NRG ONCOLOGY

NRG-HN002
ClinicalTrials.gov NCT #: 02254278

A RANDOMIZED PHASE II TRIAL FOR PATIENTS WITH p16 POSITIVE, NON-SMOKING ASSOCIATED, LOCOREGIONALLY ADVANCED OROPHARYNGEAL CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Cancer Research Group; and SWOG.

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Study Team continued on next page.

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Protocol Agent

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Participating Sites

☒ U.S.
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☒ Approved International Member Sites

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<table>
<tr><th colspan="3">CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (20-DEC-2017)</th></tr>
<tr><th>To submit site registration documents:</th><th>For patient enrollments:</th><th>Submit study data</th></tr>
<tr><td>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.</td><td>Please refer to the patient enrolment sections of the protocol for instructions in 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</td><td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions

Do <u>not</u> submit study data or forms to CTSU Data Operations. Do <u>not</u> copy the CTSU on data submissions.</td></tr>
<tr><td colspan="3">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' web site 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.</td></tr>
<tr><td colspan="3">For clinical questions (i.e. patient eligibility or treatment-related): Contact the Study PI of the Lead Protocol Organization.</td></tr>
</table>

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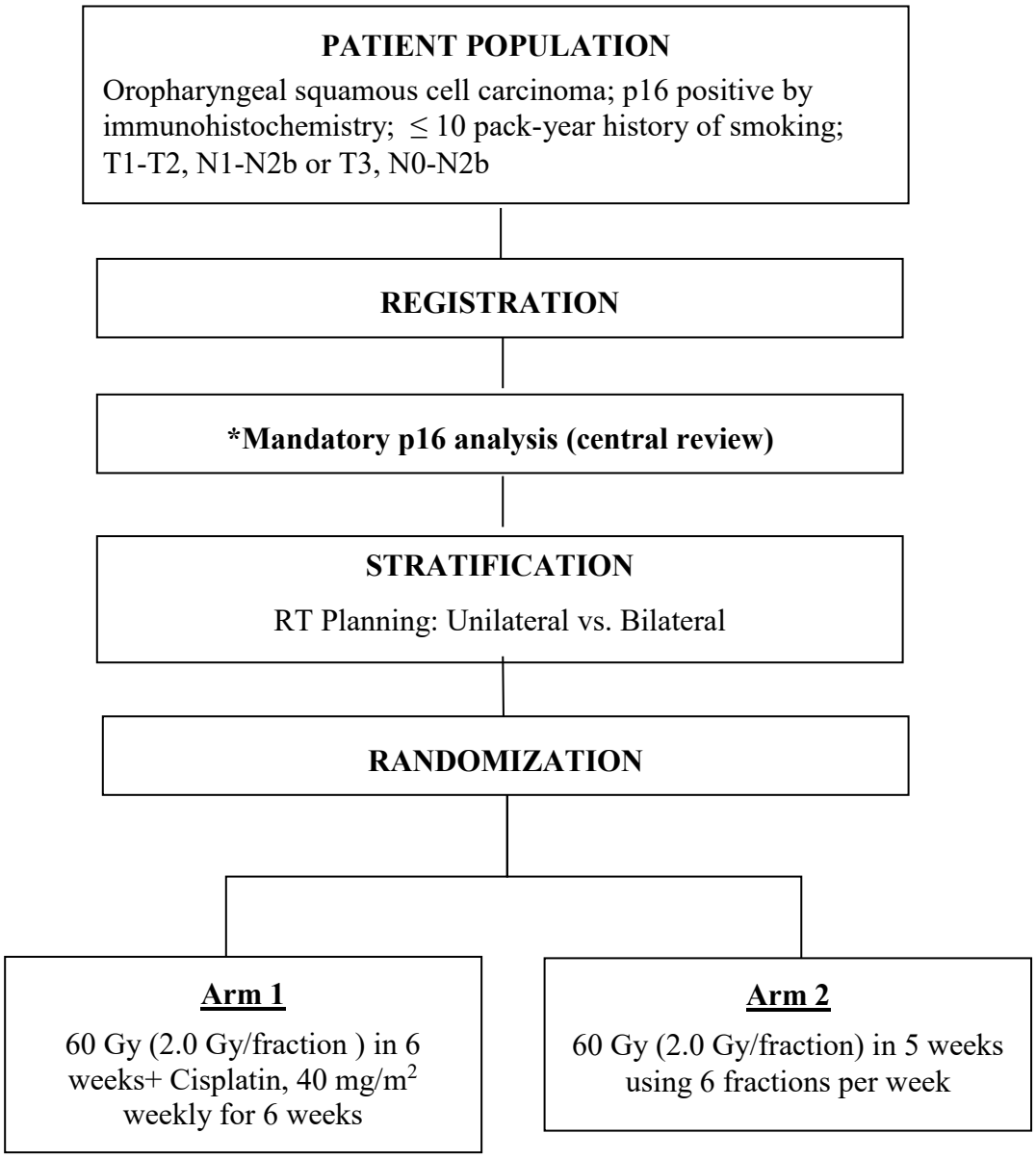
SCHEMA



*Patients must have positive immunohistochemical staining for p16, as confirmed by the NRG Oncology Biospecimen Bank, prior to randomization.

1. OBJECTIVES

1.1 Primary Objective

To select the arm(s) achieving a 2-year progression-free survival rate of ≥ 85% without unacceptable swallowing toxicity at 1 year

1.2 Secondary Objectives (5/24/16)

- To determine patterns of failure (locoregional relapse versus distant) and survival (overall and progression-free) at 6 months and 2 years;
- To determine acute toxicity profiles at the end of radiation therapy and at 1 and 6 months;
- To determine late toxicity profiles at 1 and 2 years;
- To determine patient-reported swallowing outcomes at 6 months and 1 and 2 years;
- To determine the predictive value of 12-14 week, post-treatment FDG-PET/CT for locoregional control and PFS at 2 years;
- To determine the predictive value of blood and tissue biomarkers for disease outcomes at 2 years;
- To determine swallowing recovery per videofluoroscopy imaging at 2 years.

