and L parotids combined				mean	< 26 Gy
2	midline oral avoidance		5 cc	45 Gy	50%	< 35 Gy
2	endolarynx		1 cc	50 Gy	50%	< 30 Gy
2	cricopharyngeus		1 cc	50 Gy	50%	< 30 Gy
2	esophagus		1 cc	45 Gy		
2	R and L middle and inner ear		0.1 cc	45 Gy		
2	R and L optic globe		1 cc	50 Gy		
2	R and L lacrimal gland		1 cc	40 Gy		
2	R and L lens		1 cc	30 Gy		
2	mandible		1 cc	70 Gy		
2	skin		5 cc	60 Gy		
3	submandibular gland contralateral to the side of the neck dissection [1]				50%	< 35 Gy

[1] when the contralateral level I nodal group is not part of CTV-N50

5.1.12.5 For treatment planning purposes, the dosimetric constraints that will be used for each phase of the IMRT treatment planning will be modified by a proportion that reflects the maximum dose for that phase to the total prescription dose. For example, if the maximum prescription is 60 Gy, the first phase that will deliver 50 Gy will utilize the dose constraints modified by 5/6.

5.1.13 Definitions of Dosimetric Variation - Minor Variation/Major Variation

To avoid a minor variation: no more than 3% volume of the PTV will receive greater than 108% of the prescribed dose, and no tissue (target or non-target) shall receive more than 110% of the prescribed dose. In addition, no more than 5% volume of any PTV shall receive less than 95% of the prescribed PTV dose, and no more than 1% of the PTV volume receives less than 93% of the prescribed dose.

Reported doses for PTVs shall include the prescription dose, maximum point dose for each PTV, % PTV receiving 110%, 108% and 95% and 93% dose. Also, the mean dose must be reported.

5.1.14 Repeat Simulation and Planning

There are circumstances where it may be appropriate to repeat a patient's simulation. Examples may be when there is excessive weight loss and either the thermoplast mask is no longer tight or the patient's external contour no longer matches the original contour typically due to weight loss. The original PTVs should continue to be treated to the original volume.

5.1.15 Dose Calculation and Reporting

- Digital Submission:

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  Submission of radiation therapy treatment plans in digital format as DICOM RT is required for this study. Instructions on digital data submission are available online from the IROC Rhode Island website at http://www.irocri.qarc.org/ (See Digital Data section).

- Dose Volume Histograms:

  Dose volume histograms must include GTV's, CTV's, PTV's, and organs at risk as noted above. A DVH shall also be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

- Re-planning:

  If the patient is re-simulated and re-planned on a new CT dataset, the individual plans shall be submitted. For such cases, the fused data-set with the target volumes and critical normal structures should also be submitted. If your planning system has the capability of exporting a DICOM spatial registration file, the spatial registration file shall be submitted along with the two CT scan sets. Otherwise screen captures of the fused datasets with the target volumes and critical normal structures shall be submitted.

- IMRT Plan Verification:

  The monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

5.1.16 QA Documentation

Digital Submission:

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Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. Submission may be by either sFTP or CD. Instructions for data submission are on the IROC Rhode Island web site at http://www.irocri.qarc.org/ under "Digital Data." Any items on the list below that are not part of the digital submission may be included with

the transmission of the digital RT data via sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

Please submit the following data within 3 days of the start of radiation therapy:

External Beam Treatment Planning System

- RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- If replanning is done on a new CT dataset and your planning system has the capability of exporting a DICOM spatial registration file, submit the spatial registration file along with the two CT scan sets. Otherwise screen captures of the fused datasets with the target volumes and critical normal structures delineated shall be submitted.

Supportive Data

- Copies of the pre-study diagnostic imaging used to define the GTV's and CTV's. Copies of the corresponding radiology reports, exam notes, clinical information, and copies of the endoscopic findings must also be submitted. Imaging studies shall be submitted as DICOM files and either copied to a CD or submitted via SFTP. Multiple studies for a patient may be included on a CD, but please include only one patient per CD.
- Documentation of an independent check of the calculated dose when IMRT is used.
- Prescription sheet for the entire treatment.

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Forms

- RT-1 Dosimetry Summary Form.
- A copy Appendix III (AJCC Head/Neck Staging Criteria).
- Copy of Appendix V "ECOG-ACRIN Checklist for Submission of Radiation Oncology Quality Assurance Materials"

Within 1 week of the completion of radiotherapy submit the following items:

- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.

- RT-2 Radiotherapy Total Dose Record Form.
- If emergency RT is administered, documentation should be provided in the form of the RT-2 Total Dose Record Form and the radiotherapy record (treatment chart).
- Copy of Appendix V "ECOG-ACRIN Checklist for Submission of Radiation Oncology Quality Assurance Materials"

These data should be forwarded to:

IROC Rhode Island QA Center
640 George Washington Highway, Building B, Suite 201
Lincoln, Rhode Island 02865-4207
Phone: (401) 753-7600
Fax: (401) 753 7601

E-mailed data can be sent to: DataSubmission@QARC.org

Questions related to the radiotherapy treatment planning can be directed to:

Harry Quon, MD
Johns Hopkins University
Phone: 410-502-3877
E-mail: hquon2@jhmi.edu

Questions regarding the dose calculations or documentation should be directed to:

IROC Rhode Island QA Center
Quality Assurance Review Center
640 George Washington Highway, Building B, Suite 201
Lincoln, Rhode Island 02865-4207
Phone: (401) 753-7600

If there are any changes in the patient's status (i.e., early discontinuation of protocol treatment, delay in starting radiotherapy, or break in radiotherapy) these should be communicated in writing to IROC Rhode Island by fax (401) 753-7601 or email to ECOG@qarc.org.

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5.1.17 Definitions of Deviations in Protocol Performance

Dose:

Minor deviation: The delivered dose to the prescription volume differs from protocol specification by more than 5% but less than 10%.

Major deviation: The delivered dose to the prescription volume differs from protocol specification by more than 10%.

Dose Uniformity:

Minor deviation: More than 3% of the PTV receives more than 108% of the prescription dose or more than 1% of the PTV receives less than 93% of the prescription dose.

Major deviation: More than 5% of the PTV receives more than 115% of the prescription dose.

Volume:

Minor deviation: Margins for PTV less than specified, or field(s) excessively large.

Major deviation: GTV (or corrected GTV if not appropriately drawn) not included within the 95% dose volume

Treatment Breaks:

More than two missed treatment days for any reason other than a toxicity is considered a deviation.

Minor deviation: 3-5 days.

Major deviation: > 5 days

Evaluation After Completion of Concurrent Therapy

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Patients will be re-evaluated after the completion of treatment to assess clinical and radiographic response by complete head and neck exam and imaging studies.

Patients with persistent disease will be evaluated and where indicated undergo appropriate surgical resection.

5.1.18 Administration of cisplatin

Patients on Arm D will receive cisplatin 40 mg/m^2 as an IV infusion in normal saline over 60 minutes weekly (Days 1, 8, 15, 22, 29, 36, 43) during 7 weeks of radiation therapy. Cisplatin administration outside of these specified days during radiation is only allowed in the event of holidays that do not permit drug and radiation delivery on the specified date. Subsequent chemotherapy doses should follow the protocol specified days of treatment. No cisplatin will be prior to day 1 of radiation therapy. In the event that radiation therapy is held, no cisplatin will be administered during the week of the radiation break. **The use of colony stimulating factors (G-CSF, GM-CSF) and amifostine in this trial is explicitly discouraged. Erythropoietin stimulating agents, such as erythropoietin and darbepoietin, are prohibited.**

- Cisplatin administration should be accompanied by vigorous forced hydration (1000ml delivered over 1-2 hours just prior to treatment, and immediately after treatment) and Mannitol diuresis. Hydration/diuresis may be adjusted where clinically indicated at the discretion of the investigator, or according to standard institutional or regional practice. Potassium chloride and/or magnesium sulfate may be added to the hydration solutions per institutional practice. Magnesium wasting is a well-known complication of cisplatin therapy.
- Routine premedication should include a 5 – HT3 receptor antagonist and dexamethasone. Aprepitant is encouraged for prevention of severe nausea, and should be administered on the

following schedule: aprepitant 125mg orally day 1, aprepitant 80 mg orally day 2, day 3

- Careful attention should be paid to urine output with supplemental fluids or diuretics given as appropriate. Serum potassium and magnesium levels should also be monitored regularly.
- Regular administration of aminoglycoside antibiotics, iodinated CT contrast, or other nephrotoxic agents within 48 hours of cisplatin should be avoided in view of their potentiating effect on cisplatin nephrotoxicity.
- Aluminum-containing needles should not be used for cisplatin administration.

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5.1.19 Patient Reported Outcomes (PROs)

Quality of Life (QOL) assessments will be performed at baseline, end of treatment, and at 3, 6, 12, and 24 months after completion of treatment. If an additional tumor assessment is done prior to 3 years from study entry, one final QOL assessment is requested. Please refer to Appendix V for the complete schedule.

QOL will continue to be collected for all patients post recurrence.

Paper questionnaires will be completed by the patient, and then data from the questionnaire should be entered into Medidata Rave within 7 days of completion. The original copy needs to be kept in the study subject's research binder. Refer to the ECOG website for a copy of the questionnaire.

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5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE)**: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Attribution**: An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is ***clearly NOT related*** to treatment
Unlikely	The AE is ***doubtfully related*** to treatment
Possible	The AE ***may be related*** to treatment
Probable	The AE is ***likely related*** to treatment
Definite	The AE is ***clearly related*** to treatment

- **CTCAE**: The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Any adverse event, the type or severity of which is consistent with the current investigator's brochure, product label, and/or the protocol document

5.2.3 Reporting procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)
- the FDA (1-800-FDA-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

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Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of reporting requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol E3311 and outline the specific expedited adverse event reporting requirements for study E3311.

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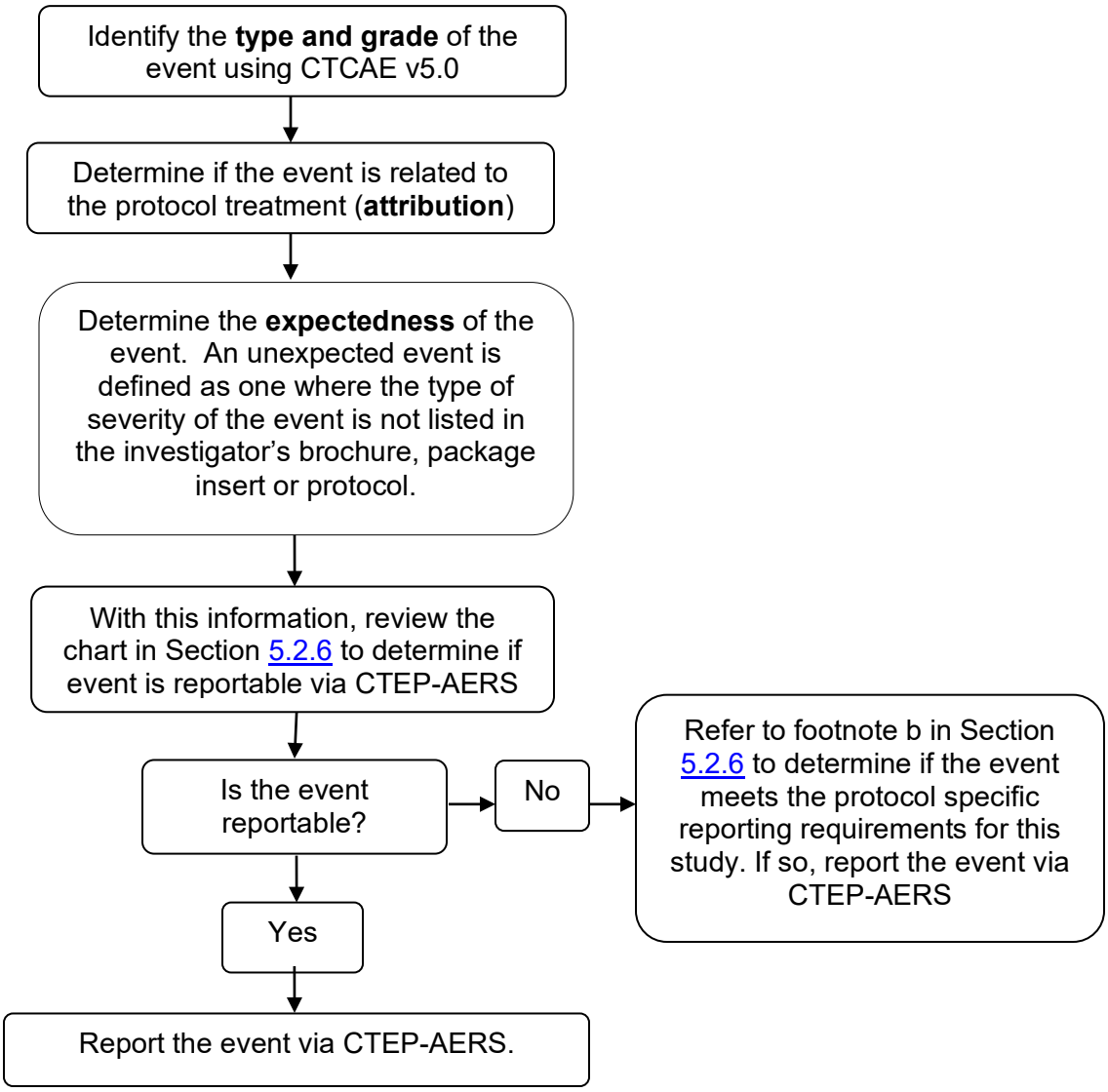
5.2.5 Steps to determine if an event is to be reported in an expedited manner



5.2.6 Expedited Reporting Requirements for Arms S, A, B, C and D on protocol E3311

Commercial Agents: Cisplatin, Carboplatin

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment regardless of attribution. **NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event**.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Bleeding: Any grade 3-4 bleeding (requiring hemostasis in the operating room), regardless of attribution or expectedness, must be reported via CTEP-AERS within 7 calendar days of learning of the event.

5.2.7 Other recipients of adverse event reports and supplemental data

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.8 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave in 14 days.
2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave in 14 days.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
     - *Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy*
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form

5.3 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.3.1 The use of colony stimulating factors (G-CSF, GM-CSF), and amifostine are explicitly discouraged. Erythropoietin stimulating agents, such as erythropoietin,and darbepoietin, are prohibited.

5.3.2 Cisplatin

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5.3.2.1 Hematologic

Cisplatin will not be given until the ANC ≥ 1000/mm^3 and the platelet count ≥ 75, 000/mm^3. Complete blood count, differential and platelets will be checked weekly during therapy. Dose modifications are as per table below:

Toxicity	Cisplatin Modification
ANC < 1000/mm^3 or Platelets < 75,000/mm^3	Hold therapy 1 week, and treat at full dose if ANC ≥ 1000 and platelets ≥ 75,000 If ANC and/or platelets have not recovered after 7 days, lower cisplatin to 30 mg/m^2 weekly and re-initiate therapy once ANC ≥ 1000 and platelets ≥ 75,000 If after dose reduction, ANC < 1000 and/or platelets < 75,000 on the next day of treatment, hold cisplatin until ANC ≥ 1000 and platelets ≥ 75,000 and restart at 20mg/m^2. If on the subsequent treatment day, ANC < 1000 and/or platelets < 75,000, discontinue further chemotherapy
Neutropenic fever	Hold cisplatin until ANC ≥ 1000, and re-start at 30mg/m^2. If cisplatin is already at 30mg/m^2, restart cisplatin at 20mg/m^2. If cisplatin was given at 20mg/m^2, discontinue further chemotherapy.

NOTE: No dose re-escalations will be allowed.

5.3.2.2 Renal

Cisplatin will not be given if the serum creatinine is > 1.6 mg/dl. Serum creatinine is required before each dose of cisplatin. Modify the cisplatin dose using the following parameters for calculated creatinine clearance determined in the well-hydrated patient using the modified Cockcroft-Gault formula:

{ (140 - age) (Wt in kg)* } /72 (serum creat mg/dL)

* Wt is actual body weight. With provision to multiply by 0.85 in women.

Calculated Cr clearance	Chemotherapy dose
> 60 ml/min	100% (40 mg/m^2)
40-60 ml/min	30mg/m^2
< 40 ml/min	Hold cisplatin

5.3.2.3 Neurotoxicity

Significant (grade 3) myopathy, weakness, or neuropathy; seizure or paralysis should prompt discontinuation of cisplatin. Carboplatin at an AUC of 2 weekly may be substituted under these circumstances.

For grade 2 neurotoxicity hold cisplatin until toxicity improves to ≤ grade 1, then reduce all subsequent doses of cisplatin to 30mg/m2.

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5.3.2.4 Ototoxicity: For clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living but that resolves prior to the next scheduled dose of cisplatin, consider obtaining an audiogram and reduction of cisplatin to 30 mg/m2 if there is evidence of significant hearing loss. If tinnitus persists on the day of treatment, or if it recurs despite this dose reduction, or for if there is new hearing loss requiring a hearing aid, discontinue cisplatin and switch to carboplatin.

Grade 3 hearing loss in the speech frequency range is an indication to discontinue cisplatin and switch to carboplatin.

5.3.2.5 Other non-hematologic toxicities: For any grade 3 or 4 toxicities not mentioned above and excluding alopecia, nausea, dehydration and mucositis, treatment with cisplatin should be delayed until < grade 2. For grade 1 or 2 toxicities no delays will occur. If cisplatin is held > 2 weeks, it will be permanently discontinued. For grade 4 toxicity requiring hospitalization, cisplatin may be interrupted at the discretion of the treating physician.

5.3.3 Carboplatin Administration Schedule

Subjects unable to tolerate cisplatin as indicated in above, may be given carboplatin instead, administered to target AUC 2. Carboplatin will be dosed using the Calvert formula:

Total dose(mg)= (target AUC) x (glomerular filtration rate [GFR] +25)

Calculated creatinine clearance will be used to estimate the GFR. The modified Cockcroft-Gault formula below should be used to calculate the creatinine clearance:

140 -age (yrs) x actual weight (kg) / 72 x Serum creatinine(mg/dl)

- Multiply by a factor of 0.85 if female
- Intended for ages 18-100, serum creatinine 0.6-7 mg/dl
- Carboplatin will be administered over 30 minutes.

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5.3.3.1 Dose Modifications for Carboplatin

Carboplatin Dose Modification Guidelines

Hematological toxicity	Carboplatin Dose
ANC < 1000 mm3	Hold dose
Platelet count < 75,000 mm3	Hold dose

NOTE: Dose modifications for carboplatin will be based on the labs on the day of treatment. If labs are above thresholds in the subsequent week, treatment can resume at the original doses.

5.3.3.1.1 Renal dysfunction: If serum creatinine increases or decreases by > 20% from

baseline, the carboplatin dose must be recalculated.