2. BACKGROUND

The current standard of concurrent chemoradiation therapy produces excellent disease-free survival (DFS) and overall survival (OS) rates in oropharyngeal cancer. The cooperative groups, NRG Oncology and GORTEC, both have established the standard of care for stage III or IV oropharyngeal cancer to be a combination of 70 Gy of radiation therapy with concurrent platinum-based chemotherapy (Ang 2010, Bourhis 2012). However, these approaches also are associated with a high level of short- and long-term toxicities. One estimation is that the short-term toxicity burden, or T-score, stemming from definitive-intent radiation therapy can be increased by as much as 300% with the addition of the current standard of concurrent platinum-based chemotherapy (Trotti 2007). Long-term toxicities are likewise increased with intensive chemoradiation therapy (Machtay 2008). In human papilloma virus (HPV) positive oropharyngeal cancer patients, whose cancer-related outcomes often are excellent with a high probability of long-term survival, both short- and long-term toxicities are a growing concern among experienced head and neck oncologists. The philosophy of "de-escalation" or "de-intensification" has become an active topic of discussion in both academic and community head and neck treatment centers (Sturgis 2012).

Furthermore, emerging data on dramatically improved outcomes in select populations of oropharyngeal cancer patients have called into question the global applicability and necessity of these standard chemoradiation paradigms. Oncogenic strains of HPV are associated with over 70% of oropharyngeal carcinomas (Chaturvedi 2011). Patients who develop HPV-associated oropharyngeal cancer are more likely to be younger, free of competing or limiting medical comorbidities, and have a lesser history of smoking. While the ultimate impact of long-term toxicities is complex and difficult to gauge, the HPV positive population has a higher likelihood of a better outcome subsequent to therapy at a younger age, thus making the conditional relevance of late toxicities and quality-of-life outcomes a more compelling issue. Furthermore, the sensitivity of advanced-stage HPV positive oropharyngeal cancer to

both chemotherapy and radiation indicates that in some cases, the standard approach may result in over-treatment. For these reasons, the head and neck cancer community has voiced concerns about continued intensification of the chemoradiation approach, which may have value in other poor-risk head and neck cancer sites but which may constitute unnecessary additional treatment for good-prognosis HPV positive oropharyngeal cancer patients (Quon 2013).

The cyclin-dependent kinase inhibitor, p16, is overexpressed as a byproduct of HPV infection, via inactivation of the retinoblastoma protein (pRb) by HPV oncoprotein E7. In orpharyngeal cancers, p16 is an immunohistochemical biomarker that is strongly indicative of HPV-related etiology and has been associated with a positive clinical prognosis. p16 is now used as a biomarker of improved prognosis enabling selection for clinical trials and has become a stratification factor for all NRG Oncology head and neck cancer trials that include oropharyngeal cancer patients. A recent analysis of RTOG 0129 separated the prognosis for advanced-stage oropharyngeal cancer patients into distinct groups based on HPV status and smoking history. The presence of oncogenic HPV DNA and the presence of p16 in primary tumors showed a high level of agreement. The HPV positive group with a history of ≤10 pack years of smoking had significantly improved outcomes on all fronts and was labeled to be at "low risk" for death. The 3-year rates of overall survival were 93.0% (95% CI, 88.3-97.7) in the low-risk group; 70.8% (95% CI, 60.7-80.8) in the intermediate-risk group; and 46.2% (95% CI, 34.7-57.7) in the high-risk group (Ang 2010). Similarly, the Princess Margaret Hospital published a retrospective review of their clinical experience with oropharyngeal cancer and identified a similar group called "low risk"; these patients were p16 positive, had ≤10 pack-year history of smoking, and were staged ≤ T3 and ≤ N2c. For these patients, the 3-year locoregional control rate was 95% (95% Cl, 91-97) and the 3-year distant control rate was 93% (95% Cl, 89-95). Based on very small numbers of patients, there was a suggestion of a lower distant control rate among minimal smokers with N2c nodal stage who did not receive concurrent chemotherapy. Importantly, there were no significant differences seen as a function of T stage in this group (O'Sullivan 2013).

For p16 positive oropharyngeal cancer patients with ≤10 pack-year history of smoking, staged T1-2 N1-N2b M0 or T3 N0-N2b M0, NRG Oncology has recorded excellent 2-year PFS results. For this "low risk" population in RTOG 0129, the 2-year PFS is estimated at 85.3% (95%CI, 76.4-94.1) and locoregional recurrence/progression as a first event is estimated at 8.2% (95%CI, 1.3-15.1) with competing events consisting of 3.3% experiencing distant metastasis or death as the first event. In RTOG 0522, the 2-year PFS is estimated at 90.8% (95%CI, 83.7-97.8) and locoregional recurrence/progression as a first event is estimated at 4.6% (95%CI, 0-9.8), with competing events consisting of 4.6% experiencing distant metastasis or death as the first event (Zhang, personal communication, 2013). Therefore, this proposal seeks to define treatment paradigms for a newly emerging disease entity, in which high PFS rates are routinely achieved, corresponding to very low rates of locoregional failure. The emerging "low-risk" oropharyngeal cancer classification offers an opportunity to develop appropriate therapeutic paradigms for what is a recently identified and distinct subtype of HPV positive oropharyngeal cancer. It is worth noting that stage III/IV patients with stage T1N1-N3 and T2N1 disease were not eligible for RTOG 0129 or RTOG 0522, but the proposed eligibility for this trial allows all stage III/IV patients with ≤ T3 and ≤

N2b; thus, the PFS projections used in the proposed trial design are conservative, as our projections are estimated from previous trials that excluded the lowest-stage patients who will be included in this trial.

2.1 Rationale for Arm 1: Modestly Reduced Radiation Dose with Concurrent Chemotherapy (60 Gy/30 fractions/6 weeks, with weekly cisplatin at 40/mg/m^2)

In the modern era, intensity-modulated radiation therapy (IMRT) given as a single-modality treatment appears to produce high rates of locoregional control for the majority of low-volume oropharyngeal cancers. For example, RTOG 0022 was a prospective phase II feasibility trial designed to define standards for the use of IMRT in a multi-institutional setting. The trial was designed for an oropharyngeal cancer population with a low to intermediate burden of disease; specific inclusion criteria allowed T1-2 N0-N1 M0 oropharyngeal cancers (AJCC group stages I-III). The protocol specified a prescribed dose to the high-dose planning target volume of 66 Gy at 2.2 Gy/fraction in 30 fractions delivered over 6 weeks. Subclinical PTVs simultaneously received 54-60 Gy at 1.8-2.0 Gy/fraction. Sixty-nine patients were accrued from 14 participating institutions. With a median follow up of 2.8 years, the 2-year locoregional failure rate was 9% (95% Cl, 2.1-15.9), the DFS was 82% (95% Cl, 72.7-91.2), and the OS was 95.5% (95% CI, 90.6-100.0). Notably, all cases of locoregional failure, metastasis, or second primary cancer occurred among patients identifiable as current or former smokers (54% of all enrolled), and no such events were seen among reported nonsmokers (defined as < 5 packs per lifetime, with a prevalence of 34% in this study) (Eisbruch 2010).

Similarly, single-institution retrospective reviews indicate that the contemporary population of HPV-positive oropharyngeal cancer patients has retained excellent outcomes when treated with radiation therapy alone. These studies suffer from negative selection bias, in that many patients included in modern radiation-alone series were not considered appropriate candidates for the administration of concomitant chemotherapy and likely had other important competing risks for death. For example, a small retrospective series of 21 patients with HPV positive oropharyngeal cancer treated to a median dose of 70 Gy with a variety of techniques found 3-year overall survival, locoregional control, and distant metastasis-free survival rates of 82%, 88%, and 88%. Both instances of locoregional failure were associated with T4 primary oropharyngeal tumors. Among the 18 HPV-positive never-smokers, 3-year overall survival and locoregional control rates were 100% (Chen 2013). A larger series from Princess Margaret Hospital included 148 patients treated with radiation therapy alone for p16 positive oropharyngeal cancers. A variety of conventional and altered fractionation radiation schemas were used, with total doses ranging from 60 to 64 to 70 Gy over 4 to 7 weeks given in either daily or twice-daily schedules. Among all 148 HPV positive oropharyngeal cancer patients, the 3-year overall survival, cause-specific survival, local control and regional control rates were 81%, 88%, 93%, and 94%. Patients with HPV positive oropharyngeal cancer who had a ≤ 10 pack-year history of smoking (n = 37) had 3-year OS, CSS, LC, and RC rates of 86%, 92%, 95% and 97%, with distant control rates of 92%. It was noted that there were important selection biases characterizing this series: 20% of all 96 HPV+ oropharyngeal cancer patients who received RT alone in this series were elderly (over 70 years of age) and of those having an age under 70 years, 39% were

deemed medically unsuitable for concurrent chemoradiation therapy (O'Sullivan 2012).

Given the promising results obtained with a variety of single-modality radiation therapy approaches, this arm tests the proposition that in combination with a systemic radiosensitizer, the standard doses of a highly effective, conventionally fractionated radiation therapy course may be modestly reduced. Radiobiological investigations indicate that the contribution of concurrent chemotherapy across a variety of chemoradiation trials may be considered equivalent to approximately 8.0-9.0 Gy_{10} of biologic effective dose (BED) (Lee 2009). One interesting study used the biologic effective dose equivalents from RTOG 90-03 to compare the gains achieved in that trial using altered fractionation against those of 14 prospective trials utilizing chemoradiotherapy. The mean additional BED contribution from concurrent chemotherapy may be at least 8.8 Gy_{10}, or the equivalent of 3.6 fractions of 2 Gy translated back into total dose prescribed in standard fractionation (Kasibhatla 2007; Fowler 2008). Thus, if an effective concurrent radiosensitizer is given, the risks of reducing the radiation dose may be mitigated. Hence, Arm 1 in comparison to Arm 2 provides the opportunity to investigate whether systemic radiosensitization provides any advantage over a radiation-alone altered fractionation approach.

Furthermore, for these HPV positive oropharyngeal cancer patients, single institutions, small informal collaborations (2-3 centers), and one formal cooperative group trial have begun to explore "de-escalation" of radiation therapy dose in combination with a variety of concurrent systemic therapies. The earliest results have been reported by ECOG, which completed accrual to E1308, a phase II study in HPV/p16 positive, stage III-IVA oropharyngeal cancer patients examining the effect of a triple-agent induction regimen of paclitaxel, cisplatin, and cetuximab for 3 cycles followed by radiation therapy combined with weekly concurrent cetuximab. The radiation dose was prescribed at 69.3 Gy in 33 fractions after a clinical assessment of partial response or stable disease, versus a de-escalation of the dose to 54 Gy in 27 fractions for patients achieving a complete clinical response. For uninvolved nodes, the elective radiation dose was 51.3 Gy in 27 fractions. The primary endpoint was a 2-year PFS rate of $\geq$ 85%. Ninety patients were accrued, of whom 80 patients were evaluable; of these, 62 patients (78%, exceeding an expected rate of 69%) achieved complete clinical response and were treated on the reduced-dose radiation arm to 54 Gy. At a median follow up of 16.2 months, the preliminary result for 1-year PFS (n=62) in the low-dose arm was 91% (95% CI, 80-96). One-year PFS for the 15 patients treated to standard radiation dose was estimated at 87% (B. Burtness, personal communication).

The ECOG trial used induction chemotherapy, which this trial does not. In addition, the doses used in the ECOG trial do not correspond to the proposed dose for this arm of 60 Gy. However, the ECOG trial is important in that a detailed breakdown of the patient subsets in the ECOG reduced dose radiation arm lends further prospectively obtained data to support the retrospective evidence forming the basis of the eligibility criteria proposed for this trial. In E1308, for patients with T1-T3 stage, the 1-year PFS was 92% (95% CI, 80-97) whereas for T4, the result was 86% (95% CI, 33-98). In patients with N0-N2b stage, the 1-year PFS was 92% (95% CI, 78-97) whereas for N2c, it was 88%

(95% CI, 61-97). For patients with ≤ 10 pack-years of smoking, the 1-year PFS was 97% (95% CI, 83-99.6) whereas for patients with more smoking history, the result was 84% (95% CI, 57-94). Recently confirmatory 2-year PFS results were issued in preliminary form, reporting 96% PFS for patients with <10 pack-year history and T1-3 N0-N2b stage who were treated on the low-dose arm (Cmelak 2014). For this reason, the early results of E1308 support the hypothesis that our trial's proposed selection criteria are likely to identify a group of patients able to achieve excellent PFS with reduced-intensity treatment approaches.

Several small prospective trials are now accruing using various combinations of reductions in radiation therapy dose, substitutions of systemic therapy for radiation therapy, and/or novel combinations of systemic and radiation therapy in an attempt to maintain high locoregional control rates with reduced toxicity (Trotti and Yom, unpublished data summary, 2013; see table below). It should be noted that many of these trials were designed prior to the release of preliminary data at ASCO 2012 from 2 important clinical trials. These 2 trials, DeCIDE and PARADIGM, were phase III trials testing the benefit of adding induction chemotherapy to a standard chemoradiation platform; neither demonstrated any additional benefits in either locoregional control or OS (Cohen 2012; Haddad 2012).