5.3.3.1.2 Other non-hematologic toxicities: For any grade 3 or 4 toxicities not mentioned above and excluding alopecia, nausea, dehydration and mucositis, treatment with carboplatin should be delayed until < grade 2. For grade 1 or 2 toxicities no delays will occur. If carboplatin is held > 2 weeks, it will be permanently discontinued. For grade 4 toxicity requiring hospitalization, carboplatin may be interrupted at the discretion of the treating physician.

5.3.4 Radiation Dose Modifications

There will be no radiation dose modifications. Radiotherapy will be interrupted for > grade 3 radiotherapy-related toxicity except for grade 3 mucositis and skin reaction that may be managed with supportive care. Treatment may resume when toxicity resolves to grade 2.

For grade 4 toxicity requiring hospitalization (even if unrelated to radiotherapy), the treatment may be interrupted at the discretion of the treating physician.

If radiation therapy is held for toxicities (whether related to protocol treatment or not) for > 4 weeks, all protocol therapy will be discontinued.

5.4 Supportive care

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5.4.1 Oral Care

Dental status must be evaluated and documented by the surgeon prior to the day of surgery. A referral and consultation with a dental hygienist may be needed prior to surgery if abnormalities are noted. Dental evaluation should include: examination with radiographs, removal of diseased teeth, restorative work, periodontal therapy, smoothing of rough or irregular dental surfaces, and assessment of dental appliances for fit. In addition, patients should be assessed for trismus and if present, patients should be provided with range of motion exercise. Patients should be provided with adequate dental education including: the risk for radiation induced dental decay, methods for maintaining good oral hygiene, the appropriate use of prescription fluoride treatment, and dietary influences on oral and dental health.

Appropriate oral hygiene includes the following: brushing teeth after each meal, flossing daily, the frequent use of oral rinses with salt and/or baking soda (every two to four hours), and the daily use of prescription fluoride therapy. Additional therapy, such as the routine use of high calcium/phosphate (Caphosol) suspensions for the prevention of mucositis and dental decay should be considered.

During therapy, patients oral should be assessed on a routine basis to determine the following: compliance with oral hygiene regimens, the development of oral infections such as candidiasis, the development of oral mucositis, and the impact oral health on dietary intake. Ongoing education regarding the importance of oral care may be needed. Oral care regimens may need to be adjusted in patients who develop severe oral mucositis. Patients who develop mucosal sensitivity may require dietary counseling to help guide food choice. Patients should be told not to wear dental appliances in the presence of inflamed or ulcerated mucosa.

After therapy is completed, patients need to resume an aggressive routine dental follow-up. In addition, patients must be encouraged to continue oral hygiene regimens, the use of prescription fluoride and maintain good dietary habits.

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5.4.2 Nutritional Support

At the time of diagnosis, it is strongly encouraged that all patients with head and neck cancer undergo an initial dietary assessment by a trained dietician. Nutritional status (weight loss) must be evaluated and documented by the surgeon prior to the day of surgery. A referral and consultation with a dietician may be needed prior to surgery if abnormalities are noted. Patients with weight loss and inadequate oral intake should receive a feeding tube prior to initiation of therapy. For patients with adequate oral intake, the prophylactic placement of a feeding tube is at the discretion of the treating physician. Patient should be followed by dieticians routinely throughout the course of treatment. Dietary recommendations should include: recommended total caloric intake, recommended intake of protein, daily requirement for free water, feeding tube should be placed. Close monitoring by dieticians is important for patients with feeding tubes, particularly immediately after tube placement as patients often experience problems with enteral feeding or formulations. All patients who have a feeding tube placed should be evaluated and monitored by the Dietitian and Speech Pathologist to ensure adequate nutrition and return to oral intake.

5.4.3 Rehabilitation

It is strongly encouraged that all patients be referred for an assessment by a certified physical therapist after the completion of concurrent therapy. Components of the evaluation should include: neck shoulder and jaw range of motion, general conditioning level, the degree of treatment related fatigue, and postural issues. Patients with significant levels of deconditioning, postural abnormalities, or decrease in range of motion may require physical therapy. Occupational therapy may be needed in patients with extreme degrees of dysfunction. Patients with lymphedema should be referred for lymphedema therapy which should include: education, manual lymph drainage and the use of compression garments.

5.4.4 Speech and Language Pathology

Swallowing assessment and therapy is considered a critical component of care for all head and neck cancer patients. An MBS study will be required at baseline and after treatment for patients from sites that have declared participation in the MBS studies, and strongly encouraged from other institutions that use the MBS study as standard-of-care for patients with swallowing dysfunction. Assessments should be done by a trained Speech-Language Pathologists (CCC-SLP). The SLP should be consulted during treatment planning and should provide routine follow-up throughout the trajectory of the patient's treatment and recovery. The treating physician should communicate with the SLP in order to coordinate care in those patients found to have significant swallowing abnormalities. Critical component of the swallowing evaluation should include: 1) identification of any swallowing abnormalities, 2) recommendations for further testing, 3) formation of a treatment plan, 4) dietary recommendations, and 5) clear identifications of patients at risk for aspiration. Patients should be referred immediately for evaluation if any of the following "trigger symptoms" are identified: coughing or clearing the throat before, during or after eating, inability to control food, liquids or saliva in the oral cavity, complaint of difficulty swallowing or food "sticking" in the throat, nasal regurgitation of food, or pocketing of food in the cheek.

5.4.5 All supportive measures consistent with optimal patient care will be given throughout the study.

5.5 Duration of Therapy

Patients will receive protocol therapy unless:

- Treatment is interrupted for 4 consecutive weeks; patient's protocol treatment will be discontinued
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued
- Patient develops unacceptable toxicity; then the patient will discontinue protocol therapy
- Patients may withdraw consent and withdraw from the study at any time for any reason

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5.6 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration.

6. Measurement of Effect

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6.1 Time to Progression

This interval will be measured from the date of entry on the study to the appearance of new metastatic lesions or objective tumor progression.

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6.2 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the disease evaluation.

6.2.1 CT and MRI

CT and magnetic resonance imaging (MRI) are the best currently available and most reproducible methods for measuring target lesions.

6.2.2 Chest X-Ray

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung. However, CT is preferable.

6.2.3 Tumor Markers

Tumor markers alone cannot be used to assess response.

6.2.4 Clinical Examination

Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

6.2.5 Cytology and Histology

Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

6.2.6 Ultrasound

Ultrasound may be used only as an alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules.

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7. Study Parameters

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7.1 Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 30 days prior to randomization/registration.
2. Prestudy CBC (with differential and platelet count) should be done ≤ 4 weeks before randomization/ registration.
3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ 4 weeks before randomization/registration – unless specifically required on Day 1 as per protocol.

Table 3.

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	Prior to Registration/ Randomization	Day of Surgery	First Post-operative week	4-6 Weeks After TORS	At completion of treatment (Arms B, C, D), observation (Arm A), or Arm S patients who do not register to Step 2	LTFU Arms B, C, D Observation (Arm A), or Arm S patients who do not register to Step 2
Medical history, PE, Vital signs	X	X	X		X	X[2]
Height	X					
Weight	X	X	X	X	X	X[2]
ECOG Performance status	X	X	X	X	X	X[2]
CBC w/diff, plts	X	X[5]	X		X	X[2]
Serum chemistry	X	X[5]	X		X	X[2]
Adverse event evaluation	X		X		X	X[2]
Disease Evaluation by clinical methods[3]	X					X
Tumor tissue	X					
CT SCAN with contrast/MRI of neck[3]	X					X
B-HCG	X					
Dental evaluation[6]	X					
Nutrition consult[6]	X					
SLP consult with MBS[4]	X			X		X[1]
Feeding tube placement			optional			
Patient Reported Outcomes	See Appendix V					
Biological specimen submissions	See Section 7.2					

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1. 6 months and 24 months after treatment. These are required for sites participating in the MBS sub-study (See Appendix V). Results of these tests are also requested from sites that perform these as standard of care. Videos should be uploaded to the cloud at MD Anderson Cancer Center.
2. Arms B, C, D assessments will be done at 10-12 weeks after completion of treatment, Arm A will be done 17-19 weeks from registration to step 2, and Arm S will be done 23-25 weeks following surgery; then every 3 months for the first 2 years, every 6 months for the third year, and every 12 months for the fourth and fifth year or until progression.

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3. Disease evaluation by clinical methods and a CT and/or MRI will be obtained at baseline (≤ 30 days before registration), 10 - 12 weeks after completion of treatment [Arms B, C, D] or 17-19 weeks from registration to step 2 [Arm A] or 23 -25 weeks following surgery [Arm S]; then every 6 months for the first 3 years, and every 12 months for the fourth and fifth year, or until progression.
4. For sites participating in the MBS substudy, MBS videos completed by the site will be stripped of patient identifiers, renames with and EA-designated ID number, and uploaded to the Box® Cloud-based storage account maintained by MD Anderson Cancer Center. EA-designated ID number is obtained via the ECOG-ACRIN Sample Tracking System. Follow the instructions for the submission of these outlined in Section 10.1.6.
5. All labs may be completed within 7 days of surgery.
6. Dental status and nutritional status (weight loss) must be evaluated and documented by the surgeon prior to the day of surgery. A referral and consultation with a specialist may be needed prior to surgery if abnormalities are noted.

7.2 Biological Sample Submissions

Samples are to be submitted as outlined in Section 11. Submission requirements are indicated by Treatment Arm in the table below.

NOTE: All samples submitted must be logged and tracked in the ECOG-ACRIN Sample Tracking System (STS).

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	Baseline	Within 4 wks post-surgery	Step 2, Week 4[2]	Step 2, End of trt	Step 2, 1st RTC appointment after EOT (~12 weeks)	q 3mon[2] x 2 yrs	q 6mon[2] x 2 yrs
MANDATORY: Submission of these materials are REQUIRED to determine patient evaluability and for surgical quality assurance review.							
Diagnostic p16 Tumor Slide	S[1]						
Pathology and Surgical Reports	S[1]	S[1]					
Per patient consent: Submit from patients who have answered "Yes" to "*I agree to provide additional specimens for research.*							
Serum, from 1 x 10 mL Red-top no anti-coagulant[4]	S	S	B,C,D	B,C,D	B,C,D		A,B,C,D, S
Peripheral Blood lymphocytes and plasma, 4 x 10mL EDTA vacuatiner[3]	S	S	B,C,D	B,C,D	B,C,D		A,B,C,D, S
Oral rinse[5,6]	S	S		B,C,D		A,B,C,D,S	
Tumor Tissue, Fixed and Frozen[4]		S					

Rev. 6/14 1. The requested pathology materials and reports are to be submitted as outlined in Section 11 upon finalization of the surgical pathology report but no later than 4 weeks following the performance of the surgery.

Rev. 2/14 2. For Arms A, B, C, and D the collection time points are from the start of Step 2 treatment. Arm S patients not registered/randomized to Step 2, collection time points are from time of surgery.

3. Collect Monday – Thursday only. Do not collect the day before a weekend or holiday. Samples are shipped the day of collection and must be processed immediately upon receipt.

Rev. 6/14 4. Frozen Samples are to be shipped on dry ice. Original diagnostic or surgical specimens may be submitted.

5. Samples may be batched and submitted on a quarterly basis.

Rev. 6/14 6. Samples should be collected 30 minutes prior to or 2 hours after eating to reduce potential contamination from food.

8. Drug Formulation and Procurement

8.1 Cisplatin

8.1.1 Other Names

Cis-diaminedichloroplatinum Cis-diaminedichloroplatinum (II), diaminedichloroplatinum, cis-platinum, platinum, Platinol , Platinol-AQ , DDP, CDDP, DACP, NSC 119875 R R

8.1.2 Classification

Alkylating agent

8.1.3 Mode of Action

Inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanisms include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

8.1.4 Storage and Stability

Intact vials of cisplatin are stored at room temperature. Solutions diluted with saline solution are stable for up to 72 hours at room temperature. Due to the risk of precipitation, cisplatin solutions should **not** be refrigerated.

8.1.5 Dose Specifics

40 mg/m^2 IV day 1, each week of radiation therapy, on Arm D only.

8.1.6 Preparation

The desired dose of cisplatin is diluted with 250-1000 ml of saline solution.

Varying concentrations of 0.225-5% sodium chloride may be used. To maintain stability of cisplatin, a final sodium chloride concentration of at least 0.2% is recommended.

8.1.7 Route of Administration

Cisplatin is administered as an intravenous infusion over 60 minutes.

8.1.8 Incompatibilities

Amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, thiotepa. Cisplatin may react with aluminum which is found in some syringe needles or IV sets, forming a black precipitate.

8.1.9 Compatibilities

Admixture: Amphotericin-B, aztreonam, carmustine, cefazolin, cephalothin, droperidol, etoposide, floxuridine, hydroxyzine, ifosphamide, leucovorin, magnesium sulfate, mannitol, potassium chloride.

Y-site: Allopurinol, bleomycin chlorpromazine, cimetidine, cyclophosphamide, dexamethasone, diphenhydramine, doxapram, doxorubicin, famotidine, filgrastim, fludarabine, fluorouracil,

furosemide, ganciclovir, heparin, hydromorphone, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, ranitidine, sargramostim, vinblastine, vincristine, vinorelbine.

Consult your pharmacist regarding specific concentrations

8.1.10 Availability

Commercially available as a 1 mg/ml solution in 50 and 100mg vials. Vials of lyophilized powder are no longer commercially available, but may be obtained directly from the manufacturer for chemoembolization use.

8.1.11 Side Effects

1. Renal: A dose-related, cumulative renal tubular injury can occur; adequate hydration and diuresis usually minimize the risk. Salt-wasting nephropathy and/or orthostatic hypotension with hyporeninemic hypoaldosteronism can occur in up to 10% of patients.
2. Neurologic: A dose-related ototoxicity, manifested by high-frequency hearing loss and tinnitus, occurs in about 30% of patients. Paresthesias, decreased vibratory, position, and touch sensations are less common; particularly at cumulative doses <400 mg/m^2.
3. Hematologic: Mild leukopenia and thrombocytopenia occur in 25-30% of patients, but are rarely dose-limiting; anemia is less common. A potentially fatal hemolytic uremic syndrome has been reported.
4. Gastrointestinal: Severe, dose-limiting nausea and vomiting occur in almost 100% of patients unless adequate antiemetic prophylaxis is given. Even with successful prophylaxis of acute nausea a delayed (72-96 hour) reaction, requiring additional therapy may occur. Anorexia and taste changes may also occur.
5. Hypersensitivity: Allergic reactions are reported in up to 20% of patients Symptoms include: rash, facial edema, wheezing, hypotension, and tachycardia. Severe anaphylaxis is rare.
6. Other: Electrolyte wasting (magnesium, potassium and sodium), papilledema, optic neuritis, retrobulbar neuritis are reported.

8.1.12 Nursing/Patient Implications

1. Prior to administration, assess:
   A. Labs: CBC, platelet count, BUN, creatinine.
   B. Urine output: 100-150 ml/hr for at least 4-6 hours.
   C. Signs of ototoxicity or neurotoxicity.
2. Administer supportive medications:
   A. Premedicate with antiemetics – prophylaxis with a 5 – HT3 receptor antagonist and dexamethasone (+/- aprepitant) is standard.

B. Hydration

C. Diuretics - may be ordered.

3. Observe for signs of allergic reaction.

8.1.13 References

Alberts DS. Carboplatin versus cisplatin in ovarian cancer. Semin Oncol 1995;22(5 Suppl 12):88-90.

Bonomi P. Platinum/etoposide therapy in non-small cell lung cancer. Oncology 1992;49(Suppl 1):43-50.

Dabholkar M, Reed E. Cisplatin. Cancer Chemother Biol Response Modifiers 1993;14:86-97.

Fram RJ. Cisplatin and platinum analogues: recent advances. Curr Opin Oncol 1992;4:1073-9.

Garrow GC, Johnson, DH. Treatment of "good risk" metastatic testicular cancer. Semin Oncol 1992;19:159-65.

Markman M. Current status of intraperitoneal therapy for ovarian cancer. Curr Opinion Obstet Gynecol 1993;5:99-104.

Ozols RF, et al. Advanced ovarian cancer. Dose intensity. Ann Oncol 1993;(4 Suppl 4):49-56.

Saxman S. Salvage therapy in recurrent testicular cancer. Semin Oncol 1992;19:143-7.

Wheeler RH, Spencer S. Cisplatin plus radiation therapy. J Infusional Chemother 1995;5:61-6.

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8.2 Carboplatin

8.2.1 Other Names

CBDCA, Paraplatin, JM-8, NSC-241240

8.2.2 Classification

Second-generation tetravalent organic platinum compound

8.2.3 Mode of Action

Like cisplatin, carboplatin binds to DNA, thereby inhibiting DNA synthesis, in a cell cycle nonspecific manner. Carboplatin must first undergo activation to produce antineoplastic activity. Bidentate carboxylate ligands of carboplatin are displaced by water forming (aquation) positively charged platinum complexes which bind to nucleophilic sites in DNA, such as the O-6 position on guanine. Carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Intrastrand crosslinks result from the formation of adducts between the activated platinum complexes of the drug and the N-7 atom (not exclusively) atom on guanine to produce 1,2 intrastrand links between adjacent guanine molecules, between neighboring guanine and adenosine molecules, or between

neighboring guanine molecules. Interstrand cross-linking within the DNA helix also occurs. Platinum adducts may inhibit DNA replication, transcription and ultimately cell division.

8.2.4 Storage and Stability

Intact vials are stored at room temperature protected from light. The reconstituted solution is stable for at least 24 hours. When further diluted in glass or polyvinyl plastic to a concentration of 10mg/mL with normal saline or 5% dextrose carboplatin is stable for 8 hours at 25 degrees C. Stability with further dilution to 0.5mg/mL has been reported for up to 8 hours. Other stability data indicate that carboplatin is stable for up to 24 hours and may be refrigerated, however, the manufacturer recommends that reconstituted solutions be discarded after 8 hours due to the lack of preservative in drug formulation.

8.2.5 Dose Specifics

Carboplatin will be given by IV at an area under the curve (AUC) dose of 2. Routine premedication should include at least a 5 – HT3 antagonist and dexamethasone. The dose of carboplatin based on target AUC is calculated using the Calvert equation:

Dose (total mg) = Target AUC X (GFR + 25). The patient's creatinine clearance (GFR) in mL/minute is calculated by the Cockgraft Gault equation.

NOTE: When using the Calvert equation, GFR should not exceed 125 mL/min. Thus, the maximum carboplatin dose is 2 x (125 + 25), or 300 mg.

8.2.6 Preparation

Add 5, 15, or 45 mL sterile water, normal saline, or 5% dextrose to the 50, 150, or 450 mg vial, respectively. The resulting solution contains 10 mg/mL. The desired dose is further diluted, usually in 5% dextrose.

8.2.7 Administration

Infuse over 30 minutes.

8.2.8 Incompatibilities

Aluminum displaces platinum from the carboplatin molecule, resulting in the formation of a black precipitate and loss of potency. Carboplatin solutions should not be prepared or administered with needles, syringes, catheters, or IV administration sets containing aluminum parts that might be in contact with the drug.