In the PARADIGM trial, patients with stage III/IV squamous cell carcinomas of the oral cavity, oropharynx, larynx, or hypopharynx were eligible, but 55% of those enrolled had oropharyngeal cancer. By the time of the early closure of the PARADIGM trial due to slow accrual, 145 patients had been randomized to either induction docetaxel/cisplatin/5FU chemotherapy followed by radiation concurrent with either carboplatin or docetaxel, versus upfront cisplatin-radiation. All patients had radiation given to 70 Gy in 2 Gy fractions. At a median follow up of 49 months, the 3-year overall survival was 73% in the arm consisting of induction chemotherapy followed by chemoradiotherapy, versus 78% in the chemoradiotherapy group. No advantage was seen with the use of induction chemotherapy for patients with oropharyngeal cancer or in the subgroups with advanced nodal stages of N2b/N2c or N3 (Haddad 2013).

No further large-scale, head-to-head trials of induction chemotherapy followed by concurrent chemoradiation versus concurrent chemoradiation are known to have been planned at this time. As both the DeCIDE and PARADIGM trials included a large majority of oropharyngeal cancer patients, further exploration of induction chemotherapy for this disease site has been deferred until the emergence of clearer indications for its application or until the mature results of E1308 are available.

Current Phase II Protocols for HPV Positive Oropharyngeal Cancer Patients

Institution Name	Systemic Agent	Dose to Gross Disease	Target Accrual	Activation Date	Planned Closure	Primary Endpoint
Univ. North Carolina, Chapel Hill	Concurrent cisplatin 30 mg/m^2 weekly	60 Gy	40	November 2011	January 2016	Pathologic response at 3 months
John Hopkins Univ.	Concurrent Cisplatin 40 mg/m^2 weekly	63 Gy to pharyngeal constrictors, larynx, parotids, mandible, and masticatory muscles +8 mm expansion, 70 Gy to remainder of PTV	60	January 2010	February 2015	Local-regional control ≥ 80%, late toxicity at 2 years
Long Island Jewish Hosp.	Induction TPF x 3, then +/- concurrent chemotherapy	Responders: 70 Gy; non-responders: 70 Gy (with concurrent chemotherapy)	50	August 2010	January 2013; no results reported	Response at 3 months
Dana Farber Cancer Institute	Induction TPF x 3, then concurrent chemotherapy	Responders receive "reduced dose"	50	September 2010	September 2015	Local-regional control at 2 and 5 years
ECOG 1308	Induction TP-cetuximab x 3, then concurrent chemotherapy	Responders: 54 Gy; non-responders: 70 Gy	90	March 2010	Closed August 2011; early results reported	PFS at 2 years in 54 Gy group
Memorial Sloan Kettering	"standard chemotherapy " (concurrent regimens)	70 Gy to primary, 60 Gy to nodes followed by neck dissection	100 HPV+, 50 HPV-	June 2004	June 2013; no final results reported	Feasibility of ^{18}F-MISO PET to detect hypoxia, 3-month neck control ≥ 80%
Univ. of California, Davis	Induction carboplatin-paclitaxel x 2, then concurrent paclitaxel	Complete response: 54 Gy; non-responders: 60 Gy	50	October 2012	October 2014	PFS at 2 years

In support of reduced total radiation doses for HPV-associated malignancy, additional consideration can be given to the experience of locally advanced cervical and anal squamous cell carcinomas, both entities etiologically related to oncogenic HPV strains

in a manner similar to "low risk" HPV positive oropharyngeal squamous cell carcinoma. Anal and cervical squamous cell carcinomas share a standard treatment of radiation or chemoradiation, frequently cisplatin-based. Typical goals of protocol-based radiotherapy treatments for these cancer types are to achieve a radiation dose equivalent to gross disease of approximately 54-60 Gy in conventional fractionation, in combination with systemic radiosensitizing chemotherapy (Ajani 2008). For cervical cancer, weekly cisplatin chemotherapy at 40 mg/m2 is established as a highly effective concurrent platform that shows activity in concert with radiation therapy (Lanciano 2005, Kim 2008) and weekly cisplatin, due to its lesser toxicities, has for the most part replaced 5-FU-based regimens. While dosing to cervical cancers may incorporate brachytherapy implant to achieve the aforementioned dose goals, anal cancers are exclusively treated with external beam radiation therapy. For the earliest stages of anal cancer, a minimum dose of 45 Gy is given, but doses of 50.4-55.8 Gy are commonly recommended for bulky disease. Even for the most advanced cases of anal cancer, doses of 55.8-59.4 Gy are generally prescribed (Poggi 2010). Therefore, there is precedent among other HPV associated cancers to be treated to lower radiotherapy doses than typically used in the head and neck cancer community.

Reduced-total dose radiation therapy is expected to diminish both acute and long-term toxicity and if similar survival outcomes are preserved, these efforts will rapidly redefine the landscape of oropharyngeal cancer clinical investigations. Therefore, in order to remain at the forefront of clinical research initiatives in HPV-associated oropharyngeal cancer, the study investigators propose that these principles of "de-escalation" be incorporated into clinical investigations.

2.2 Rationale for Arm 1 Radiosensitizer Regimen: Weekly Cisplatin at 40 mg/m^2

Cisplatin is an established, effective radiosensitizing agent in head and neck cancer therapy. Cisplatin has been established as the concurrent systemic treatment of choice in multiple head and neck cancer protocols (Adelstein 2008). It also is the preferred systemic agent of choice in the NCCN guidelines. However, bolus cisplatin doses at 100 mg/m^2 have been of a subject of concern due to the known toxicities, particularly in terms of emetogenesis, renal impairment, blood counts, and ototoxicity. NRG Oncology head and neck cancer trials have traditionally employed 2-3 cycles of bolus cisplatin given every 21 days. For example, RTOG 0129 used cisplatin given for 3 cycles at 100 mg/m^2, whereas RTOG 0522 used a similar regimen but reduced the number of cisplatin cycles to 2. RTOG 1016 uses 2 bolus cycles of cisplatin.

Weekly cisplatin has been investigated as an alternative to cisplatin cycles given at 100 mg/m^2 with a lower overall toxicity profile. For nasopharyngeal cancer, where the burden of toxicity from systemic chemotherapy administration is particularly high, weekly cisplatin at 40 mg/m^2 is well-established in practice as a concurrent radiosensitizing drug and has demonstrated a survival advantage over radiotherapy alone, while producing lower toxicities than the standard schedule (Chan 2002; Chen 2008; Qi 2011). In head and neck cancer more generally, a French randomized trial showed that patients treated with radiation plus weekly cisplatin at a fixed weekly dose of 50 mg (roughly equivalent to 30 mg/m^2/week) had superior outcomes compared to those receiving radiation alone (Bachaud 1996). Another positive randomized trial combined cisplatin, 6 mg/m^2/day

(equivalent to 30 mg/m^2 per week) with radiation versus radiation alone (Jeremic 2004). However, an older ECOG trial (Quon 2011) used 20 mg/m^2/week of cisplatin; the reduced efficacy seen in this study may be attributable to the lower cumulative dose achieved.

A review of combined modality trials indicated that cisplatin schedules delivering a cumulative dose of about 200 mg/m^2 concomitantly during radiation were associated with positive outcomes (Ang 2004); this principle may explain the radiosensitizing efficacy seen with cisplatin doses fractionated in a multitude of ways (daily dosing, weekly dosing, fractionated over a couple of days to a week for each cycle). Based on these various lines of evidence, weekly cisplatin at a dose of 40 mg/m^2 per week is used as a concurrent regimen in NRG Oncology trial designs going forward in nasopharyngeal cancer (NRG-HN001) and high-risk postoperative head and neck cancer (RTOG 1216). For the purposes of this trial, we are therefore choosing weekly cisplatin administration at 40 mg/m^2, in order to maintain excellent cancer control and further reduce toxicity in this arm of the phase II trial and to be consistent with the emerging generation of NRG Oncology trials using weekly cisplatin.

2.3 Rationale for Arm 2: Modestly Accelerated Reduced Dose Radiation Therapy (60 Gy/30 fractions/5 weeks)

In major head and neck cancer trials over the past decade, modestly accelerated radiation therapy has been shown to be tolerable, even in the context of concurrent systemic therapy delivery. For example, RTOG 0129 tested a randomization to either a standard versus concomitant boost radiation therapy regimen in combination with cisplatin for 3 versus 2 cycles, respectively; while no advantage was seen from the radiotherapy acceleration, a reduction in systemic radiosensitizer was shown to be possible with accelerated fractionation (Ang 2010). As a result, subsequent head and neck cancer trials, RTOG 0522 and RTOG 1016, have utilized a standard arm consisting of a modestly accelerated regimen of 70 Gy over 6 weeks delivered with 2 cycles of cisplatin. In both of these trials, patients were treated with 6 fractions of radiation therapy per week, utilizing a minimum 6-hour interfraction interval to assure normal tissue repair between fractions. Thus, a modest acceleration of the radiation regimen has been accepted as a feature of treatment for patients enrolled on NRG Oncology trials over the past decade.

Radiation alone is already considered a standard treatment option for all patients with low and low-intermediate stages of oropharyngeal cancer. For T1-2, N0 oropharyngeal cancers, the NCCN guidelines support a treatment plan of radiation therapy alone to doses of 66-74 Gy, given in mildly accelerated or conventional fractionation at the standard evidence level of 2A. The addition of systemic radiosensitizer is only considered for T2N1M0 cancers and set at a lower evidence level of 2B. One should note that these treatment recommendations were found to be effective and installed as standard treatment recommendations in an era when HPV status was not known to be a critical prognostic factor and thus, these are considered to be standard recommendations independent of a patient's HPV status.

The University of Texas – M.D. Anderson Cancer Center has frequently utilized 66 Gy in

30 fractions over 6 weeks as a standard treatment for "small primary" (T1-T2) oropharyngeal cancers; patients who receive concurrent chemoradiation are typically prescribed approximately 70 Gy. Recently, information was shared from the MD Anderson institutional database with the study investigators. For 214 patients with stage T1-T2 oropharyngeal cancer with any degree of nodal involvement (i.e. AJCC stage III-IVB) who had ≤ 10 pack-year history of smoking and who were treated with radiation therapy alone, the 2-year locoregional control rate was 95.3% and the OS rate was 90.2%. For 109 patients with these same characteristics treated with radiation therapy and some form of concurrent systemic therapy (with or without induction chemotherapy), the 2-year locoregional control and OS rates were 92.7% and 91.8% (Garden, personal communication, 2012). While there were undoubtedly strong selection biases in assigning patients to radiation therapy alone versus concurrent chemoradiotherapy, these results lend additional support to the hypothesis that the use of systemic radiosensitizer may not be necessary to achieve excellent results in low-risk HPV positive oropharyngeal cancer patients.

For this trial, there is interest in pursuing radiation therapy alone as a viable treatment option to offer to selected "low risk" oropharyngeal cancer patients. Thus, the proposed arm is designed to explore a further modest de-escalation using radiation therapy alone, without the addition of a systemic radiosensitizer. This fractionation schema would be given in a manner similar to those delivered in previous NRG Oncology trials, in which 6 fractions would be delivered each week in order to produce a modest acceleration of the treatment course. These recent head and neck cancer trials have successfully delivered 70 Gy in this modestly accelerated manner at 6 fractions per week, in conjunction with systemic cisplatin chemotherapy; and in one arm of RTOG 0522, this modest acceleration was accompanied by not only concurrent cisplatin but concurrent cetuximab administration. Therefore, it is expected that modestly accelerated radiation therapy alone given in this way to a total dose of 60 Gy should be very well tolerated.

Substantial total dose reduction has been previously implemented in Europe using altered fractionation schemas without apparent losses in locoregional control. For example, from 1966-1975, one prospectively randomized study including 734 patients with laryngeal and hypopharyngeal cancers demonstrated that a total dose reduction of 18-22% could be achieved using combinations of shortened treatment time and hypofractionation with no differences in laryngectomy-free survival or OS at 10-year follow up (Wiernik 1990). In the early 1990s, the Medical Research Council ran a multicenter trial involving 11 centers and 918 patients in which patients with head and neck cancer from stages II-IVB were randomized to either 66 Gy in 33 fractions given over 6.5 weeks or a regimen of 54 Gy in 36 fractions given at 1.5 Gy/fraction 3 times daily over 12 consecutive days (CHART). At a follow-up time of over 6 years, no differences were seen between the 2 arms in locoregional control, disease-free interval, freedom from metastasis, or survival, and 10-year follow up likewise showed no difference in survival endpoints (Dische 1997; Saunders 2010). Thus, the principle of using accelerated schedule to decrease the total radiation dose has been clinically validated as effective.