8.2.9 Drug Interactions

Concomitant myelosuppressive drugs or radiation therapy may potentiate the hematologic toxicity of carboplatin.

Concomitant nephrotoxic drugs may potentiate the nephrotoxicity of carboplatin, particularly when carboplatin is given in high-dose chemotherapy regimens.

8.2.10 Compatibilities

Carboplatin (0.3 mg/mL) and etoposide (0.4 mg/mL) are chemically compatible in normal saline or 5% dextrose for 24 hours at room temperature.

8.2.11 Availability

Commercially available as a lyophilized powder in 50, 150, or 450 mg vials.

8.2.12 Side Effects

1. Hematologic: Thrombocytopenia (dose limiting), neutropenia, leukopenia, anemia.
2. GI: Nausea and vomiting (frequent but less severe than with cisplatin), treatable with appropriate antiemetic prophylaxis. Anorexia, diarrhea and constipation have also been reported.
3. Dermatologic: Rash, urticaria. Rarer reactions include alopecia, mucositis, and hypersensitivity reactions.
4. Hepatic: Abnormal liver function tests, usually reversible with standard doses.
5. Neurologic: Rarely peripheral neuropathy is seen. May be more common in patients greater than 65 years of age. May also be cumulative, especially in patients with prior cisplatin treatment. Ototoxicity (rare).
6. Renal: Elevations in serum creatinine, BUN; electrolyte loss (Mg, K, Na, Ca).
7. Miscellaneous: Pain, asthenia, flu-like syndrome.

8.2.13 Nursing Implications

1. Monitor CBC and platelet count routinely.
2. Premedicate with antiemetics – prophylaxis with a 5HT3 receptor antagonist and dexamethasone (+/- aprepitant) is standard.
3. Monitor fluid status – maintain adequate hydration.
4. Assess skin/mucous membranes.
5. Assess for signs of peripheral neuropathy – coordination, sensory and hearing loss.

8.2.14 References

1. American Hospital Formulary Service 2003-Drug Information.
2. Calvert AH, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 7: 1748-56, 1989.
3. Carboplatin package insert, Princeton, NJ; Bristol Laboratories Oncology Products 1998; June
4. Christian MC. Carboplatin. In: Principles and Practice of Oncology, PPO Updates 3(11): 1-16, 1989.
5. Woloschuk DMM, Pruemer JM, Cluxton RJ. Carboplatin: A new cisplatin analog. Drug Intell Clin Pharm 22;843-9, 1988.

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9. Statistical Considerations

This is a phase II trial of $p16^+$ (using immunohistochemistry (IHC)) OPSCC patients that will undergo transoral surgery (TOS, Step 1) followed by risk-adjusted radiotherapy (Step 2). Patient risk status is determined after surgical excision and is defined in Section 5.1. Patients with low-risk will be assigned to the observation group (Arm A). Patients with intermediate-risk (the primary study group) will be equally randomized to receive radiotherapy IMRT 50 Gy (Arm B) or 60 Gy (Arm C), stratified by current/former smoking history (≤ 10 vs. > 10 pack-years). Patients with pathological N2C/N3 disease without extensive ECS (and do not meet the high risk feature) will be directly assigned to Arm C receiving IMRT 60 Gy. Patients with high-risk will receive concurrent cisplatin and IMRT 66 Gy (Arm D). Among the first 10 patients enrolled on Arm A, if 2 or more progress or die within 1 year, currently enrolled and subsequently enrolled patients with low risk who have not progressed will be directly assigned to radiotherapy 50 Gy (details are given below).

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The study requires 180 evaluable patients with intermediate risk (to be randomized between Arms B/C). Based on results from the interim analysis prepared for the Fall 2015 DSMC meeting, the overall proportion of evaluable patients with intermediate risk is estimated to be 35% (~73% patients are evaluable, among whom ~48% are intermediate risk), which is lower than the originally estimated 48% (80% evaluable, among whom 60% would be intermediate risk). Here, patients who are eligible and started treatment on step 2 are considered as evaluable. As stated in the original design, if the observed proportion of patients with intermediate risk is off over 5% from the anticipated 60%, accrual goal would be adjusted. Therefore, the current section incorporates a sample size increase from the originally proposed 377 to 515 (180/0.35=515), to ensure 180 evaluable patients with intermediate risk to be randomized. Based on the observed accrual rate of 18.5 patients per month, this new accrual goal can be achieved in February, 2017.

9.1 Objectives

The primary objectives of this phase II study are: 1) to examine the **feasibility** of a prospective multi-institutional study of TOS followed by risk-adjusted adjuvant therapy in this patient population; and 2) to assess the oncologic **efficacy** of the proposed treatment strategy (TOS + reduce dose radiotherapy) for the intermediate risk group. The accrual rate, patient risk distribution (especially the proportion of the intermediate risk group), and surgical quality are used to evaluate feasibility of the study. The 2-year progression-free survival (PFS) rate will be used to evaluate the efficacy in the intermediate risk group. The table below gives a summary of the stopping rules / decision rules to be implemented with regard to these two primary objectives. Details are given in following sections.

Objective	Endpoint	Assessment Time point	Suspension rules / Decision Rules
Efficacy	1-year PFS rate	First 10 patients in arm A followed for 1 year	Currently enrolled and subsequent patients who have not progressed will receive radiotherapy 50 Gy if 2 or more patients progress or die within 1 year
Rev. 2/15	1-year PFS rate	First 10 patients with p N2C/N3 disease followed for 1 year	Currently enrolled and subsequent patients with p N2C/N3 disease who have not progressed will receive IMRT 66 Gy + cisplatin (Arm D treatment) if 2 or more patients progress or die within 1 year
	1-year PFS rate	First 40 patients in each of arms **B** and **C** followed for 1 year	Suspend trial and review if ≥ 6 patients (per arm) progress or die within 1 year
	2-year PFS rate	End of study	Treatment worthy of further study if higher limit of the 90% CI > 85%
Feasibility	Accrual	13-18 months post-activation	Accrual will be monitored by DSMC and NCI (see section below)
	Risk distribution	First 59 patients evaluated for risk	Suspend trial and review if ≤ 21 patients with intermediate risk
	Surgical quality	First 59 patients completed transoral resection and have CTCAE forms submitted	Suspend trial and review if ≥ 13 patients reported with grade 3-4 bleeding or positive margins

Secondary objectives include assessing quality of life (QOL) and swallowing function before and after treatment, evaluating toxicity, and investigating the prognostic effects of various biomarkers (details follow).

9.2 Sample Size and Accrual Rate

We plan to accrue 515 patients, expecting ~376 (73%) total patients would be evaluable (eligible and treated on step 2), among whom 180 would be intermediate risk. Observed accrual rate (18.5 patients per month) is higher than the original assumption of 8 patients per month, so accrual of 515 patients is expected to complete in February, 2017.

9.3 Primary Objective: Efficacy

Primary Endpoint—2-year PFS rate

The sample size calculations are based on the efficacy endpoint of 2-year PFS rate, which is defined as the proportion of patients alive and progression-free at 24 months measured from date of registration onto Step 1. Patients who die without disease progression within 24 months and patients who begin non-protocol therapy without evidence of progression within 24 months will not be
Rev. 6/14 considered to be progression-free at 24 months. The 2-year failure proportions that include second primary cancers from the head and neck region as event will also be reported.

The regimen of TOS + low-dose radiation (Arm B and Arm C, separately) may be considered worthy of further study if the true 2-year PFS rate is close to 85% (the observed rate among high-dose radiation patients in E2399).

Assuming 90 analyzable patients per arm for the intermediate group, the following table displays the exact 90% binomial confidence intervals (CIs) for the 2-year PFS rate for each of Arm B and C, assuming various observed 2-year

PFS rate. For example, if 79 out of 90 analyzable patients per arm are alive and progression free at 2 years, the 90% confidence interval will be 81% to 93% with a width of 12%. This study will need 180 analyzable patients in total for the two randomized arms (Arms B + Arm C).

	Number of Alive and Progression Free at 2 Years			
	71	75	79	83
90% CI	(0.71, 0.86)	(0.76, 0.89)	(0.81, 0.93)	(0.86, 0.96)

With regard to p16 status, while central evaluation of pathology reports will be conducted retrospectively, actual assays will not be run or reviewed centrally. Patients who drop-out prior to radiation therapy due to any reason will also be excluded from the primary analysis .

In the original design, the risk distribution was assumed to be 10% low risk, 60% intermediate risk, and 30% high risk, and an interim analysis for the first 59 patients who complete transoral resection was scheduled. Based on the analysis results, among the 104 evaluable patients (not ineligible based on current evaluation, and started treatment on step 2), the estimated risk distribution is: 8% low risk, 48% intermediate risk and 32% high risk (13 (12%) patients had potentially misclassified risk category/ arm based on their surgical data and the study team is taking various actions trying to improve this). As was stated in the original design, in case the proportion of the intermediate risk patients is off over 5% from the anticipated 60%, the accrual goal would be adjusted, With this new accrual goal, we expect at the end of the study ~180 evaluable patients would be intermediate risk, ~120 high risk, and ~30 low risk.

In analyzing the 2-year PFS rate, 90% exact binomial confidence intervals will be computed for each arm. Only eligible patients with confirmed $P16^+$ status who started radiotherapy will be analyzed (by arm). The regimen will be considered worthy of further study if the higher limit of the computed 90% CI exceeds 85%.

Comparisons of 2-year PFS rates between Arms B and C, Arms B and D, and Arms C and D are exploratory endpoints. Since one of the randomized arms proposed in this study is likely to be selected for a follow-up phase III study, the exploratory comparison of 2-year PFS rate between the two randomized arms is more important and a p-value ≤ 0.05 will be considered statistically significant. For the other two comparisons (Arms B and D; Arms C and D), the Type I error rate of 5% will be divided by the two tests (i.e., 0.05/2 considered statistically significant). Therefore, the family-wise error rate of 0.10 will be protected for the multiple comparisons in the 2-year PFS rate among arms. Power for various differences in the 2-year PFS rate is shown below, assuming a two-sided Fisher's exact test and 90 analyzable patients in Arms B or C, and 120 analyzable patients in arm D.

Difference in 2-year PFS rate between arms	Arm C vs. Arm B	Arm B (or C) vs. Arm D
10% (85% vs. 75%)	0.32	0.27
15% (85% vs. 70%)	0.62	0.58
20% (85% vs. 65%)	0.85	0.83
25% (85% vs. 60%)	0.96	0.96

Interim Analysis—1-year PFS rate

To safeguard against an unacceptably high failure rate for Arm B and Arm C, in which both the radiation dose is reduced and chemotherapy is removed, an interim look at 1-year PFS rate will be performed for the first 40 eligible and treated patients in Arm B and Arm C, separately. It is expected, for either arm, 90% of patients will be alive and progression free at 1 year (Fakhry, C, JNCI, 2008). The event rate will be deemed too high if 6 or more such events are observed within 1 year, which corresponds to an empirical progression rate of 15%. In this case, the trial will be suspended and a panel review will be called. The following table summarizes the probability of suspending the trial under various true 1-year progression rates in Arm B (and Arm C). For instance, the probability of suspending the trial is at least 84% if the true 1-year progression rate is 20% or higher. The study will continue accrual while we are waiting for the decision from this interim analysis.

True 1-yr progression rate for patients with intermediate risk	0.10	0.15	0.20	025	0.30
Probability of suspending the trial	0.21	0.57	0.84	0.96	0.99

Similarly, to safeguard against an unacceptably high failure rate for the observational Arm A, an interim look at 1-year PFS rate will also be performed for the first 10 eligible and treated patients (a total of 38 patients is expected to be accrued to this arm). Among these 10 patients, if 2 or more patients progressed or died within 1 year, currently enrolled and subsequently enrolled low risk patients who have not progressed will be directly assigned to radiotherapy IMRT 50 Gy. The same interim monitoring rule will be applied to the patients with pathological N2C/N3 disease who are directly assigned to Arm C (expected to be 5% of the total population). That is, if 2 or more patients among the first 10 such patients progress or die within the first year, currently and subsequently enrolled patients with p N2C/N3 disease will be treated with IMRT 66 Gy + cisplatin (Arm D treatment). The following table summarizes the probability of observing 2 or more events, under various true 1-year PFS rate for this group of patients.

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True 1-yr PFS rate	0.10	0.15	0.20	025	0.30
Probability of observing 2 or more events	0.26	0.46	0.62	0.76	0.85

9.4 Primary Objective: Feasibility

Three endpoints will be used to evaluate the feasibility of the proposed trial.

Accrual Rate of the Entire Study

The following monitoring plan for accrual was specified in the original design. If the accrual during quarters 5 and 6 (that is, during months 13-18 after activation) is ≤ 20% of the projected rate during that period, then the study will be terminated. If the quarter 5-6 accrual rate is > 20% but < 50% of the planned rate, then the study team will be given 6 months to improve accrual. If the average accrual rate in quarter 8 is still < 50% of the planned rate, then the study design will be amended to reflect the actual accrual rate. The currently observed accrual rate is 18.5 patients per month.

Risk Distribution

Given the distribution of the histologic risk is unknown, this trial provides an opportunity to find out patient distribution in each risk cohort. A 90% binomial confidence interval will be estimated for the percentage of patients in each risk group. All eligible patients on Step 2 will be analyzed. It was expected 60% patients would be intermediate risk in the original design.

An interim analysis was planned in the original design: among the first 59 patients who have completed transoral resection and have risk status evaluated, if 21 (36%) or fewer are intermediate risk, the percentage will be deemed too low. Based on results from the interim analysis, the estimated proportion for the intermediate risk category is 48%, among the 104 evaluable patients.

Surgical Quality

Frequency and percentage will be used to report grade 3-4 bleeding events during surgery and positive margins after surgery, separately. A 90% binomial confidence interval will be estimated for these events as well. All eligible and surgery treated patients will be analyzed. For any targeted event (bleeding or positive margins), if the lower limit of the 90% CI is above the expected rate, transoral resection surgery is deemed infeasible for future study.

An interim analysis was planned in the original design for grade 3-4 bleeding and Positive Margins. It was expected 3% of patients will experience grade 3-4 bleeding during surgery (requiring hemostasis in the operating room). It was anticipated 5% of patients with transoral surgery would have positive margins. Among the first 59 eligible patients who have completed transoral resection, had data submitted, and the surgical results are known, the percentage would be deemed too high if 13 (22%) or more patients are reported with grade 3-4 bleeding in the operating room or with positive margins.An interim analysis was performed for the Fall 2015 DSMC meeting. Among the first 59 patients with surgical data submitted in iMedidata Rave (59th patients registered on January 15, 2015), 5 grade 3 bleeding events and 2 positive margins were reported (total 7 events), and among the 10 patient who entered prior to January 15, 2015 with no surgical data, no bleeding event was reported. Based on results from the interim analysis, the specified stopping rule was not met.

9.5 Secondary Objectives

Secondary endpoints include toxicity, overall survival, swallowing function, and patient-reported outcomes.

Toxicity. For each arm, all treated patients (regardless of eligibility) will be evaluated by CTCAE version 4.0. Descriptive statistics will be provided (by arm). Difference between the low-dose RT arm (Arm B and Arm C separately) and Arm D and between Arm B and Arm C will be evaluated using Fisher's exact test.

Overall Survival. Overall survival will be determined as the time from registration onto the study until death from any cause. Patients who were alive at the time of analysis will be censored at the date last known alive. Kaplan-Meier estimates will be calculated, along with their corresponding 95% confidence intervals. The median, 1-year, and 2-year survival rates will be estimated. Only eligible and treated patients will be analyzed for overall survival (by arm).

Swallowing Function and Voice. Descriptive statistics will be provided (by arm) for swallowing function, evaluated using the MBS ratings, PSS-HN normalcy of diet scale, and the validated survey MDADI instrument. Longitudinal analysis will be performed, by arm, on each of these measures. All eligible and treated patients (on both steps) will be analyzed for PSS-HN diet scale, MDADI, and VHI-10. The MBS analysis will be performed on eligible and treated patients only if accrued at vetted participating centers.

Quality of Life. The primary variable of interest in the QOL analysis is the individual change in the FACT-H&N total score from baseline (prior to TOS) to 6 months post-RT. Patient QOL will be grouped as "improved" (change ≥ 7 points, 6 mo post-RT vs. baseline), "worsened" (change ≤ -7 points) and "stable" (-6 ≤ change ≤ 6). QOL data is very limited in this setting ($P16^+$ OPSCC patients treated with TOS + RT), and estimates from this phase II trial may serve as the basis of choosing an effect size in a possible future phase III trial comparing TOS + RT vs. primary CRT treatment.

In the primary QOL analysis, we plan to combine the post-operative RT arms (B & C) and compare to patients selected for post-operative chemoRT (arm D), which would be expected to have toxicity similar to, but less severe than, a primary CRT approach. This comparison is most similar to the setting of a possible future phase III trial. From a prior trial of CRT approach, about 25% of the patients had improved FACT-H&N from baseline to 6 months, 25% were stable, and 50% worsened, which is expected to be similar to, or slightly worse than the experience of arm D in this phase II trial. Given the more severe overall toxicity and probable greater late toxicity associated with the use of both radiation and chemotherapy, we hypothesize that a higher proportion of patients in arm B/C will have recovered their FACT-H&N scores to baseline level or higher at 6 months, and we consider a difference, or Delta, of 10% (Arms B/C vs. Arm D) to be important outcome. Comparison between Arm B and Arm C (in mean score change and/or proportion of patients with improved/stable score at 6 months) is also important endpoint but this will be only exploratory. Any comparison results will be interpreted with caution. Descriptive statistics will be provided for FACT-H&N and MDASI-HN at various measurement points.

The table below shows the power of detecting various Delta value (Arms B/C vs. D) under various compliance rate (the proportion of patients who complete PRO surveys at both baseline and 6 months post-RT visits), using a one-sided Fisher's exact test with type I error rate of 0.10, assuming 48% intermediate risk patients and 32% high risk patients among evaluable patients.

Compliance Rate	No. of analyzable pts (Arms B/C vs. Arm D)	Delta (Arms B/C vs. D)		
		10% (65% vs. 55%)	15% (70% vs. 55%)	20% (75% vs. 55%)
40%	120 (72 vs. 48)	0.35	0.58	0.79
60%	180 (108 vs. 72)	0.46	0.73	0.91
80%	240 (144 vs. 96)	0.56	0.83	0.96

One of the randomized arms is likely to be selected for a future phase III study. Although the QOL endpoint is not built into the primary selection criteria, in case that the efficacy outcomes for the two randomized arms are similar, the 50Gy schedule will be considered in the phase III study with the expectation that QOL will also be better in this arm, unless there is evidence otherwise.

9.6 Handling Missing Data

The primary analysis will treat missing data as missing at random then analyze cases with complete data. The method of multiple imputation will be used to handle missing data if more than 20% of the cases have missing data in the variables of interest. If so, sensitivity analysis will be performed to compare results from the complete case analysis and imputation analysis. In case of discrepancies, possible explanations will be discussed. For longitudinal data, given the expected high level of missingness in these data, data will be analyzed according to the methods described in Schluchter (1992) and in Schluchter, Greene, and Beck (2001). These methods take into account the possibility of informative missingness by jointly modeling the longitudinal response and the time to dropout.