However, late toxicities have been a concern in such aggressively shortened treatment courses, and most investigators favor a more moderate approach to treatment acceleration. Most recently, NRG Oncology has adopted an acceleration schema modeled after that undertaken in the Danish Head and Neck Cancer Study Group (DAHANCA) using 6 fractions of standard radiation given per week. In the DAHANCA 6&7 randomized trial, 1476 patients with stage I-IV squamous cell carcinomas of the oral cavity, pharynx, or larynx receiving the hypoxic radiosensitizer nimorazole were assigned to either 5 or 6 fractions per week, to a total radiotherapy dose of 66-68 Gy in 33-34 fractions (except for T1 larynx cancer which was assigned to a lower dose). This trial showed improved 5-year locoregional control and DFS, with only transient acute morbidity related to the acceleration (Overgaard 2003). No significant differences were seen in late endpoints at a median follow-up time of over 4 years (Mortensen 2012). A report on this trial analyzing the effect of p16 expression found improvements in locoregional control, disease-specific survival, and OS associated with p16 positivity, as well improvements in locoregional control and disease-specific survival from accelerated radiation therapy among both p16 positive and p16 negative tumor groups. Among p16 positive patients, the hazard ratios for the 6 fractions per week regimen as compared to the standard were 0.73 [0.59-0.92] and 0.43 [0.22-0.82]) for 5-year disease-specific survival and OS, respectively (Lassen 2011). The conclusion of the authors was that the use of a moderately accelerated radiotherapy regimen in this context specifically was advantageous for HPV/p16 positive head and neck squamous carcinoma.

Clinically-based precedent exists for reduced-total dose radiation at 60 Gy delivered over a period of 5 weeks. In the Princess Margaret Hospital's series of 449 oropharyngeal cancer patients treated with radiation therapy alone using a variety of schedules ranging from 60-70 Gy over 4-7 weeks, the most commonly used schedule was 60 Gy in 25 fractions given at 2.4 Gy per fraction over 5 weeks. Of note, among 148 p16 positive oropharyngeal cancer patients in this series, 41% had T3-T4 tumors and 87% had stage grouping of III-IVB. Patients with p16 positive oropharyngeal cancer who had a $\leq$ 10 pack-year history of smoking (n = 37) had 3-year overall survival, cause-specific survival, local control, and regional control rates of 86%, 92%, 95% and 97%, with distant control rates of 92% (O'Sullivan 2012). Despite these excellent overall results, there were negative predictive factors identified among the p16 positive patients; T4 stage was an adverse predictor for cause-specific survival, and 13/24 patients with p16 positive N3 disease died. These findings, similar to those consistently seen in other retrospective and prospective series, further confirm the decision to exclude these patients with a very high burden of disease from de-intensified approaches.

On this basis, for patients where excellent outcomes are most likely using reduced-dose approaches, the study investigators have chosen a schedule of 6 fractions per week based on its efficacy at producing improvements in tumor control, specifically in p16 positive patients (based on evidence from the DAHANCA experience), without intensifying the late effects of treatment. It is hypothesized that shortening of the total treatment time to 5 weeks, similar to the treatment package time used in the Canadian experience, will

compensate for a modest reduction of the total dose.

In summary, modestly accelerated radiation therapy using an IMRT technique has been shown to be feasible, safe, and able to be properly delivered within single institutions and the national clinical trial setting as an effective single modality treatment for "low-risk" oropharyngeal cancer. In this highly selected, good-prognosis population, DFS and OS results with modestly accelerated IMRT alone appear to be comparable to those achieved with chemoradiation therapy. Thus, Arm 2 offers a validated, de-escalated treatment for selected "low-risk" oropharyngeal cancer patients.

As assistance in assessing the proposed efficacy of these regimens, we have provided a table of relative biologic effective dose (BED) differences between common standard schemas and this trial's proposed arms, which are spread over a fairly small range of values (John Murnane, personal communication, 2013).

Relative BED for Standard and Proposed Radiation Schedules

Fractionation	Acute BED	Late BED
70 Gy in 35 fx in 7 weeks + cisplatin	84.0 Gy_{10} + additional cisplatin effects	116.7 Gy_3 + additional cisplatin effects
66 Gy in 30 fx in 6 weeks (RTOG 0022)	80.5 Gy_{10}	114.4 Gy_3
60 Gy in 25 fx in 5 weeks (Princess Margaret accelerated schedule)	74.4 Gy_{10}	108 Gy_3
ARM 1: 60 Gy in 30 fx in 6 weeks + cisplatin	72 Gy_{10} + additional cisplatin effects	100 Gy_3 + additional cisplatin effects
ARM 2: 60 Gy in 30 fx in 5 weeks	75.2 Gy_{10}	100 Gy_3

*The tumoricidal acute effect of Arm 2 is expected to be similar to that of the Canadian experience but with less late effect BED as compared to hypofractionated regimens.

2.4 Measuring Patient-Reported Outcomes (PROs) and Quality of Life (QOL) (20-DEC-2017)

The purpose of collecting PRO/QOL data in this phase II study is to evaluate the potential reduction in the burden of toxicity from the patient's perspective as compared between 2 different methods of treatment de-intensification, either using reduced-dose radiation with weekly cisplatin, or modestly accelerated, reduced-dose radiation alone. These findings will inform the selection of the least toxic arm from the patient's perspective with respect to achieving a better swallowing related QOL outcome, while maintaining at least 85% PFS. The hypothesis is that among the 2 approaches in this trial, swallowing-related QOL will be superior in the radiation-alone arm compared to the chemoradiation

arm at 1 year. The specific aim is to determine patient reported long-term swallowing outcomes (≥ 6 months to 2 years) in p16 positive oropharyngeal carcinoma patients treated with a reduced total dose radiation therapy approach +/- concurrent chemotherapy.

Participation in the PRO component of the MD Anderson Dysphagia Inventory-Head and Neck (MDADI-HN) instrument is mandatory in this study. To complete the MDADI, the patient must comprehend verbal English or one of the validated written translated versions of the MDADI. All protocol-eligible patients will be asked to participate in the additional, optional PRO component of this study which is comprised by the University of Washington QOL questionnaire. In order to participate in this PRO assessment, patients must be able to comprehend verbal English.

The selection of the primary PRO instrument (MDADI) has been limited to maintain a primary focus on the evaluation of late dysphagia (defined as ≥ 6 months to 2 years). Sample size will adjust for patients at Canadian centers who are unable to complete the MDADI in English (estimated at 12% based on prior enrollment to NRG Oncology head and neck cancer trials). Patients who are blind or illiterate may have questions and responses read verbatim by the investigator or research associate; non-validated translation of instruments is not allowed. To assess swallowing function, the MDADI (see Section 11.2 for details of this assessment) will be administered in each arm prior to the start of treatment (baseline), at completion of radiation therapy, and then at 6, 12 and 24 months from the end of radiation. We also will compare patient-reported swallowing outcome to objective clinical measures using CTCAE, v. 4 clinician-reported toxicity and documented gastrostomy tube retention rates at each follow-up visit. Additionally, baseline performance status and co-morbidities will be collected by chart extraction for patients in each treatment arm using the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) and the Charlson Comorbidity Index (CCI). The MDADI constitutes the primary tool being used for this assessment; the PSS-HN, CTCAE, v. 4 graded toxicities, and CCI are exploratory, secondary tools.

<u>The MDADI as Primary PRO/QOL Instrument</u>
The MDADI has been validated in head and neck cancer patients in a single institution series (Chen 2001). Reliability (internal consistency reliability) was established with the overall Cronbach α coefficient = 0.96, suggesting that each item of the MDADI addresses the same concept. Stability was tested with test and retest reliability coefficients of the subscales ranging from 0.69-0.88 (global, 0.69; emotional, 0.88; functional, 0.88 and physical, 0.86). Spearman correlation coefficients between MDADI and Short Form 36 (SF-36) demonstrated construct validity. The MDADI also was able to detect differences in groups of patients with head and neck cancer who were expected to be functioning at different levels and also by head and neck site and pathological findings (Chen 2001). MDADI scores also discriminate clinically meaningful differences in swallowing performance among aspirators and non-aspirators, gastrostomy dependent, and gastrostomy-free patients, and various levels of oral intake (Hutcheson 2015).

To be considered an acceptable arm in this trial, the MDADI results for the “superior” arm must be clinically acceptable (mean total MDADI score at 1 year ≥ 60). It is

expected that this baseline of clinical acceptability should be met by one or both arms, but the ability to meet this basic criterion has been set as a required part of the primary endpoint for this trial. Furthermore, to compare between arms, the primary QOL endpoint will measure the mean individual change in total MDADI score at 1 year from baseline in each arm. One of the arms will be deemed inferior to the other only if there is a mean change score of ≥ 5 points from baseline for that arm and there is a ≥ 5 point difference between the 2 arms that is statistically significant. The minimum important difference (MID) is defined as the smallest difference in score in the domain of interest that patients perceive as important, that would lead to consider a change in the patient's management (King 2011). The MID for the MDADI has not been previously published; however, an important methodological proposal is that the MID should be within 5 to 10% of the instrument range (Ringash 2007). Since the MDADI score ranges from 0-100, a change of 5% (5 points) in the score is considered meaningful.

Secondary analyses will evaluate the percentage of patients in each arm with poor swallowing QOL, defined as an individual patient MDADI score of ≤ 60 at 1 year. Secondary analyses also will evaluate poor swallowing QOL based on the subscale scores of the MDADI inventory, particularly the physical and functional subscales at 1 year.

Oropharyngeal dysphagia after chemoradiation or radiation alone can have a significant impact on QOL. Multiple factors are thought to contribute to the severity of oropharyngeal dysphagia, including multimodality therapy (surgery, radiation, chemotherapy), total radiation dose, and dosimetry to organs at risk (OARs), including the larynx, oral cavity, and pharyngeal constrictors (Eisbruch 2002, Eisbruch 2011, Caudell 2010), as well as intrinsic patient radiosensitivity and susceptibility to late fibrosis. These factors will be addressed in this trial by the reduction of radiation dose, with improvements in dosimetric outcomes, as well as by the removal of chemotherapy from 1 arm. Therefore, this trial has high potential to improve post-treatment dysphagia and as a result, patient-reported swallowing related QOL.

<u>Correlation of MDADI to Measures of Dysphagia</u>

Bhide, et al. (2009) assessed dose volume histogram (DVH) data for superior, middle, and inferior constrictors in 37 head and neck cancer patients undergoing IMRT and correlated these to NRG Oncology-graded dysphagia at 1 year and MDADI scores in patients undergoing induction chemotherapy followed by high-dose cisplatin chemoradiation. While this study did not find a statistically a significant correlation between pharyngeal constrictor dose and objective measurements of dysphagia and MDADI parameters, only 1 time point was measured at 1 year post-treatment, and baseline pre-treatment QOL assessments were not obtained. Lack of correlation may have been due to small patient numbers and the possible confounding effects of induction chemotherapy and high dose cisplatin. In the patients treated with a primary chemoradiation approach, Bhide, et al. reported a 1-year median MDADI total score of 74 (range, 24-100), global 4/5 or 80, PT of 27 (range, 4-40) or 67.5, ET of 23 (range, 8-30) or 76.7, and FT of 20 (range, 5-25) or 80 (latter when scored out of 100). It also was noted that there was a significant correlation between observer-rated, RTOG graded dysphagia and all the MDADI parameters. Hence, MDADI was a valid endpoint to

measure swallowing toxicity from the patient's perspective. Levendag, et al. (2007) also studied the relationship between pharyngeal constrictor dose, observer-reported dysphagia, and patient-reported swallowing QOL using the MDADI, in an oropharyngeal cancer population treated with chemoradiation using both IMRT and 3DCRT. A cross-sectional survey was taken at a mean follow up of 18 months; the QOL response rate was 88%. When these authors compared chart-reviewed dysphagia rates corresponding to NRG Oncology grade 3 and 4 dysphagia (in 23% of patients) to MDADI scores, a total MDADI score of ≤ 50 was found in 26%, and a significant correlation was found between observer-rated grade 3 and 4 dysphagia and MDADI total score.