9.7 Laboratory Endpoints

When sufficient information is available from the parent study, a separate correlative science proposal (or a protocol amendment) detailing the scientific hypothesis, research plan, assay methods for use of the biospecimens, and a complete statistical section (with adequate power justification and analysis plan) would be submitted and reviewed by CTEP in accordance with the NCI National Clinical Trials Network (NCTN) review policies.

9.8 Randomization Scheme

Patients enrolled into this study will be assigned to one of the four treatment arms after transoral surgery based on their histologic risk status. Patients with low-risk will be assigned to the observation group (Arm A). Patients with intermediate-risk will be randomized (with a 1:1 allocation ratio) into either Arm B (IMRT 50 Gy) or Arm C (IMRT 60 Gy). Patients with high-risk will receive post surgery concurrent cisplatin and IMRT 66 Gy (Arm D). The method of permuted blocks will be used for randomization with current/former smoking history (≤ 10 vs. > 10 pack-years) as stratification factor.

9.9 Monitoring Plan

This study will be monitored by the Data Safety and Monitoring Committee (DSMC). The DSMC meets twice each year, and all monitored studies are

reviewed for safety and progress toward completion. The toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meetings. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required as specified in the protocol.

9.10 Gender and Ethnicity

The total accrual goal will be 515 patients. Based on previous data from E1308, the anticipated accrual in subgroups by gender and race is/as follows:

Racial Categories	Ethnic Categories				Total
	Hispanic or Latino		Not Hispanic or Latino		
	Females	Males	Females	Males	
American Indian or Alaskan Native	0	0	0	0	0
Asian	0	0	0	12	12
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	24	24
White	6	36	24	413	479
Total	6	36	24	449	515

The accrual targets in individual cells are not large enough for definitive subgroup analyses.

Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Functional Outcomes, Patient Reported Outcomes and Quality of Life

10.1 Observer-Assessed Outcomes

10.1.1 *Performance Status (PS):* Performance status will be assessed using the ECOG performance status scale and must be 0-1 at baseline for study eligibility. Changes in ECOG PS will be tracked at all PRO endpoints.

10.1.2 *Weight Loss:* The degree of weight loss may contribute to fatigue, weakness and deconditioning. Weight loss during therapy will be documented as well as post-treatment weight changes.

10.1.3 *Tracheostomy and Enteral Feeding Tube Status*: The presence of either assistive device will be tracked prospectively at all PRO time points.

10.1.4 *Charlson Comorbidity Index*: Comorbidity will be documented by chart abstraction at baseline.

10.1.5 *Head and Neck Cancer Specific Performance Status*: The Performance Status Scale (PSS-HN)[49] is a clinician-rated instrument consisting of 3 questions: normalcy of diet, public eating, and understandability of speech. The PSS-HN has been psychometrically validated and recommended by the National Comprehensive Cancer Network for measurement of swallowing and speech performance in patients with head and neck cancer. It is not a PRO; it can be completed quickly by the trialist without adding to patient burden.

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10.1.6 *Swallowing Endpoint:* Swallowing outcomes will be measured as a secondary endpoint of this trial using modified barium swallow (MBS) studies according the assessment schedule in Appendix V (baseline, within 4 weeks of TORS, 6 months pos-treatment, and at 2-years). Participating institutions will be vetted prior to study activation to ensure adherence to a standard protocol. Institutions must be assessed and declare their participation in this aspect of the study prior to site opening to accrual; facilities unable to participate in the MBS assessments may still enter patients on the study. Facilities must use a standardized contrast medium (Varibar® thin liquid and pudding contrast, Bracco Diagnostics, Inc. Princeton, NJ) and digitally record MBS studies (30 frames/second). Three swallowing outcomes will be rated by the SLP conducting the MBS study and reported by research staff: 1) laryngeal penetration (yes, no); 2) aspiration (no, sensate, silent), and 3) pharyngeal residue (no, < 50%, > 50%). These have been selected as universal items generally reported by swallowing clinicians that have been shown to significantly predict pneumonia in patients with oropharyngeal cancers. Prevalence of these dysphagia endpoints will be estimated at each time point, and compared between arms.

Sites are to complete the required MBS credentialing checklist (Appendix VI) and fax to the ECOG-ACRIN Operations Office - Boston at 617-632-2990, Attention DA E3311.

Questions related to MBS studies can be directed to:

University of Texas MD Anderson Cancer Center
Phone: 713-792-6364
Email: E3311_MBS@jimmy.harvard.edu

Submission of MBS Videos to MD Anderson:

Upon completion of the credentialing checklist, the designated site contact will be given access to the MD Anderson Box® Cloud-based storage account to upload MBS videos to the cloud. Please contact E3311_MBS@jimmy.harvard.edu for questions regarding access and questions for Box® Cloud-based storage.

Videos must be uploaded in .mpeg or .avi format.

To ensure the security of the uploaded video all patient identifiers are to be removed and the video files are to be re-labeled with a unique identification code.

To obtain the code:

1. Log the videos into ECOG-ACRIN's *Sample Tracking System* (STS), indicating the "Ship Date" as the date the video is to be uploaded to the MD Anderson Box Cloud Account. Be sure to select the correct protocol-specified time point for the video. (e.g., Baseline, after surgery…). Remember to save the shipment data before exiting the application. Generation of a shipment manifest is not necessary.

   https://webapps.ecog.org/Tst/

2. Exit *STS* and enter the *Patient Video Identifier Lookup* application. Select the protocol and enter the ECOG-ACRIN E3311 patient identifier to pull up the patient specific information. The code is the "Sample ID" and is a unique code linked to the patient and the time point of the video as entered into STS.

   https://webapps.ecog.org/PatientVideoIdentifyLookup/

Rename the electronic video file using only the STS-generated sample ID prior to uploading to the MD Anderson Cloud. For more complete guidelines pertaining to allowed upload formats and guidelines on removing patient identifiers, see Appendix IX.

10.2 Patient Reported Outcomes (PROs)

10.2.1 *Quality of Life:* Quality of life will be assessed using the Functional Assessment of Cancer Therapy – Head and Neck Cancer (FACT-H&N). The FACT-H&N (version 4)[51] consists of a cancer-specific questionnaire, FACT-G, in addition to 12 H&N cancer-specific items (the HN subscale). FACT-G is a 27-item measure that assesses general cancer quality of life [Cella, 1993; Cella, 1997]. The FACT-G contains 4 subscales: physical, social/family, emotional, and

functional well-being. Individuals are asked to indicate how true 27 statements are for them, using the past 7 days as the timeframe. Responses range from not at all (0), to very much (4) on a 5-point scale. Psychometric properties of the FACT-G have been examined in a variety of oncology populations with alpha coefficients ranging from .65 to .89 [Cella, 1997]. After reverse coding selected items in the physical and emotional subscales, items are summed to provide total subscale scores, which will be used in our analyses. Using this scoring, higher values reflect better quality of life. [52]. The full FACT-H&N provides a summary score for overall head and neck cancer related QOL and has been used frequently in clinical trials.

10.2.2 *Head and Neck Symptom Burden:* The MD Anderson Symptom Inventory-Head & Neck (MDASI-HN[53]) measures treatment related symptom burden in head and neck cancer patients. The MDASI measures both severity and burden of symptoms and their effect on patients' daily activities, using a numeric rating scale of 0-10. This instrument includes 13 core symptoms and 9 head and neck specific items. The instrument was validated in a cohort of more than 200 patients. The coefficient alpha was highly reliable. The MDASI takes less than 5 minutes for patients to complete.

10.2.3 S*wallowing and Voice:* Data regarding swallowing perception and performance and voice outcomes will be obtained from the MD Anderson Dysphagia Inventory (MDADI) [50] and Voice Handicap Index-10 (VHI-10).

The MDADI measures swallowing-related quality of life (QOL) in patients with swallowing dysfunction in a 20 – item written questionnaire. It evaluates the patient's physical (P), emotional (E) and functional (F) perceptions of swallowing dysfunction. This instrument has been psychometrically validated in head and neck cancer patients.

The VHI-10 [55]is a patient self-assessment instrument that quantifies patients' perception of their voice handicap. It evaluates patient's physical (P), emotional (E), and functional (F) perceptions of voice and has shown to be highly reliable for internal consistency and test-retest stability. The VHI-10 utilizes a 10-item questionnaire in which the patient circles the response that most accurately reflects his or her own experience on a linear scale (from "never" to "always").

10.2.4 *Return to work*: Return to work will be tracked prospectively following treatment using an instrument currently in use on the RTOG 1016 trial. While this data is patient reported, it does not generate a score requiring psychometric validation. It has been judged to have face validity and is brief and practical for use in a clinical trial.

11. Specimen Submissions

Representative original diagnostic and surgical pathology materials are required to be submitted for diagnostic review and classification for purposes of determining patient evaluability AND quality review of the surgery. Blood specimens and additional tissue specimens are requested for the research studies from consenting patients.

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All specimens must be labeled with the ECOG-ACRIN protocol number, the patient's initials and ECOG-ACRIN sequence number, the collection date, and the type of sample. For pathology materials, it is strongly recommended that full patient names be provided. All specimens must be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS) Web Application (Section 11.5) and submitted with an STS generated shipping manifest.

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Direct questions regarding submission of specimens to the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org or phone (1-844-744-2420).

11.1 Collection and Submission Schedule

See Section 7.2 for a table summarizing the submission requirements.

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11.1.1 Pathology Materials from ALL PATIENTS

11.1.1.1 MANDATORY

Mandatory submissions are to be submitted upon completion of the surgical pathology report by the site, but no later than 4 weeks following completion of the surgery.

11.1.1.2 Consenting patients:

Fixed and frozen (if available) tissue are to be submitted.

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11.1.2 Specimens from consenting patients

Collect from patients who answer "Yes" to "*I agree to provide additional specimens for research"* at the following timepoints:

A. Plasma, Serum and Peripheral Blood are to be collected:
   - Prior to surgery (Arm S)
   - Within 4 weeks after surgery (Arm S)

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   - Step 2, Week 4 (Arms B,C, D)
   - Step 2, End of Treatment (Arms B, C, D)
   - Step 2, at first end of treatment follow-up visit (Arms B,C,D)
   - Months 6, 12, 18 and 24 from start of Step 2 treatment (Arms A,B,C,D)
   - Months 6,12, 18 and 24 from time of surgery (Arm S patients who did not register to Step 2)

B. Oral Rinse is to be collected:
   - Prior to surgery (Arm S)
   - 4 weeks after surgery (Arm S)
   - Step 2 End of Treatment (Arms B,C,D)

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   - Months 3, 6, 9, 12, 15, 18, 21 and 24 from start of Step 2 treatment (Arms A,B,C,D)

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- Months 3, 6, 9, 12, 15, 18, 21 and 24 from time of surgery (Arm S patients who did not register to Step 2)

Peripheral blood samples are to be shipped day of collection, and are to be collected Monday – Thursday only. Plasma, serum and saliva specimens are to be batched at <-70ºC and shipped on a quarterly basis. If a <-70ºC freezer is unavailable, store at -20 ºC and ship on dry ice within 24 hours (or next business day if drawn on Friday).

11.2 Specimen Collection Guidelines

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11.2.1 Tissue Submission

Guidelines for pathologists are provided in Appendix I. Representative tumor specimens of the following are to be submitted:

- **MANDATORY**:
  - Original p16 tumor slide. Stained slides from cytology blocks are acceptable.
- **From consenting patients** who answer "Yes" to "I agree to provide additional specimens for research"
  - Fixed, paraffin-embedded primary tumor tissue block. Either pre-trial diagnostic or surgical specimen may be submitted.

    NOTE: If blocks are not available for submission, the following alternative is to be submitted: 1 H&E (from the source block), 1-2 core punches (4 mm minimum) and 20 unstained slides. Slides, including the H&E, are to be numbered consecutively in the order cut.
  - Frozen surgical specimen, if available

The following forms MUST be submitted via Medidata Rave. Additionally, the relevant pathology and surgical reports must accompany all tissue submissions:

- Copy of the original diagnostic Pathology Report
- The p16 IHC report from the original diagnostic specimen must be submitted
- Surgical pathology and surgical procedure reports.

  Histopathologic assessment of surgical pathology must include examination for perineural invasion (PNI) [absent or present], lymphovascular invasion (LVI) [absent or present], and extracapsular extension (ECE) [absent, present-minimal, present-beyond minimal]

  Surgical margin status must be reported as i) *Negative* (tumor ≥ 3mm from designated margin); ii) *Close* (tumor < 3mm of the designated margin); or iii) *Positive* (tumor at the cut specimen edge not superseded by another margin)
- Other Immunologic and cytologic reports
- STS generated shipping manifest for all submitted tissue.

11.2.2 Additional Submissions

From patients who consent "Yes" to *"I agree to provide additional specimens for research."*

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Draw the blood tubes in the following order: no anti-coagulant (red top or SST), EDTA (purple top). Note that vacutainer top color are for BD vacutainers. Verify tube contents prior to the collection of any samples.

Ship Frozen →

1. Serum
   - At each time point specified, draw one (1) 10mL vacutainer (no anti-coagulant)
   - Allow to coagulate at room temperature for 20 minutes
   - Separate by centrifugation at approximately 1200g x 20 minutes
   - Aliquot serum into four cryovials. Discard residual cells
   - Samples will be batched and shipped on dry ice.

Ship Ambient →

2. Peripheral Blood, EDTA

   As these samples are to be shipped the day of collection, they are to be drawn Monday – Thursday. Do not draw on a Friday or day before a holiday as the receiving laboratory is not open on weekends or holidays. This is essential so the time between collection and processing by the central laboratory is minimized.
   - At each time point specified, draw four (4) 10mL potassium EDTA (purple top) vacutainer, invert gently 4-5 times.
   - Ship the day of collection at ambient temperature overnight.

   Upon receipt at the central laboratory, tubes will be processed to isolate plasma and buffy coat peripheral blood lymphocytes (PBL). The second tube will be used for the isolation of DNA.

Ship Ambient →

3. Oral Rinse. For oral rinse, the patient should pour approximately 15cc of mouthwash or saline into his/her mouth and vigorously swish it against the cheeks for 10 seconds and deliver the solution with a sterile beverage straw into a labeled 15cc polypropylene test tube. Among mouthwashes, the Scope brand fares best in collecting oral DNA/cells for the preparation of high-quality DNA in high yield. Ship the day of collection at ambient temperature overnight.

11.3 Shipping Procedures

The mandatory pathology materials are to be submitted upon completion of the surgical pathology report, but no later the 4 weeks from time of surgery. Tissue samples are to be shipped at ambient (use a cool pack in warm weather).

It is requested that the frozen tissue and blood samples be batched and shipped frozen on dry ice (at least 5 pounds) on a quarterly basis. If -70°C freezer is not available, blood samples are to be stored at -20°C and shipped on dry ice within 24 hours of collection. Frozen samples are to be shipped SUNDAY THROUGH

THURSDAY only via overnight courier. Do not ship samples the day before a Holiday.

Shipping manifest generated from the ECOG-ACRIN STS system must accompany the samples.

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Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

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Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506

11.4 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Any case reimbursements associated with specimen submissions will not be credited if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

Study Specific Notes

If the STS is unavailable, the Generic Specimen Submission Form (#2981) is to be used as a substitute for the STS shipping manifest. The completed form is to be faxed to the receiving laboratory the day the samples are shipped. Indicate the appropriate Lab ID# on the submission form:

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- ECOG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

11.5 Use of Specimens in Research

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA.

The appropriate materials will be distributed to investigators for the diagnostic reviews and research studies.

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined reviews and research studies, will be retained in an ECOG-ACRIN-designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility. Specimens will be de – identified prior to distribution for any approved research products.

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If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

11.6 Sample Inventory Submission Guidelines

Inventories of all samples submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for the will be submitted by the laboratory to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

12. Specimen Analyses: Diagnostic Review and Research Studies

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12.1 Diagnostic Review and Classification (MANDATORY)

Original diagnostic and surgical pathology materials (tissue and reports) will be retrospectively reviewed by Dr. Joaquín García at Mayo Clinic Rochester. The results of the evaluations will not be reported to the sites and will not impact patient participation in the trial, but will be used to determine the evaluability of patient data in the analysis of the clinical data.

Surgical materials will be evaluated for:

A. Perineural Invasion, surgical: Reported as absent or present
B. Lymphovascular Invasion, surgical: Reported as absent or present
C. Extracapsular Extension, surgical: The absence or presence of ECE should be documented in the final surgical pathology report in the following manner:
    - absent (nodal metastasis with smooth/rounded leading edge confined to thickened capsule/pseudocapsule),
    - present - minimal (tumor extends ≤1 mm beyond the lymph node capsule), or
    - present - beyond minimal (gross, tumor extends >1 mm beyond the lymph node capsule (includes soft tissue metastasis)

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The p16 status and reporting from the original diagnostic assessments will be also be reviewed to confirm patient evaluability. p16 immunohistochemistry must have been performed in a CLIA laboratory. Positivity is defined by strong cytoplasmic immunoreactivity noted in ≥ 70% of tumor cells.

Data from the preoperative CT/MRI scans analyzed for nodal stage and prediction of ECE will be correlated with final pathologic nodal stage, presence and extent of ECE (≤ or > 1mm).

12.2 Research Studies

The following correlative studies are proposed as outlined below. Final analysis of the proposed studies require the results of the parent study. Specifically, the percentage of patients distributed into each Arm of the trial is necessary to carry out a realistic statistical power calculations, but cannot be ascertained until the parent study is well underway. When sufficient information is available from the parent study, a planned early interim analysis to assess futility and accrual/distribution proportions of patients into each Arm, a full correlative science proposal or amended protocol document with formal statistical analysis plan for the marker studies will be submitted to and reviewed by CTEP.

12.2.1 Mutational Analyses: Tumor *TP53* and common cancer-related genes

Tumor *TP53* and a panel of 200 common cancer-related genes will be sequenced in one assay using formalin-fixed and paraffin-embedded tumors to determine prognostic and/or predictive biomarkers

12.2.2 Excision Repair Cross-complementation Group 1 (ERCC1) Single Nucleotide Polymorphism (SNP) and Protein Expression

ERCC1 SNP (Thr259Thr) and ERCC1 protein expression in paraffin-embedded tumor tissue will be analyzed.

12.2.3 Quantification of EGFR Expression

EGFR protein levels will be analyzed by automated quantitative analysis (AQUA) technology

12.2.4 Serum cytokines/chemokines.

Baseline and posttreatment cytokines are potentially predictive of outcome. Furthermore, the association between serologic markers (detected in blood at baseline and two other timepoints, including cytokines, chemokines, growth factors, and angiogenic factors in blood and treatment efficacy will also be examined.

Multiplex analysis of circulating soluble inflammatory/immunosuppressive mediators will be measured

12.2.5 Markers of p16+ OPSCC Susceptibility

Future correlatives are proposed to determine gender differences in carcinogen metabolism, as well as further evaluation of the importance of various hormone pathways in lung cancer. Analysis will be done on both tissue and blood samples submitted.

12.2.6 HPV DNA measurement and alteration in blood and saliva

Given the ability to detect HPV DNA in salivary and blood specimens, we will perform an exploratory correlation between pre-treatment and post-treatment (1- and 2- year) HPV DNA, using QRT-PCR for HPV E6/E7. HPV DNA and seropositivity to HPV antigens will also be measured quatitatively and qualitatively measure stability and predictive ability over time in a prospective treated population.

DNA from buffy coat or PBMCs will be analyzed for quantitative and qualitative alterations in HPV DNA. These analyses will be performed under the direction of Robert L. Ferris, MD, PhD.

The data will be used to determine the feasibility and potential value of incorporating this potential biomarker into the future randomized phase III trial.

12.2.7 Tumor antigen specific cellular immunity

We and others have characterized the antigen specific cellular immune response to OPSCC, including HPV-, EGFR- and other antigens. PBL from pretreatment and post treatment patients will be correlated with disease recurrence, DFS, and OS. in tumor-bearing individuals, an hypothesis to be tested in the correlative phase of this proposal.

Lymphocyte Markers

- Baseline and on-treatment absolute lymphocyte count (ALC) monitoring

- T cell activation status: CD3, CD4, CD8, HLA-DR, ICOS1 and CD45RO (memory marker),Tregs and MDSCs (TAMs)
- Profiling of tumor infiltrating lymphocytes using pretreatment tissue and PNMC will also be considered as markers for TIL, CD8, CD4, FoxP3, CD33 (MDSC marker), etc.
- Monitoring adaptive and humoral immune responses toward specific tumor antigen [such as p53 and EGFR(76-78) and HPV E6 and E7 antigens (65, 79, 80)
- Expression of checkpoint/inhibitory receptor expression on PBMC/TIL, i.e. CTLA-4, PD-1, TIM-3, BTLA-4, LAG3, etc.

12.2.8 Quality of Life Associated Biological Correlatives:

Rapid telomere shortening has been documented in head and neck cancer patients undergoing radiation based treatment. In addition, telomere shortening has been associated with fatigue. We plan to measure telomere length at baseline and 1 and 6 months post treatment.

In the general population, ACE polymorphisms have been correlated with the ability to build muscle mass. In the cancer lung patient population, there is data to indicate that ACE levels correlate with weight loss. We propose to measure ACE polymorphisms and correlate them with weight loss, fatigue and the level of general physical functioning.

Finally, we plan to measure inflammation using c-reactive protein level.

12.3 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates.

13. Electronic Data Capture

Please refer to the E3311 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office - Boston to CTEP by electronic means.

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13.1 ECOG-ACRIN Radiation Oncology Quality Assurance Materials

All radiotherapy quality assurance materials should be submitted to the IROC Rhode QA Center (QARC). See Section 5.1.16.

Electronic submission via sFTP for all radiation data is preferred. Alternatively the supportive data and forms may be sent to:

IROC Rhode Island QA Center
ATTN: ECOG-ACRIN Materials
640 George Washington Highway, Building B, Suite 201
Lincoln, RI 02865-4207
Tel:(401) 753-7600
Fax: (401) 753-7601

14. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

15. References

1. Hayat MJ, Howlader N, Reichman ME, Edwards BK: Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist 12:20-37, 200
2. Forastiere A, Koch W, Trotti A, Sidransky D: Head and neck cancer. N Engl J Med 345:1890900, 2001
3. Shiboski CH, Schmidt BL, Jordan RC: Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20-44 years. Cancer 103:1843-9, 2005
4. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, Zahurak ML, Daniel RW, Viglione M, Symer DE, Shah KV, Sidransky D: Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 92:709-20, 2000)
5. Kreimer AR, Clifford GM, Boyle P, Franceschi S: Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev 14:467-75, 2005.)
6. Gillison ML: Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. Semin Oncol 31:744-54, 2004)
7. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML: Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 356:1944-56, 2007

8. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML: Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 26:612-9, 2008
9. Herrero R, Castellsague X, Pawlita M, Lissowska J, Kee F, Balaram P, Rajkumar T, Sridhar H, Rose B, Pintos J, Fernandez L, Idris A, Sanchez MJ, Nieto A, Talamini R, Tavani A, Bosch FX, Reidel U, Snijders PJ, Meijer CJ, Viscidi R, Munoz N, Franceschi S: Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 95:1772-83, 2003
10. Fakhry C, W. Westra, S. Li, A. Cmelak, J. Ridge, H. Pinto, A. Forastiere, M. Gillison: Prognostic significance of human papillomavirus (HPV) tumor status for patients with head and neck squamous cell carcinoma (HNSCC) in a prospective, multi-center phase II clinical trial.Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 6000)
11. Adelstein DJ. Induction chemotherapy in head and neck cancer. Hematol Oncol clin North Am 1999;13:689-698
12. Remenar E: A randomized phase III multicenter trial of neoadjuvant docetaxel plus cisplatin and 5-fluorouracil versus neoadjuvant PF in patients with locally advanced, unresectable squamous cell carcinoma of the head and neck. Final analysis of EORTC 24971. Proc Am Soc Clin Oncol, 2006
13. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, Tjulandin S, Shin DM, Cullen K, Ervin TJ, Murphy BA, Raez LE, Cohen RB, Spaulding M, Tishler RB, Roth B, Viroglio Rdel C, Venkatesan V, Romanov I, Agarwala S, Harter KW, Dugan M, Cmelak A, Markoe AM, Read PW, Steinbrenner L, Colevas AD, Norris CM, Jr., Haddad RI: Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 357:1705-15, 2007)
14. M. S. Kies, A. S. Garden, C. Holsinger, V. Papadimitrakopoulou, A. K. El-Naggar, K. Gillaspy, J. Lewin, C. Lu, S. Villalobos, B. S. GlissonInduction chemotherapy (CT) with weekly paclitaxel, carboplatin, and cetuximab for squamous cell carcinoma of the head and neck (HN). Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 5520
15. H. J. Wanebo, M. Ghebremichael, B. Burtness, S. Spencer, J. Ridge, A. Forastiere, M. Ghebremichael:Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 6015
16. A. E. Argiris, M. K. Gibson, D. E. Heron, R. P. Smith, R. L. Ferris, S. Y. Lai, S. W. Kim, B. F. Branstetter, J. T. Johnson, J. R. Grandis . Phase II trial of neoadjuvant docetaxel (T), cisplatin (P), and cetuximab (E) followed by concurrent radiation (X), P, and E in locally advanced head and neck cancer (HNC). J Clin Oncol 26: 2008 (May 20 suppl; abstr 6002
17. Bonner J, Harari P, Giralt J, et al. Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2006 Feb 9;354(6):567-78
18. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA: Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 23:8646-54, 2005
19. Grégoire V, De Neve W, Eisbruch A, Lee N, Van den Weyngaert D, Van Gestel D. Intensity-modulated radiation therapy for head and neck carcinoma. Oncologist. 2007 May;12(5):55564

20. Duggan, M. Beach, B.A. Murphy, M. Teng, D. Hallahan, B. Burkey, J. Netterville W. Yarbrough, P. Murphy, C.H. Chung, R. Young, L. Butler, W. Kirby, A.J. Cmelak. Intensity-Modulated Radiation Therapy (IMRT) with Concurrent Taxane-Based Chemotherapy for Locally-Advanced Head and Neck Cancer (LAHNC): Feasibility, Technique, and Toxicities. J Clin Oncol Proc ASCO #5536 p.509s, 2008.
21. Lee NY, O'meara W, Chan K, Della-Bianca C, Mechalakos JG, Zhung J, Wolden SL, Narayana A, Kraus D, Shah JP, Pfister DG. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. Int J Radiat Oncol Biol Phys. 2007 May 8.
22. Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy Added to Locoregional Treatment for Head and Neck Squamous-Cell Carcinoma: Three Meta-analyses of updated individual data – MACH-HN Collaborative Group: Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 355:949-955, 2000
23. Hall E. Radiobiology. Lippincott, 1993
24. Mu, D., D.S. Hsu, and A. Sancar, Reaction mechanism of human DNA repair excision nuclease. J Biol Chem, 1996. 271(14): p. 8285-94.;
25. Zamble DB, Mu D, Reardon JT, Sancar A, Lippard SJ. Repair of cisplatin--DNA adducts by the mammalian excision nuclease. Biochemistry. 1996 Aug 6;35(31):10004-13.
26. Handra-Luca, A., et al., Excision repair cross complementation group 1 immunohistochemical expression predicts objective response and cancer-specific survival in patients treated by Cisplatin-based induction chemotherapy for locally advanced head and neck squamous cell carcinoma. Clin Cancer Res, 2007. 13(13): p. 3855-9.
27. Jun HJ, Ahn MJ, Kim HS, Yi SY, Han J, Lee SK, Ahn YC, Jeong HS, Son YI, Baek JH, Park K. ERCC1 expression as a predictive marker of squamous cell carcinoma of the head and neck treated with cisplatin-based concurrent CRT. Br J Cancer. 2008 Jul 8;99(1):167-72.
28. Carles, J., et al., *Single-nucleotide polymorphisms in base excision repair, nucleotide excision repair, and double strand break genes as markers for response to radiotherapy in patients with Stage I to II head-and-neck cancer.* Int J Radiat Oncol Biol Phys, 2006. 66(4): p. 1022-30.
29. Rubin Grandis, J., et al., *Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival.* J Natl Cancer Inst, 1998. 90(11): p. 824-32.
30. Ang, K.K., et al., *Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma.* Cancer Res, 2002. 62(24): p. 7350-6.
31. Cohen, E.E., et al., *Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck.* Clin Cancer Res, 2005. 11(23): p. 8418-24
32. Engelman, J.A., et al., *MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling.* Science, 2007. 316(5827): p. 1039-43.
33. Psyrri, A., et al., *Quantitative determination of nuclear and cytoplasmic epidermal growth factor receptor expression in oropharyngeal squamous cell cancer by using automated quantitative analysis.* Clin Cancer Res, 2005. 11(16): p. 5856-62.

34. Hirsch, F.R., et al., *Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis.* J Clin Oncol, 2003. 21(20): p. 3798-807.
35. Cappuzzo, F,Hirsch, F. R.,Rossi, E et al*., Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer*
36. Chung CH, Ely K, McGavran L et al *Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas* JCO, 2006
37. Temam S, Kawaguchi H, El-naggar AK, et al; *Epidermal growth factor receptor copy number alterations correlate with poor clinical outcome in patients with head and neck squamous cancer* JCO, 2007
38. Slebos RJ, Yi Y, Ely K, Carter J, Evjen A, Zhang X, Shyr Y, Murphy BM, Cmelak AJ, Burkey BB, Netterville JL, Levy S, Yarbrough WG, Chung CH.. Gene expression differences associated with human papillomavirus status in head and neck squamous cell carcinoma. Clin Cancer Res. 2006 Feb 1;12(3 Pt 1):701-9.
39. Frederick BA, Helfrich BA, Coldren CD, et al; *Epithelial to mesenchymal transition predicts gefitinib resistance in cell lines of head and neck squamous cell carcinoma and non-small cell lung carcinoma* Mol Cancer Ther 2007
40. P. Kountourakis, E. Pectasides, B. A. Burtness, D. Pectasides, A. Psyrri, G. Fountzilas Molecular prognostic markers in squamous cell carcinoma of the head and neck: the role of Ecadherin. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 6040)
41. Poeta ML, Manola J, Goldwasser MA,et al *TP53 mutations and survival in squamous-cell carcinoma of the head and neck* NEJM, 2007
42. Tax WJ, Tamboer WP, Jacobs CW, Frenken LA, Koene RA. Role of polymorphic Fc receptor Fc gammaRIIa in cytokine release and adverse effects of murine IgG1 anti-CD3/T cell receptor antibody (WT31). Transplantation 1997;63(1):106-12.
43. Warmerdam PA, van den Herik-Oudijk IE, Parren PW, Westerdaal NA, van de Winkel JG, Capel PJ. Interaction of a human Fc gamma RIIb1 (CD32) isoform with murine and human IgG subclasses. International immunology 1993;5(3):239-47.
44. Zhang W, Gordon M, Schultheis AM*, et al.* FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer patients treated with single-agent cetuximab. J Clin Oncol 2007;25(24):3712-8.
45. Musolino A, Naldi N, Bortesi B*, et al.* Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. J Clin Oncol 2008;26(11):1789-96.
46. Taylor RJ, Chan SL, Wood A*, et al.* FcgammaRIIIa polymorphisms and cetuximab induced cytotoxicity in squamous cell carcinoma of the head and neck. Cancer Immunol Immunother 2008.
47. Hathaway B, Landsittel DP, Gooding W*, et al.* Multiplexed analysis of serum cytokines as biomarkers in squamous cell carcinoma of the head and neck patients. The Laryngoscope 2005;115(3):522-7.
48. Linkov F, Lisovich A, Yurkovetsky Z*, et al.* Early detection of head and neck cancer: development of a novel screening tool using multiplexed immunobead-based biomarker profiling. Cancer Epidemiol Biomarkers Prev 2007;16(1):102-7.

49. Hickok JT, Morrow GR, Roscoe JA, Mustian K, Okunieff P. Occurrence, severity, and longitudinal course of twelve common symptoms in 1129 consecutive patients during radiotherapy for cancer. J Pain Symptom Manage. 2005 Nov;30(5):433-42. PMID: 16310617
50. Mustian KM, Griggs JJ, Morrow GR, McTiernan A, Roscoe JA, Bole CW, Atkins JN, Issell BF. Exercise and side effects among 749 patients during and after treatment for cancer: a University of Rochester Cancer Center Community Clinical Oncology Program Study. Support Care Cancer. 2006 Jul;14(7):732-41. Epub 2006 Feb 16. PMID: 16482444 [PubMed -indexed for MEDLINE]
51. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9. PMID: 8445433 [PubMed -indexed for MEDLINE
52. Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. Semin Hematol. 1997 Jul;34(3 Suppl 2):13-9. PMID: 9253779 [PubMed -indexed for MEDLINE]
53. Lango MN, Andrews GA, Ahmad S, et al. Postradiotherapy neck dissection for head and neck squamous cell carcinoma: pattern of pathologic residual carcinoma and prognosis. Head Neck 2009;31(3):328-37
54. Eisbruch, A., T. Lyden, et al. (2002). "Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer." Int J Radiat Oncol Biol Phys 53(1): 23-28.
55. Rosenthal, D. I., J. S. Lewin, et al. (2006). "Prevention and treatment of dysphagia and aspiration after CRT for head and neck cancer." Journal of Clinical Oncology 24(17): 2636-2643.
56. Hutcheson, K. A., J. S. Lewin, et al. (2012). "Late Dysphagia After Radiotherapy-Based Treatment of Head and Neck Cancer." Cancer In Press
57. Ringash J, Fisher R, Peters L, O'Sullivan B, Trotti A, Kenny L, Young R, Rischin D. Impact of p16 status on the QOL effects of CRT for locally advanced oropharynx cancer: Results of RTOG 02.02. ASCO 2012, Chicago, USA, June 2012;
58. Sharma A, Mendez E, Yueh B, et al, HPV positive oral cavity and oropharyngeal cancer patients do not have better quality of life trajectories. Otolaryngol Head Neck Surg 2012; in press
59. Schwartz DL, Hutcheson K, Barringer D, et al. Candidate dosimetric predictors of long-term swallowing dysfunction after oropharyngeal intensity-modulated radiotherapy. ? Int J Radiat Oncol Biol Phys. 2010;78:1356-65.
60. Caudell, J. J., P. E. Schaner, et al. (2009). "Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer." Int J Radiat Oncol Biol Phys 73(2): 410-415.
61. Eisbruch, A., H. M. Kim, et al. (2011). "Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates." Int J Radiat Oncol Biol Phys 81(3): e93-99.
62. Caglar HB, Tishler RB, Othus M, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2008;72:1110-8.

63. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. ? Int J Radiat Oncol Biol Phys. 2007;68:1289-98.
64. List MA, D'Antonio LL, Cella DF, Siston A, Mumby P, Haraf D, Vokes E. The performance status scale for HNC patients and the functional assessment of cancer therapy-head and neck scale. A study of utility and validity. Cancer. 1996;77:2294-2301
65. Carrara-de Angelis, E., O. Feher, et al. (2003). "Voice and swallowing in patients enrolled in a larynx preservation trial." Arch Otolaryngol Head Neck Surg 129(7): 733-738.
66. Hutcheson, K. A., D. A. Barringer, et al. (2008). "Swallowing outcomes after radiotherapy for laryngeal carcinoma." Arch Otolaryngol Head Neck Surg 134(2): 178-183.
67. Francis, D. O., E. A. Weymuller, Jr., et al. (2010). "Dysphagia, stricture, and pneumonia in head and neck cancer patients: does treatment modality matter?" Ann Otol Rhinol Laryngol 119(6): 391-397.
68. Hunter, K. U., Lyden T., Haxer, F. et al. (2011) What Is The Clinical Relevance Of Objective Swallow Studies In Head And Neck Cancer (HNC) Patients Receiving Chemoirradiation (CRT)? Analysis Of Aspiration In Swallow Studies Vs. Risk Of Aspiration Pneumonia. ASTRO 2011: poster 1037.
69. Gillespie, M. B., M. B. Brodsky, et al. (2004). Swallowing-related quality of life after head and neck cancer treatment. Laryngoscope. 2004 Aug;114(8):1362-7.
70. Sinclair CF et al. Patient-perceived and objective functional outcomes following transoral robotic surgery for early oropharyngeal carcinoma. Arch Otolaryngol Head Neck Surg. 2011 Nov;137(11):1112-6.;
71. Hurtuk A et al. Quality-of-life outcomes in transoral robotic surgery. Otolaryngol Head Neck Surg. 2012 Jan;146(1):68-73.
72. Genden EM et al. The Role of Reconstruction for Transoral Robotic Pharyngectomy and Concomitant Neck Dissection. Arch Otolaryngol Head Neck Surg. 2011;137(2):151-156.
73. Weinstein GS et al. Transoral Robotic Surgery for Advanced Oropharyngeal Carcinoma. Arch Otolaryngol Head Neck Surg. 2010;136(11):1079-1085.
74. Moore EJ et al. Transoral robotic surgery for oropharyngeal squamous cell carcinoma: a prospective study of feasibility and functional outcomes. Laryngoscope. 2009 Nov;119(11):2156-64.
75. Weinstein et al. Transoral Robotic Surgery: Radical Tonsillectomy. Arch Otolaryngol Head Neck Surg. 2007;133(12):1220-1226.
76. Langendijk, J.A., et al., A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. Radiother Oncol, 2009. 90(2): p. 189-95.
77. Withers HR, Peters LJ, Taylor JM. Dose-response relationship for radiation therapy of subclinical disease. Int J Radiat Oncol Biol Phys. 1995 Jan 15;31(2):353-9.
78. Kubik M, Mandal R, Albergotti W, Duvvuri U, Ferris RL, Kim S. Effect of transcervical arterial ligation on the severity of postoperative hemorrhage after transoral robotic surgery. Head Neck. 2017 Aug;39(8):1510-1515.

79. Gleysteen J, Troob S, Light T, Brickman D, Clayburgh D, Andersen P, Gross N. The impact of prophylactic external carotid artery ligation on postoperative bleeding after transoral robotic surgery (TORS) for oropharyngeal squamous cell carcinoma. Oral Oncol. 2017 Jul;70:1-6.

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Appendix I

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Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists

Guidelines for Submission of Pathology Materials

E3311: Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Pathologic Analysis of Surgical Specimens

Within RTOG / ECOG-ACRIN centers, a surgical pathologist should be designated as the primary pathologist responsible for quality control of surgical pathology material processing, evaluation and reporting at their respective institution.

Histopathologic Assessment: Histopathologic assessment of surgical pathology frozen and permanent sections must include examination for perineural invasion (PNI) and lymphovascular invasion (LVI) and reported as absent or present. The absence or presence of extracapsular extension (ECE) requires gross and microscopic assessment and should be reported in the following manner:

- absent (negative or nodal metastasis with smooth/rounded leading edge confined to thickened capsule/pseudocapsule),

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- present - minimal (tumor extends ≤ 1 mm beyond the lymph node capsule), or
- present - extensive (tumor extends > 1 mm beyond the lymph node capsule (includes soft tissue metastasis)

p16 Immunohistochemistry assessment of the original diagnostic biopsy,

Immunophenotyping of tumor cells using p16 immunohistochemistry must be performed in the following manner:

- Validated immunostaining performed using p16 antibody obtained from Roche mtm laboratories AG (CINtec®, clone E6H4™) within a CLIA certified laboratory

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- Strong cytoplasmic immunoreactivity noted in ≥70% of tumor cells qualifies as a positive result while less immunoreactivity qualifies as negative

The following materials are to be submitted upon completion of the surgical pathology report by the site, but no later than 4 weeks following completion of the surgery

Pathology materials required for pathology review and, per patient consent, research

Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, will expedite any required communications with the institution (including site pathologists).

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1. Representative tumor specimens of the following are to be submitted:
   - **MANDATORY**:
     - Original p16 tumor slide

       NOTE: If blocks are not available for submission, the following materials are to be submitted: 1-2 core punches (4 mm minimum) and 20 unstained slides.
   - **From consenting patients**
     - Fixed Paraffin-embedded tumor tissue block. Original diagnostic or surgical specimen may be submitted.

       NOTE: If blocks are not available for submission, the following materials are to be submitted: H&E from the relevant source blocks, 1-2 core punches (4 mm

minimum) and 20 unstained slides. Slides, including the H&E are to be numbered consecutively in the order they are cut.

- Frozen tumor tissue specimen, if available

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2. Forms and reports:
   - Copy of the original diagnostic pathology report
   - Surgical pathology and surgical procedure reports. Reports, documentation must be included.
     - Histopathologic assessment of surgical pathology must include examination for perineural invasion (PNI) [absent or present], lymphovascular invasion (LVI) [absent or present], and extracapsular extension (ECE) [absent, present-minimal, present-beyond minimal]
     - Surgical margin status must be reported as i) *Negative* (tumor ≥ 3mm from designated margin); ii) *Close* (tumor < 3mm of the designated margin); or iii) *Positive* (tumor at the cut specimen edge not superseded by another margin)
   - Other Immunologic and cytologic reports
3. Mail pathology materials to:

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ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone or email.

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

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MEMORANDUM

TO: _____

(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

Rev. 6/14 **SUBJECT:** *Submission of Pathology Materials for* E3311: *Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer*

Materials are requested from a patient who has been entered onto the above ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for central pathology review and laboratory research studies.

Rev. 2/15 The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned upon written request for purposes of patient management.

> Please note: Since blocks are being *used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.*

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility 1-844-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address: _____

Phone: _____

Thank you.

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Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Appendix III

AJCC Head/Neck Staging Criteria

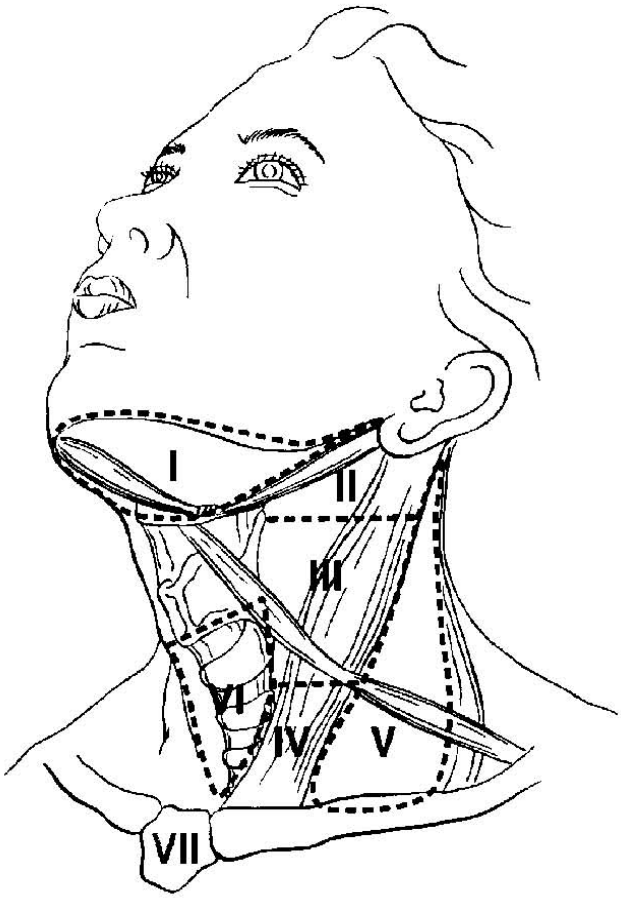


FIG 2.1. Schematic diagram indicating the location of the lymph node levels in the neck as described in the text.

Level IV: Contains the lower jugular lymph nodes from the level of the cricoid cartilage superiorly to the clavicle inferiorly.

Level V: Contains the lymph nodes in the posterior triangle bounded by the anterior border of the trapezius muscle posteriorly, the posterior border of the sternocleidomastoid muscle anteriorly, and the clavicle inferiorly. For descriptive purposes, Level V may be further subdivided into upper, middle, and lower levels corresponding to the superior and inferior planes that define Levels II, III, and IV.

Level VI: Contains the lymph nodes of the anterior central compartment from the hyoid bone superiorly to the suprasternal notch inferiorly. On each side, the lateral boundary is formed by the medial border of the carotid sheath.

Level VII: Contains the lymph nodes inferior to the suprasternal notch in the superior mediastinum.

Metastatic Sites. The most common sites of distant spread are in the lungs and bones; hepatic and brain metastases occur less often. Mediastinal lymph node metastases are considered distant metastases.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
*N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
*N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
*N2a Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
*N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
*N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
*N3 Metastasis in a lymph node more than 6 cm in greatest dimension

**Note:* A designation of "U" or "L" may be used to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

PHARYNX (INCLUDING BASE OF TONGUE, SOFT PALATE, AND UVULA)

Hospital Name/Address	Patient Name/Information

Type of Specimen _____ Histopathologic Type _____

Tumor Size _____ Laterality: ☐ Bilateral ☐ Left ☐ Right

DEFINITIONS

Clinical	Pathologic	Primary Tumor (T)	
☐	☐	TX	Primary tumor cannot be assessed
☐	☐	T0	No evidence of primary tumor
☐	☐	Tis	Carcinoma *in situ*
		Oropharynx	
☐	☐	T1	Tumor 2 cm or less in greatest dimension
☐	☐	T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
☐	☐	T3	Tumor more than 4 cm in greatest dimension
☐	☐	T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
☐	☐	T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Regional Lymph Nodes (N)

		Oropharynx and Hypopharynx	
☐	☐	NX	Regional lymph nodes cannot be assessed
☐	☐	N0	No regional lymph node metastasis
☐	☐	N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
☐	☐	N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
☐	☐	N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
☐	☐	N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
☐	☐	N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
☐	☐	N3	Metastasis in a lymph node more than 6 cm in greatest dimension

PHARYNX (INCLUDING BASE OF TONGUE, SOFT PALATE, AND UVULA) (continued)

Clinical	Pathologic	Distant Metastasis (M)	
☐	☐	MX	Distant metastasis cannot be assessed
☐	☐	M0	No distant metastasis
☐	☐	M1	Distant metastasis

Biopsy of metastatic site performed ..... ☐Y ..... ☐N

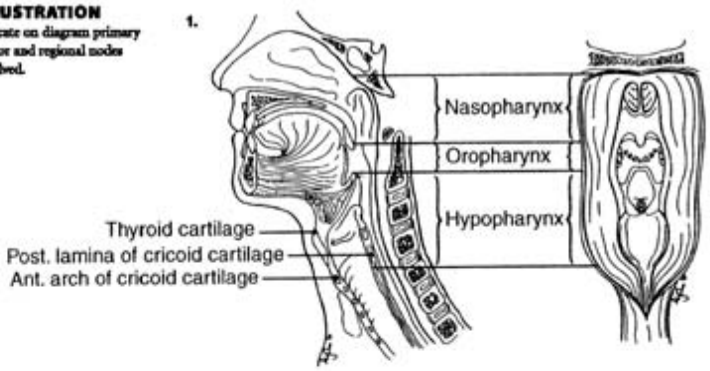
Source of pathologic metastatic specimen _____

Clinical	Pathologic	Stage Grouping: Oropharynx and Hypopharynx			
☐	☐	0	Tis	N0	M0
☐	☐	I	T1	N0	M0
☐	☐	II	T2	N0	M0
☐	☐	III	T3	N0	M0
			T1	N1	M0
			T2	N1	M0
			T3	N1	M0
☐	☐	IVA	T4a	N0	M0
			T4a	N1	M0
			T1	N2	M0
			T2	N2	M0
			T3	N2	M0
			T4a	N2	M0
☐	☐	IVB	T4b	Any N	M0
			Any T	N3	M0
☐	☐	IVC	Any T	Any N	M1

PHARYNX *(INCLUDING BASE OF TONGUE, SOFT PALATE, AND UVULA)* *(continued)*

ILLUSTRATION
Indicate on diagram primary tumor and regional nodes involved.

1.



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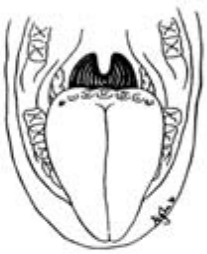

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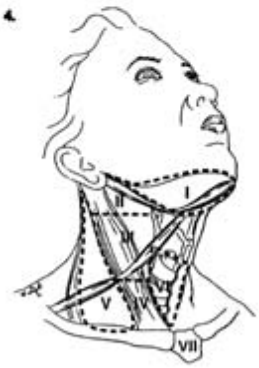

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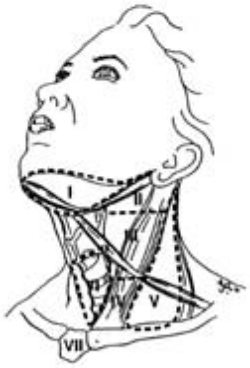

Physician's Signature _____ Date_____

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Appendix IV

Rev. 1/16

ECOG-ACRIN Checklist for Submission of Radiation Oncology Quality Assurance Materials

Rev. 7/13

Attention: ECOG-ACRIN Materials Address
Building B, Suite 201
640 George Washington Highway
Lincoln, RI 02865-4207

Checklist for Submission of Radiation Oncology Quality Assurance Materials

Patient Initials: _____ Registration #: _____

RT Start Date: _____

Sender's Name: _____

Phone #: _____

Email:_____

Radiation Oncologist:

Email:_____

Please *enclose a copy of this Checklist* together with the RT materials you submit. All materials must be labeled with the protocol and assigned registration number.

Digital treatment plan, screenshots of other RT data and diagnostic imaging may be submitted via sFTP or on CD. For data sent via sFTP, a notification email should be sent to sFTP@qarc.org with the **protocol # and registration # in the subject line**. Please refer to IROC Rhode Island website for instructions on sending digital data (www.QARC.org).

Data not sent via sFTP may be sent via email to datasubmission@qarc.org with the **protocol # and registration # in the subject line.** Data may also be sent via courier to the address below.

The following materials must be submitted within 3 days of the start of radiotherapy for review:

DATE SUBMITTED	
_____	Copy of pre-study diagnostic imaging AND radiology report (s), exam notes and endoscopy reports used to define the GTVs
_____	Digital RT Treatment Plan (DicomRT or RTOG format)
_____	Prescription sheet for entire treatment
_____	Treatment planning system summary report that includes the MU calcs, beam parameters, calculation algorithm, and volume of interest dose statistics
_____	DVH for "unspecified tissue (this is included in the digital RT Plan)

_____ If replanning is done on a new CT dataset and your planning system has the capability of exporting a DICOM spatial registration file, submit the spatial registration file along with the two CT scan sets. Otherwise screen captures of the fused datasets with the target volumes and critical normal structures delineated shall be submitted.

_____ Copy of Appendix III (AJCC Head/Neck Staging Criteria)

_____ RT-1 Dosimetry Form www.qarc.org/forms/IROC_RT-1DosimetrySummaryForm.pdf

Final Review materials must be submitted <u>within 1 week</u> of the completion of radiation:

_____ Completed RT Daily Treatment Chart, including prescription, daily and cumulative doses

_____ RT-2 Total Dose Record www.qarc.org/forms/IROC_RT2RadiotherapyTotalDoseRecord.pdf

Please contact study CRA by email (ECOG@qarc.org) or phone: (401) 753-7600 for clarification as necessary. Thank you for your ongoing co-operation.

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

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Appendix V

Patient Reported and Functional Outcomes (PRO) Administration

Questionnaires will be available on-line for centers to print as need. They will be administered by trained personnel. It is recommended that PROs be administered to patients at the time of a clinic visit, before the patient is assessed by the doctor. In the event that a patient needs extra time, it is permissible for the instruments to be taken home for completion and mailed back; trialists should follow-up by telephone within 1 week to insure the instrument has been completed and if necessary, complete it over the phone by reading items and responses verbatim.

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Rev.7/13, Rev.2/15, 6/15, 9/16 Rev. Add8

At each time point, the completed questionnaires must be entered into Medidata Rave by the site. Please note that in the chart below, the top two rows specify when each assessment should be done in relation to the completion of step 1 or step 2 treatment. Within Rave, it is ECOG-ACRIN's convention that the reporting periods for all Long-term Follow-up (LTFU) folders are based off of the patient's registration to step 1, and this applies to all arms of E3311. Therefore, the reporting periods within the LTFU forms and protocol-specified assessments should be looked at separately. In order to determine which LTFU folder an assessment should be reported in, you should look at the third row, entitled "Time (from registration to step 1)" to determine when this assessment will occur in relation to step 1 registration. As an example, if you had a patient that was registered on 01/01/2016 and completed RT on 06/15/2016, the follow-up assessments that are supposed to be completed 6 months post RT would occur around 12/15/2017. Row 3 of the chart notes that the 6 months post RT assessments should be done 42-28 weeks after registration to step 1 registration, which is between 10.5 and 12 months post step 1 registration. Therefore, this assessment would not fall within the 6 months post-registration LTFU folder, and would instead fall within the 12 months post-registration LTFU folder.

Assessment	***Baseline***	***4-6 wk post TORS-TOS***	***End of RT***	***3 mo post RT***	***6 mo post RT***	***1 year post RT***	***2 year post RT***
Time (post TORS/TOS)	Baseline		12-16 wk	24-28	36-40	60-64	112-116
Time (from registration to Step 1)*			18-24	30-36	42-48	70-76	122-128
Clinical							
Weight	X	X	X	X	X	X	X
ECOG PS	X	X	X	X	X	X	X
Trach y/n	X	X	X	X	X	X	X
Feed tube y/n	X	X	X	X	X	X	X
PSS-HN	X	X	X	X	X	X	X
Charlson	X						
Swallowing							
MBS	X	X			X		X

Assessment	*Baseline*	*4-6 wk post TORS-TOS*	*End of RT*	*3 mo post RT*	*6 mo post RT*	*1 year post RT*	*2 year post RT*
Pros							
FACT-H&N	X	X	X	X	X	X	X
MDADI	X	X				X	X
MDASI-HN	X	X	X	X	X		X
VHI-10	X	X				X	X
EQ-5D			X				
Cost Questionnaire			X				
Ret to work	X			X	X	X	X

Rev. 7/13, Rev. 2/15 *** Arm A patients and Arm S patients who do not register to Step 2: QOL submission will be based on "Time (From registration to Step 1)" schedule/row.**

Rev. 7/13, 2/14 **PLEASE NOTE: QOL will continue to be collected for all patients post recurrence.**

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Appendix VI

Modified Barium Swallow (MBS) Credentialing Checklist

Rev. 7/13

This form needs to be completed by the institution before patients can be registered to E3311. Once the form is complete, please fax this to the ECOG-ACRIN Operations Office - Boston at (617) 632-2990, Attention: E3311 Data Manager. You will receive an email from the ECOG-ACRIN Data Manager confirming the receipt of the checklist.

1. Do you conduct modified barium swallow (MBS) studies to evaluate swallowing disorders in your institution?

   YES_____ NO_____

   If "NO", skip to number 8; if "YES", please answer questions 2-8.

2. Are your MBS videos recorded digitally at a minimum frame rate of 30 frames/second (i.e., accurate to 0.01 time code imprints)?

   YES_____ NO_____

3. Do you use the Kay Pentax Digital Swallowing Workstation (this is NOT mandatory for participation)?

   YES_____ NO_____

4. Do you use Varibar contrast agents specified in this protocol, including Varibar Thin Liquid and Varibar Pudding?

   YES_____ NO_____

   a. If no, can you access Varibar contrast agents for MBS studies conducted per E3311

      YES_____ NO_____

5. Are you (speech pathologists) willing to follow the MBS protocol as written in E3311 (including the sequence of bolus administration, use of Varibar products, and volumes/viscosities specified)?

   YES_____ NO_____

6. Please provide the following data specific to your site:

   a. Number of speech pathologists at your institution who perform MBS studies?

      _____

   b. Average number of total MBS studies conducted at your institution each week?

      _____

   c. Average number of MBS studies conducted on patients who have head and neck cancer each week? _____

7.	8.
Signature of Speech Pathologist completing this form	**Institution Name**
	Contact Person
Printed Name of Speech Pathologist	**Telephone Number**
Name and email of person registering to cloud account and uploading video	**Email Address**
Fax Number	**Site ECOG-ACRIN Institution Number/ CTEP ID Number**

Rev. 2/15

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Appendix VII

Surgeon Credentialing Questionnaire

1. This study requires careful documentation of stage of disease prior to registration. CT MR and PET scan findings are not accepted as sole criteria of the extent of the primary tumor. Pre-treatment endoscopy, even in the operating room, if deemed appropriate, is sometimes necessary for patients. Is this a procedure that you perform routinely and would you agree to do for this protocol, if needed?

   YES _____ NO_____ Comments:

2. Please check the item that best describes the scope of your practice:

   _____ General Otolaryngology

   _____ Head and Neck Surgery with some endoscopic surgery (TLM or TORS)

   _____ Head and Neck Surgery with a focus on endoscopic surgery (TLM or TORS)

3. Please estimate the number of neck dissections you perform per year. _____

4. Please estimate the number of transoral endoscopic surgical procedures you perform each year (TLM or TORS). _____

5. As attending surgeon, have you performed a minimum number of 20 cases of transoral excision for oropharyngeal carcinoma as the primary surgeon?

   YES_____ NO_____

6. As attending surgeon, have you performed at least 5-10 transoral resections of oropharyngeal carcinoma in the past 12 months?

   YES_____ NO_____

7 Please upload paired pathology report and operative notes for **ten** transoral eHNS cases, including at least one tonsil and one tongue-base primary tumor.

8. If there are other surgeons at your institution who will be participating in this program, have they also completed one of these forms?

   YES_____ NO_____

NOTE: This form is for reference only. The information will be entered directly into Medidata Rave in the "E3311/RTOG-1221 H&N Surgeon's Questionaire – Credentialing" database.

Rev. 2/14

NOTE: Only transoral oropharynx cancer resections are applicable; oral cavity and larynx surgeries are not applicable, even if transoral in approach.

Rev. 2/15

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Appendix VIII

Modified Barium Swallow Study Form

MBS **Modified Barium Swallow Study Form**

E3311: Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

INSTRUCTIONS: To be filled out by the speech pathologist after the modified barium swallow study**. Dates are recorded as** mm-dd-yyyy **unless otherwise specified.**

MBS PROTOCOL:

All MBS studies must follow a standard protocol as outlined below.

Additional bolus presentations or swallowing strategies may be tested after completing bolus trials in the study protocol, at the discretion of the clinician conducting the MBS study.

Studies will be done in lateral and AP views with focus fixed on the soft palate superiorly, cricopharyngeus inferiorly, lips anteriorly, and cervical spine posteriorly.

Video-recordings will require time code imprints accurate to 0.01 seconds (30 frames/second). Video-recordings between 15-30 frames/second will be accepted as long as the recording rate is clearly documented in advance. Video-recordings below 15 frames/second will not be accepted.

Studies must be recorded in AVI or MPEG format. All centers must use the Kay Digital Swallowing Workstation for the studies; or alternatively, have the ability to convert files to AVI of MPEG format.

Centers must use Varibar products. Consistencies and quantities are listed below. Liquids must be administered first to avoid confounding the results from remaining residue in the pharynx after solid consistencies.

A dime must be taped to the subject's chin during the swallowing study. The circular shape of the dime minimizes the impact of head rotation and the known diameter of the dime allows for calibration of pixels per cm and thus calculation of distances and areas on the lateral view of the x-ray.

Lateral view:

- 5mL thin (2 trials, tsp). Instruction to the patient: *please hold this in your mouth until asked to swallow.*
- 20mL thin (1 trial). Instruction to the patient: *please try to take the whole amount and hold it in your mouth until I ask you to swallow*. Self administration is optimal, but clinician administration is acceptable.
- 5mL pudding (1 trial tsp). Instruction: *swallow when you are ready.*
- 1/2 cookie or cracker, barium coated - coated with 3 ml (1/2 tsp) of Varibar pudding (1 trial). Instruction to the patient: *chew this up and swallow when you feel comfortable and ready to swallow.*

A-P view:

10mL thin (1 trial). Instruction: slightly raise your chin (neutral position, not tucked or extended), hold this in your mouth until asked to

RATING RULES:

Rate MBS outcomes below on the basis of bolus trials in the ECOG-ACRIN protocol. Do not rate based on additional bolus trials that are administered outside of the protocol or based on bolus trials in which a swallow strategy/posture was tested. Please select a SUMMARY RATING based on the highest level of impairment you observe on any bolus trial in the protocol.

MBS Modified Barium Swallow Study Form

E3311: Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

1 DATE OF MBS _____-_____-_____	**2** ☐ **TIME OF MBS** 1. Baseline 2. After surgery (before adjuvant therapy) 3. Six months after treatment 4. Twenty-four months after treatment

Outcome Variables	Definition	Scoring Rules (Rate the worst of impairment across all bolus trials in the MBS protocol)	Rating
3 LARYNGEAL PENETRATION	PENETRATION: Bolus enters the larynx but does not pass below the TVFs	Select "1" if LARYNGEAL PENETRATION occurred on any bolus in the protocol.	□ No penetration (0) □ Penetration (1)
4 ASPIRATION	ASPIRATION: Bolus enters the larynx and passes below the TVFs. SENSATE: attempts to eject aspirate from airway (e.g., cough, throat clear) SILENT: no effort to eject aspirate from airway (no cough, throat clear)	Select the highest level of aspiration that occurred during the protocol. Select "1" if SENSATE ASPIRATION ocurred on any bolus in the protocol, but silent aspiration NEVER occurred. Select "2" if SILENT ASPIRATION occurred on any bolus in the protocol.	□ No aspiration (0) □ Yes, sensate (1) □ Yes, silent (2)
5 PHARYNGEAL RESIDUE	RESIDUE: bolus remaining on or within the pharynx at the conclusion of the initial swallow. The conclusion of the initial swallow is when the hyoid bone returns to rest. If the patient spontaneously swallows several times to clear the bolus, residue is rated after the 1st swallow attempt.	Rate the highest level of residue that occurred during the protocol. Select "0" is no residue or only pharyngeal coating occurred during the protocol. Select "1" if pharyngeal residue of <50% of the original bolus remained in the pharynx on any bolus in the protocol. Select "2" if pharyngeal residue of half or more of the original bolus remained in the pharynx on any bolus in the protocol.	□ No residue (0) □ <50% pharyngeal residue (1) □ ≥ 50% pharyngeal residue (2)
PERSON COMPLETING FORM:			

NOTE: This form is for reference only. The MBS information for each registered patient will be entered directly into the Medidata Rave database. MBS Videos will be uploaded to a cloud account held by MD Anderson Cancer Center. Instructions on how to upload the videos can be found in Section 4.1.5.7.

Rev. 6/15
Rev, Add8

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Appendix IX

Letter Explaining Modified Barium Swallow Video Upload Instructions

Dear [CRA SALUTATION],

Thank you for participating in the MBS data collection efforts for ECOG-ACRIN protocol E3311, "Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer."

E3311 will archive MBS video files on MD Anderson Cancer Center's Box® Cloud-based storage account. You are receiving this e-mail because you were designated as the individual who will be responsible for uploading and archiving MBS video files to Box.

Details regarding the HIPAA compliance and MD Anderson's Business Association Agreement associated with the Box Cloud account can be found at:

http://www.mdanderson.org/about-us/for-employees/employee-resources/box-cloud-storage/faqs.html#security

Additional information regarding the security of Box is located at:

https://support.box.com/hc/en-us/articles/200526618-Box-HIPAA-and-HITECH-Overview-and-FAQs

Shortly, you will receive e-mail notification that you have been added as a collaborator to the E3311 MBS Video Files folder on Box. Upon receipt of the e-mail, click on the icon that reads "View Folder." You will then be taken to a webpage that asks you to create an account with Box. When you are ready to upload video files in the future, you will need to return to this site (www.box.com) and log in. Once logged into your account, click on the shared folder. To upload videos, click on the grey button entitled "Upload" in the top left-hand corner of your screen and select Upload Files from the drop-down menu (please make sure that you are uploading your files inside of this folder). If you forget your password, please click the link labeled "Reset Password" (below the space where you would log into Box) for instructions on obtaining a new password.

To ensure the security of the uploaded video all patient identifiers are to be removed and the video files are to be re-labeled with a unique identification code. To obtain the code:

3. Log the videos into ECOG-ACRIN's *Sample Tracking System* (STS), indicating the "Ship Date" as the date the video is to be uploaded to the MD Anderson Box Cloud Account. Be sure to select the correct protocol-specified time point for the video. (e.g., Baseline, after surgery…)

https://webapps.ecog.org/Tst/

4. Exit *STS* and enter the *Patient Video Identifier Lookup* application. Select the protocol and enter the ECOG-ACRIN E3311 patient identifier to pull up the patient specific information. The code is the "Sample ID" and is a unique code linked to the patient and the time point of the video as entered into STS.

https://webapps.ecog.org/PatientVideoIdentifyLookup/

Videos must be uploaded in .mpeg or .avi format. Rename the electronic video file using only the STS-generated sample ID prior to uploading to the MD Anderson Cloud. For example, if the sample ID obtained from STS is “123456” and the video is in .avi format, the file to be uploaded should be named “123456.avi”. Any and all PHI contained within the video or as part of its name must be removed prior to upload on Box.

We have attached instructions for saving video files in the desired format as well as editing tips that may be helpful for removing PHI from the MBS videos prior to upload to the Box account.

Should your site have a change in staff responsible for upload of video files to Box, please notify E3311_MBS@jimmy.harvard.edu with the name and e-mail address of the individual requesting access to Box.

Please do not hesitate to contact us should you need further assistance or encounter problems uploading videos.

Regards,

MD Anderson Cancer Center

Department of Head and Neck Surgery

Section of Speech Pathology and Audiology

T: 713-792-6364

Rev, Add9

Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Appendix X

E3311LGS1
Identification of novel biomarkers and therapeutic targets of higher-risk disease in ECOG 3311

Principal Investigator: Robert L. Ferris, MD PhD
Statistician: Yael Flamand, PhD

Co-Investigators: Xiaosong Wang, PhD
Danielle Normolle, PhD
Daniel Faden, PhD
Barbara Burtness, MD

The majority of Human papillomavirus- (HPV) mediated head and neck squamous cell carcinoma (HNSCC) have favorable outcomes compared to non-HPV mediated HNSCC. Thus, much interest is focused on treatment de-intensification in HPV-mediated disease in an attempt to maintain this survival advantage while decreasing treatment morbidity. Currently, no biomarkers exist in HPV-mediated HNSCC to predict patients who can safely undergo treatment de-intensification.

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1) Objectives

The primary objective is to identify genomic biomarkers in HPV-mediated HNSCC that predict an aggressive tumor phenotype and, thus, patients who should not undergo treatment de-intensification with trans-oral robotic surgery (TORS).

a. **Objectives: 1)** Develop a predictive model that, using Whole Exome Sequencing and RNA-Seq, predicts risk stratification and clinical outcome after observation, radiation alone, or chemoradiation. Generate a rich genomic and transcriptomic dataset for a novel, rapidly increasing subset of H&N cancers to provide collaborative opportunities for translational research to understand this newly emerging cancer. **2)** In an independent set of samples from ECOG 3311, test the one-side null hypothesis that the AUC of the ROC curve of the predictive model is less than 0.6 at α=0.05. This test is to be performed by the ECOG Statistical Center to ensure independence of the validation from the training.

b. **Hypotheses: 1**) A predictive model that can be used to predict patients with HPV-mediated who are candidates for de-intensification can be developed using Whole Exome Sequencing and RNA-Seq. **2)** In an independent validation set, it can be demonstrated that the AUC of the ROC curve of this predictive model is greater than 0.6.

2) Background and Rationale

Traditionally, the major risk factors for Head and Neck Squamous cell carcinoma (HNSCC) were tobacco and alcohol exposure [1-3]. However, HPV is now recognized as the major risk factor for HNSCC of the lingual and palatine tonsils. Molecular and epidemiologic studies have confirmed that nearly 70% of HNSCC of the oropharynx (OPSCC) are HPV-mediated [4, 5]. Risk of death from HPV-mediated OPSCC patients is 50 percent lower than for non-HPV mediated OPSCC. This improvement is portended both by the favorable biology of HPV-mediated OPSCC, but is also related to the younger age and decreased medical comorbidities seen in this patient population. While <15% of HNSCC in the TCGA are HPV-mediated, it has become clear that these tumors have distinct genomic underpinnings compared to non-HPV mediated HNSCC.

Favorable tumor biology, in combination with the younger age of HPV-mediated HNSCC patients, leads to not only improved overall survival, but more potential life years after cure. Thus, interest is now focused on reducing treatment-associated morbidity. In particular, attention has been brought to the development of late effects from chemoradiotherapy, as an organ-preservation approach has become a standard of care. In E2399, 49% of OPSCC patients had moderate-to-severe swallowing impairment at 3 months following treatment, and some patients were still PEG dependent after 12 months. Severe swallowing dysfunction following radiation therapy to the oropharynx is a major source of decreased QOL in HPV mediated OPSCC patients.

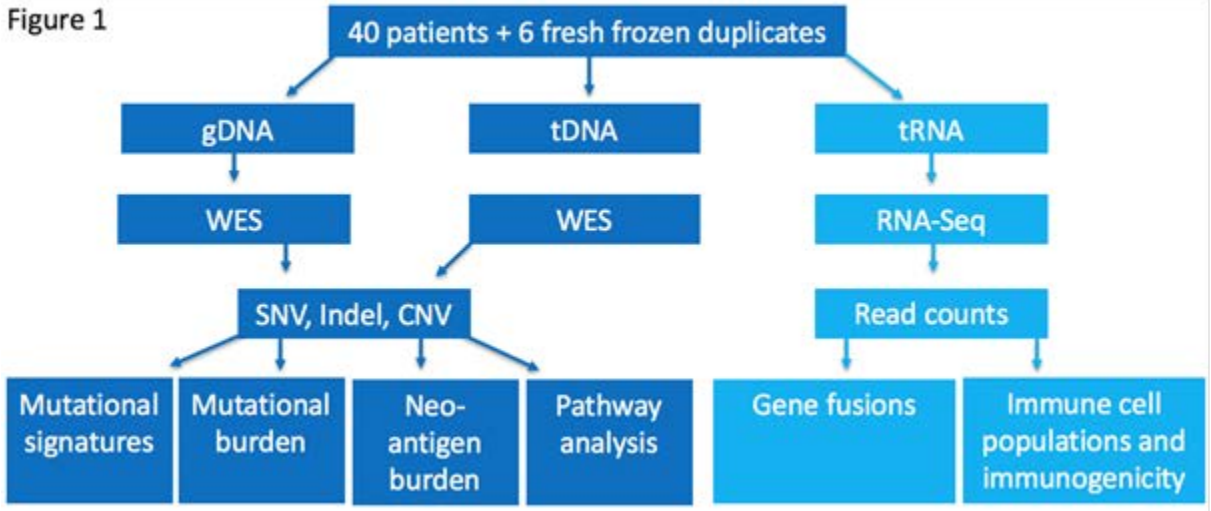
Traditionally, surgical resection of OPSCC carried significant morbidity due to the difficulty of accessing the oropharynx, necessitating aggressive surgical maneuvers. More recently, trans-oral surgery (TOS) has gained favor as a method for achieving surgical extirpation with limited morbidity. TOS has been shown to be able to achieve complete surgical extirpation of

T1/T2 OPSCC with oncologic outcomes similar to chemoradiotherapy in single institution studies [6]. Further, TOS has improved QOL measures and swallowing outcomes, compared to chemoradiotherapy [6-8]. As expected, patients who receive single-modality TOS have improved swallowing outcomes, compared to patients who receive adjuvant radiation [9]. ECOG 3311 was designed to explore the role of TOS in treatment de-intensification for HPV-mediated OPSCC.

Preliminary evaluation of ECOG 3311 arm stratification has shown that ~30% of patients enrolled were stratified into arm D (tri-modality therapy), based on adverse pathologic risk factors. Tri-modality therapy is well established to have a more severe side effect profile, compared to surgery alone and surgery with adjuvant radiation, particularly, in regards to swallowing. Thus, identification of patients with biologically more aggressive cancers prior to treatment decision-making is vital for avoiding tri-modality therapy, if not absolutely necessary. All patients enrolled in ECOG 3311 have cT1 or T2 and cN1, N2a, or N2b disease, based on clinical or radiographic criteria, and are thus indistinguishable pre-operatively. At this time, no biomarkers exist that predict a more aggressive tumor phenotype or clinical pathologic features that would necessitate stratification into arm D of ECOG 3311 and, thus, tri-modality therapy. ECOG 3311 presents a unique opportunity to investigate such biomarkers in a cohort of HPV+ OPSCC patients with tightly annotated clinical and pathologic data. Of note, Dr. Ferris is the PI, the highest accruing surgeon nationally to E3311, and personally funded the preliminary genomic/transcriptomic analysis and characterization, using UPMC specimens, to provide feasibility for the proposed studies using additional specimens from this trial.

Our primary preliminary objective was to determine the feasibility of identifying genomic biomarkers that would predict patients who stratify into arm D, pre-operatively. Identifying these patients prior to surgery would allow practitioners to choose alternative therapies, avoiding tri-modality therapy. We first sought to better define the genomic profile of HPV-mediated HNSCC in general. Existing data support HPV-mediated HNSCC having a distinct genomic profile from non-HPV mediated HNSCC [10]. However, a limited number of HPV-mediated HNSCCs had been comprehensively profiled and available to the scientific community. For example, TCGA contains <75 HPV-mediated HNSCCs. From that cohort, and others, we knew that HPV-mediated HNSCC typically lack TP53 mutations, the most common driver mutation in non-HPV mediated HNSCC and CDK2NA alterations, and instead possess high rates of PIK3CA mutations and E2F1 amplifications. However, how specific genomic and transcriptomic alterations relate to tumor behavior within HPV mediated HNSCC is not known. While many potentially promising biologic pathways and hypotheses have been reported to be of importance in HPV mediated HNSCC, for example, the presence of TRAF3/CYLD mutations has been shown to correlate with tumor behaviors [11], to date, no established biomarkers exist.

Figure 1

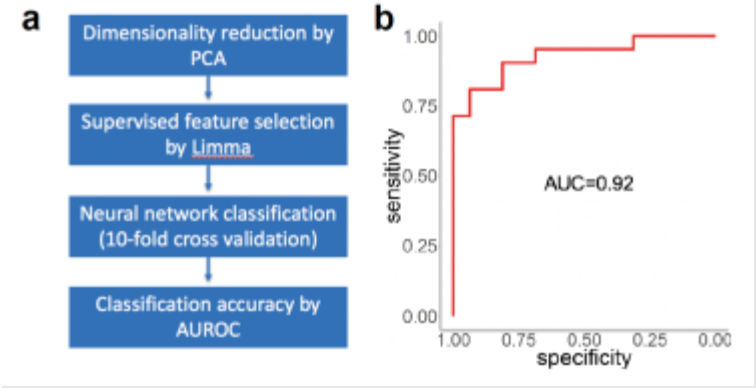


To determine if the approach was feasible, we generated and analyzed WES and RNA-Seq datasets for 40 patients from the University of Pittsburgh. Briefly, after pathologic review, DNA and RNA was extracted from 43 HNSCC tumors (FFPE), as well as germline DNA from peripheral blood. One patient had low quality nucleic acid on QC and was removed. Tumor and germline DNA underwent WES at 85% of targeted bases at 50X or greater coverage (~150X MTC) paired end reads for the tumor DNA and 85% of targeted bases at 20X or greater coverage (~60X MTC) for germline DNA. Tumor RNA underwent RNA-Seq at 50M paired end reads at the Broad Institute using standard library prep and sequencing approaches (76-bp paired end on Illumina HiSeq 2500). Two patients had low coverage or failed fingerprint SNP analysis and were removed. Our workflow for the remaining 40 patients is represented in **Figure 1**. More detailed methods are presented in Laboratory Methods.

Predictive Gene Expression Signature

In order to investigate gene expression signatures that could predict arm stratification, we divided our patients into two cohorts and performed principal component analysis (PCA) for dimensionality reduction (see workflow in **Figure 2a**). We used Limma for supervised feature selection between cohorts, which identified 231 differentially expressed genes (DEGs). We then applied a neural network to the 231 DEG expression matrix to compute a classification score. The ROC curve of the resulting classifiers is presented in **Figure 2b**. The resulting area under the receiver operating characteristic (AUC) is 0.92. This estimate of the AUC, being based on the training set, is optimistically biased and we do not anticipate a validated AUC this close to 1, but it demonstrates the feasibility of the approach. Developing a clinically actionable predictive model requires a larger training set and an independent validation set from the ECOG 3311 cohort.

Figure 2



Ongoing work

The predictive signature discussed above employs only gene expression data. However, numerous genomic features may be important in predicting arm stratification. Thus, we are currently employing more advanced and comprehensive modeling to generating predictive signatures which include more varied data input including from both DNA and RNA (**Figure 3**). These more comprehensive approaches will help refine and improve the accuracy of our predictive signature.

Figure 3

Funding for the project will come from Hillman Cancer Center funds, and R01 submission in progress (depends on a support letter from ECOG providing and ensuring access to the national specimens, beyond the UPMC -enrolled patients which comprise the preliminary data).

3) Biospecimen Requirements

Tissue (slides, cores, etc.): 10 tumor blanks (or 1 3-4mm core) or if pre-processed 300ng DNA (>20ul and >10ng/ul) and 1ug total RNA (>20ul and >10ng/ul)

Blood (tube type, volume, etc.): 5ml of blood or if pre-processed 300ng DNA (>20ul and >10ng/ul). Blood can come from any time collection point

1 of each sample type is to be requested per case.

266 cases in the trial currently have these sample types available and all 266 will have these samples requested. This analysis will not exhaust any cases of material.

4) Sample Processing/Laboratory Methods

Tissue

Microdissection of FFPE primary tumor from 10 FFPE slides at 5 microns will be performed manually using an inverted microscope (Nikon Eclipse TE200) to obtain a minimum of 95% tumor cells avoiding domains with infiltrating inflammatory cells, necrotic tissue or normal cells. Dissection involves scraping tumor cells from unstained sections of 5 micron thickness on slides aligned in register with serially cut hematoxylin and eosin stained specimens including tumor domains demarcated by consensus analysis of two surgical pathologists or as provided by ECOG

Whole Exome Sequencing (WES)

DNA extraction and QC: Genomic DNA will be purified from tumors using the Qiagen QIAamp FFPE DNA protocol (Qiagen, Valencia, CA). DNA concentration and quality will be determined by fluorometry and spectrophotometry respectively (Qubit 2.0 fluorometer, Thermo Fisher, Waltham, MA; Nanodrop ND-1000 spectrophotometer, NanoDrop, Wilmington, DE) and molecular size distribution (20Kb to 150Kb) is evaluated on the Bioanalyzer 2100 (12000 DNA Chip, Agilent Technologies, Santa Clara, CA). Samples that do not meet the minimum picogreen quantified input requirements (≥300ng DNA, preferred concentration 10ng/ul, or a minimum Kapa quality score of > 0.3) will be held for further evaluation.

Library construction: Library construction will be performed at the Broad Institute according to established protocols with the ligation-based KAPA HyperPrep Library Preparation Kit followed by hybrid capture with the Rapid Capture Exome enrichment kit (Illumina) with 38Mb target territory. All samples will be validated against the Fluidigm Fingerprint Check to confirm sample identity and fidelity. One positive control, NA12878 is included in each library preparation.

Sequence generation: All libraries will be sequenced to 85% of targets covered at greater than 50x coverage (+/- 5%) (~150X MTC) for tumor samples, and 80% of targets covered at greater than 20x coverage (+/- 5%) for matched-normal samples utilizing the Laboratory Picard bioinformatics pipeline. All sequencing will be performed on the Illumina HiSeq instruments with 76 base pair, paired-end sequencing. The Picard pipeline will aggregate all data from a particular sample into a single BAM file which will include all reads, all bases from all reads, and original/vendor-assigned quality scores.

Somatic variant calls and copy number variants (CNV): GATK best practices core variant calling workflow including pre-processing and Variant Discovery will be used. Pre-processing includes mapping (BWA mem) and duplicate marking for individual sequencing output. Local indel realignment is subsequently performed jointly on the tumor normal pair, prior base quality score recalibration (BQSR), and contrastive evaluation between the tumor and normal using Mutect and Indelocator in order to provide somatic SNV and Indel calls. These variants are further annotated and visualized using maftools.

Whole Transcriptome Sequencing (WTS)

RNA extraction and QC: Specimens with projected yield >1 µg RNA will be extracted with the Qiagen FFPE RNeasy kit (#73504, Qiagen, Inc., Venlo, Netherlands) while specimens with

projected yields less than that utilize the Zymo RNA FFPE extraction kit (#R1008, Zymo Research, Irvine, CA). Total RNA purity will be measured by the absorbance ratio (260nm/280nm) in Tris buffer (10mM TRIS-Cl, pH 7.5) using the Nanodrop 1000 spectrophotometer (ThermoFisher, Wilmington, DE) with a pure RNA A260/280 of 2.0 and low cutoff of 1.8. Samples ≥1.8 undergo further processing. The concentration of RNA (> 20 nucleotides) is determined on the Qubit fluorometer (ThermoFisher) High Sensitivity assay on RNA diluted to 50ng/µl using the Nanodrop concentration. The micro-RNA Qubit assay will then be used to quantitate RNA that is present <20 nucleotides length. Agilent Bioanalyzer 2100 (Agilent Technologies, Santa Clara, CA) will be used to determine the RNA size profile (RNA Integrity Index: RIN) and the DV200% of the eluted RNA using the RNA Nano chip assay (>50 ng) or the Pico chip for RNA samples with less than 50 ng. Samples that do not meet the minimum quantified input requirements (≥550ng RNA, preferred concentration 10ng/ul, DV200 score >0.3) will be held for further evaluation.

Library construction: Library construction will be performed at the Broad Institute according to established protocols with the True-Seq RNA Exome Kit (Illumina). All samples will be validated against the Fluidigm Fingerprint Check to confirm sample identity and fidelity.

Sequence generation: All libraries will be sequenced to 50M reads aligned in pairs (+/- 5%) at 76bp read length using the Illumina HiSeq platform as measured using the Picard bioinformatics pipeline. The Picard pipeline aggregates all data from a particular sample into a single de-multiplexed, aligned BAM file which includes all reads, all bases from all reads and original/vendor assigned quality scores.

Read counts: Quality checked and adapter trimmed fastq reads will be mapped to the reference genome using HISAT2 aligner and gene level quantitation performed using HT-Seq counts. Count data are used to perform differential gene expression between two conditions using edgeR, a bioconductor R package.

Informatics for Objective 1.

The predictive model will be developed as follows based on the sequencing from 200 samples (100 samples from UPMC and 100 samples from Arms A+B+C of ECOG 3311). For RNA-seq data, the gene level, transcript level, and exon level expression profiles will be extracted and submitted to unsupervised PCA analysis, to observe the PCA clusters that can facilitate stratification. In addition, we will use TopHat2 and MapSplice2, together with the fusion zoom pipeline we developed, to detect splice junctions and gene fusions from RNAseq data, and use MuTect2 and GATK4 to detect somatic mutations, such as SNVs and indels, and CNVs from WXS data, which can be used as additional levels of genomic features for stratification. The individual discriminative features for arm stratification will be selected and Autoencoder will be applied to transform these discriminative features into synthetic features for dimensionality reduction. We will then classify tumor samples based on these synthetic features using Neural Network, Ridge, Lasso, and Elastic Net, selecting the method with the best cross-validated predictive performance. In addition to these machine learning methods, we will also apply a Universal Genomic Signature Analysis (uniGenSig), developed in our laboratory, to explore the universal genomic correlates that can be deployed for stratification. This method does not require dimensionality reduction, but instead extracts the universal genomic correlates via feature selection and then eliminates their redundancy by assessing their co-occurrence in large cohorts of human tumors. Together, these comprehensive genomic analyses will characterize the individual, synthetic, and universal genomic correlates for stratification.

Informatics for Secondary Objectives in 1.

1. Generate genomic and transcriptomic profile of all tumors from ECOG 3311. From DNA, SNVs, indels and CNVs for each sample will be annotated and collated. From RNA, as well as gene expression and gene fusions will be generated. Profiles will be compared against existing HPV+ samples from TCGA. This data will be available to the scientific community as a reference for investigation.
2. Test if TRAF3/CYLD mutation presence predicts arm stratification: Somatic alterations, including CNVs in TRAF3 and CYLD will be annotated for each tumor and grouped by arm to examine differences between arm D and others.
3. Neoantigen prediction requires three components: somatic variant calls, expression levels of mutant genes and HLA genotyping. Somatic variant calls and gene expression will be generated as part of the primary objective, HLA genotyping will be performed using the BWAkit and Polysolver algorithms from the WES data. Neoantigen prediction will then be performed according to the methods described by Rooney[12]. Number of neoantigens will then be pooled and averaged across study arms and compared between arms.
4. Test if APOBEC mutational burden predicts arm stratification: APOBEC mutational burden will be calculated for each sample using established functions[13], pooled and averaged by study arm, and compared between arms.
5. Test if an inflamed expression profile predicts arm stratification: Keck and Seiwert have defined an inflamed expression profile for a subset of HPV+ HNSCCs[14]. We will apply this inflamed vs classical expression profile to all samples and test if expression subtype predicts arm stratification according.
6. Test if CYT score and T-cell infiltrate predicts with arm stratification. Rooney et defined an immune cytolytic activity score (CYT) based on transcript levels of granzyme A and perforin[12]. Using RNA-Seq data will we calculate CYT scores for each sample and correlate this with arm stratification. Senbabaoglu et al defined methods for establishing T-cell infiltration scores using RNA-Seq data via ssGSEA[15]. Mandal et al later applied these methods to HNSCC[16]. We will calculate T-cell infiltration scores using ssGSEA methodology as defined by Senbabaoglu for each sample. Scores will then be correlated with arm stratification.
7. Clinical outcome and progression-free survival will also be modeled in a fashion similar to that of the primary informatics objective, but this is considered exploratory and will not be submitted to validation.

Nucleic acid extraction will be performed at the UPMC Hillman Genomics Core. Over the last 2 years, this group has extracted DNA and RNA from >200 FFPE samples that have gone on to NGS with success, including the 40 FFPE patient samples from patients at University of Pittsburgh. Robert Ferris will oversee this process.

QC, library preparation and sequencing will be performed at the Broad Institute of MIT and Harvard in collaboration with Daniel Faden (MEEI/MGH/HMS). Robert Ferris will oversee this process. Broad Genomics has a 25-year track record of leading the field of genomics (Human Genome Project, 1000 Genomes Project, The Cancer Genome Atlas, etc.) and is the largest producer of human genomic information in the world, producing genomic data at a rate of one 30X human whole genome every 12 minutes. The group has processed more than 1.5 million samples from more than 1400 groups in over 50 countries. Their success is well published.

5) Statistical Considerations

Shu Li, PhD and Xiaosong Wang, MD, PhD will be responsible for the Bioinformatics analysis, while Daniel Normolle, PhD will be responsible for statistical analysis of the predictive model during the training stage (Objective 1). The ECOG Statistical Center will be responsible for the independent validation in Objective 2.

Endpoints (outcomes): The primary objective of this project is to develop and then independently validate a predictive model to distinguish between HPV-mediated HNSCC patients who may receive de-intensified treatment versus patients who should undergo more intensive treatment, including trans-oral robotic surgery. All participants in ECOG 3311 underwent such surgery, and then were classified into three strata; patients from the intermediate-risk strata were then randomized to two levels on de-intensification. These populations are represented by Arm D of ECOG 3311, versus Arms A-C. While the development of the model will be primarily the responsibility of the bioinformatics component at the University of Pittsburgh, the statistical validation of the model, including the estimation of the area under the receiver operating curve (AUC) using an independent validation set, will be responsibility of the ECOG Statistical Center.

Case selection: For training, 100 cases from ECOG 3311 Arms A+B+C are requested; the University of Pittsburgh will supply 100 cases similar to those from ECOG 3311 Arm D. For validation, 70 cases from ECOG 3311 Arms A+B+C and 70 cases from Arm D are requested. We will request up to 90 cases of each category to obtain at least 70 with sufficient material for DNA/RNA extraction and sequencing.

Statistical analysis plan for addressing the primary objectives: Please see **Section 9.f.d**, Informatics for Objective 1, for the plan for the development of the predictive model. The statistical analysis plan applies to Objective 2, independent validation of the predictive model, which is to be carried out by the ECOG Statistical Center. The 140 ECOG 3311 samples with sufficient material for sequencing will be assayed for somatic alterations and gene expression profiles in a similar fashion to the training set, and then submitted to the ECOG Statistical Center so that they can perform an independent validation of the trained model. They will generate an ROC curve and calculate the area under that curve with a 90% confidence interval to test the null hypothesis that AUC<0.60.

Statistical justification for sample size

Sample size estimate: Objective 1: 100 samples from Arms A+B+C; the University of Pittsburgh will provide 100 samples similar to those of Arm D. Objective 2: 140 samples; 70 from Arm D and 70 from Arms A+B+C.

Rationale for the sample size estimate: Objective 1: Systematic determination of required sample sizes for training of predictive models has proven intractable, but, based on our previous experience and the preliminary work described in **Section 8.e**, 200 samples should be adequate for an effective classifier. Objective 2: The method presented in Pepe [17] (pp. 224-227) for determining the sample size for a test on AUC using binormal ROC curves was used, based on a one-sided null hypothesis test AUC<0.6 at α=0.05 and 80% power. We used the binormal parameters a0=0.36 and b0=1 for the reference AUC (0.6) and a1=0.81 and b1=1 for the expected AUC (0.72). It was determined that we will achieve the stated power if the true AUC≥0.75 on independent samples, which we believe is achievable based on our preliminary analysis, where we observed AUC>0.9 on the training set.

6) References

1. Hayat MJ, Howlader N, Reichman ME, Edwards BK: **Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program**. *The oncologist* 2007, **12**(1):20-37.
2. Ragin CC, Taioli E: **Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis**. *International journal of cancer Journal international du cancer* 2007, **121**(8):1813-1820.
3. Forastiere A, Koch W, Trotti A, Sidransky D: **Head and neck cancer**. *The New England journal of medicine* 2001, **345**(26):1890-1900.
4. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W *et al*: **Human papillomavirus and rising oropharyngeal cancer incidence in the United States**. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011, **29**(32):4294-4301.
5. O'Sullivan B, Huang SH, Su J, Garden AS, Sturgis EM, Dahlstrom K, Lee N, Riaz N, Pei X, Koyfman SA *et al*: **Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study**. *The lancet oncology* 2016, **17**(4):440-451.
6. Ling DC, Chapman BV, Kim J, Choby GW, Kabolizadeh P, Clump DA, Ferris RL, Kim S, Beriwal S, Heron DE *et al*: **Oncologic outcomes and patient-reported quality of life in patients with oropharyngeal squamous cell carcinoma treated with definitive transoral robotic surgery versus definitive chemoradiation**. *Oral oncology* 2016, **61**:41-46.
7. Sharma A, Patel S, Baik FM, Mathison G, Pierce BH, Khariwala SS, Yueh B, Schwartz SM, Mendez E: **Survival and Gastrostomy Prevalence in Patients With Oropharyngeal Cancer Treated With Transoral Robotic Surgery vs Chemoradiotherapy**. *JAMA otolaryngology-- head & neck surgery* 2016, **142**(7):691-697.
8. Albergotti WG, Jordan J, Anthony K, Abberbock S, Wasserman-Wincko T, Kim S, Ferris RL, Duvvuri U: **A prospective evaluation of short-term dysphagia after transoral robotic surgery for squamous cell carcinoma of the oropharynx**. *Cancer* 2017, **123**(16):3132-3140.
9. Sethia R, Yumusakhuylu AC, Ozbay I, Diavolitsis V, Brown NV, Zhao S, Wei L, Old M, Agrawal A, Teknos TN *et al*: **Quality of life outcomes of transoral robotic surgery with or without adjuvant therapy for oropharyngeal cancer**. *The Laryngoscope* 2018, **128**(2):403-411.
10. TCGA: **Comprehensive genomic characterization of head and neck squamous cell carcinomas**. *Nature* 2015, **517**(7536):576-582.
11. Hajek M, Sewell A, Kaech S, Burtness B, Yarbrough WG, Issaeva N: **TRAF3/CYLD mutations identify a distinct subset of human papillomavirus-associated head and neck squamous cell carcinoma**. *Cancer* 2017, **123**(10):1778-1790.
12. Rooney MS, Shukla SA, Wu CJ, Getz G, Hacohen N: **Molecular and genetic properties of tumors associated with local immune cytolytic activity**. *Cell* 2015, **160**(1-2):48-61.
13. Faden DL, Thomas S, Cantalupo PG, Agrawal N, Myers J, DeRisi J: **Multi-modality analysis supports APOBEC as a major source of mutations in head and neck squamous cell carcinoma**. *Oral oncology* 2017, **74**:8-14.
14. Keck MK, Zuo Z, Khattri A, Stricker TP, Brown CD, Imanguli M, Rieke D, Endhardt K, Fang P, Bragelmann J *et al*: **Integrative analysis of head and neck cancer identifies two biologically distinct HPV and three non-HPV subtypes**. *Clinical cancer research*

: an official journal of the American Association for Cancer Research 2015, **21**(4):870-881.

15. Senbabaoglu Y, Gejman RS, Winer AG, Liu M, Van Allen EM, de Velasco G, Miao D, Ostrovnaya I, Drill E, Luna A *et al*: **Tumor immune microenvironment characterization in clear cell renal cell carcinoma identifies prognostic and immunotherapeutically relevant messenger RNA signatures**. *Genome biology* 2016, **17**(1):231.
16. Mandal R, Senbabaoglu Y, Desrichard A, Havel JJ, Dalin MG, Riaz N, Lee KW, Ganly I, Hakimi AA, Chan TA *et al*: **The head and neck cancer immune landscape and its immunotherapeutic implications**. *JCI insight* 2016, **1**(17):e89829.
17. Pepe M: **The Statistical Evaluation of Medical Tests for Classification and Prediction**. Oxford: Oxford University Press; 2003.