Use of MDADI to Determine Poor Swallowing QOL Outcome

While the MDADI has been most extensively used in head and neck cancer patients treated with surgery, limited baseline and longitudinal data for the MDADI exist to define an acceptable level of swallowing QOL outcome in patients treated with either surgery or chemoradiation therapy. In a cross-sectional study of patients with stage III/IV head and neck squamous cell carcinoma (HNSCC) (Gillespie 2004), the MDADI-HN was administered to patients at least 12 months after treatment. Patients receiving primary chemoradiation for oropharyngeal primary tumors demonstrated significantly better scores on the emotional (p=0.03) and functional (p=0.02) subscales of the MDADI than patients receiving surgery and post-operative radiation. However, in this study, surgical techniques varied including more extensive surgery with some patients receiving wide excision with reconstruction involving skin graft, radial forearm free flap, or levator scapular flap. Mean subscale MDADI scores for the group receiving surgery with postoperative radiation ranged from 52.5 to 62.5, while the primary chemoradiation group was 64.5 to 86.4. In more recent surgical series, with emerging endoscopic transoral surgery approaches, improved swallowing outcomes have been observed. Data from prospective single institutional series (Sinclair 2011) suggest that patients undergoing transoral robotic surgery (TORS) for T1 and T2 oropharyngeal squamous cell carcinomas have an initial decrease in mean scores on the MDADI-HN in the immediate postoperative period when compared to baseline pre-operative scores, although increasing improvement was observed over time. Additionally, global and physical subscales were most affected in the immediate post-operative period with recovery of scores observed at last follow up. Factors which predicted poorer physical MDADI outcomes included nodal status (p=0.049), less than 12 months follow up (p=0.01), and pre-operative physical scores of < 100 (p=0.01). Similar trajectories have been shown in nonsurgically treated cohorts (Roe 2014, Schwartz 2012, Hutcheson 2014).

Expected QOL Outcomes Using the MDADI

Since the Gillespie study (2004) describes a fairly wide range of mean subscale MDADI scores for patients receiving primary chemoradiation from 64.5 to 86.4 from the pre-IMRT era, it is important to prospectively collect PRO swallowing data at baseline and interval follow up in this study of modestly reduced radiation therapy dose in the modern IMRT era.

Swallowing PROs previously have not been studied in a prospective, randomized, multi-institutional setting to evaluate the benefit from the patient's perspective of treatment de-intensification using a primary radiation approach.

In the proposed study, since there will be 1 radiation-alone arm, and the other concurrent chemoradiation arm will be using weekly cisplatin, putative dosimetric and treatment-specific factors may be more closely examined with regards to dysphagia outcome using serial measurements of swallowing-related toxicity and PROs before and after treatment and with and without the potential confounding effects of high-dose chemotherapy. Based on the studies by Gillespie (2004), Chen (2001) and Bhide (2009), it is expected that with a primary radiation approach that expected scores would approximate mean total MDADI ≥ 70 and global ≥ 80, with subscales for PT ≥ 65, ET ≥ 75, FT ≥ 80 when scored out of 100.

Rationale for including a General QOL Instrument, the University of Washington QOL Questionnaire, for this Trial

Oncologists now accept the quality of survival, in addition to the length of survival as an important clinical endpoint in trial design for patients with locally advanced cancers. While clinician-reported toxicity is able to detect adverse clinical events, PROs are paramount in this regard because they directly measure the patient's perception of symptom burden from the treatment of the disease and its impact on QOL without bias from the clinician. As the treatment for HPV positive oropharyngeal carcinoma evolves, a high rate of acute and late normal tissue complications from definitive radiation-based treatment may no longer be considered acceptable, if alternatives evolve to produce similar rates of cure but improved QOL.

In a study of 177 patients with head and neck cancer, using the University of Washington QOL Questionnaire (UW-QoLv.4), data suggests that QOL and long-term swallowing outcome in the HPV positive oropharyngeal carcinoma population are significantly better compared to the HPV negative population at baseline and at 6 months to 1 year after treatment (Maxwell 2013). Moreover, since HPV positive oropharyngeal carcinoma patients are expected to have superior baseline QOL, with few co-morbidities compared to the HPV negative population, such patients may be less likely to accept additional acute or long-term toxicities, which generally have been associated with definitive head and neck radiotherapy even in the IMRT era. In this study we also will explore other exploratory QOL outcomes in this population receiving dose de-escalated radiotherapy with regards to the patient's perception of pain, their appearance, activity, recreation, chewing, speech, shoulder, taste, saliva function, mood and anxiety using the UW-QoLv.4 at the same time points, in addition to the primary QOL endpoint of swallowing. Such items are quite applicable to this group of patients, who are relatively high-performing and have concerns beyond (but also including) dysphagia. Other, more general instruments were considered in choosing UWQoLv. 4 and were judged to contain excessive overlap with the MDADI and, moreover, to cover too many items resulting in excessive burden given the exploratory nature of this instrument in the novel setting of reduced dose radiation therapy .

Adding the UW-QoLv.4 is justified, since this treatment paradigm essentially represents a new disease entity entailing a novel treatment paradigm, and there is no pre-existing data on the nature of outcomes in such patients receiving 60 Gy. The targeted patient group is a potentially more favorable group both in terms of oncologic and long term QOL outcomes, and having these additional data from the UW-QoLv.4 may aid decisions about next research steps, particularly if no significant differences in dysphagia are found in either arm. As such, both the primary and exploratory QOL data from this trial will inform which of the 2 arms may proceed to a future phase III randomized trial comparing our paradigm to other treatment de-intensification approaches such as surgery or standard dose chemoradiation.

Employment/Work Status and Return to Work after Radiotherapy

An exploratory objective will be to determine the impact of radiotherapy de-escalation on the patient's work status before and after treatment. In a study of 85 patients in head and neck cancer survivors in the Netherlands (Verdonck-de Leeuw 2010), it was found that the median time to return to work was 6 months (range 0-24 months), while 71% patients returned to work within 6 months. The hypothesis is that dose de-escalation of radiotherapy will lead to decreased acute and late toxicities resulting in earlier return to the work and improved retention in the work force compared to conventional dose radiotherapy with or without chemotherapy.

Multiple QOL factors may affect the ability of the patient to return to work including anxiety, oral dysfunction including xerostomia, trismus, sticky saliva, problems with dentition, appetite, and social eating. Descriptive statistics will be used to assess work status before and after treatment. Work status will be tested for associations with concurrent chemotherapy use, age, gender, marital status, education level, tumor factors, and health-related QOL using the UW-QoLv.4.

Work status in head and neck radiotherapy is currently being evaluated in depth in RTOG 1016 using a detailed PRO instrument. In HN002, a very limited number of questions completed by the investigator and/or research associate will be integrated into the demographic evaluation of the patient before and after radiotherapy to assess baseline employment/work status and return to work status after treatment. These questions are not completed by patients and will not add to their burden.

Optional Online Completion of QOL Assessments

Missing data are a significant problem, particularly for QOL assessments. Unlike data for traditional endpoints, such as survival, QOL data can never be obtained retrospectively if it is not provided by the patient at the appropriate time point. This limits researchers' ability to accurately perform QOL statistical analyses and negatively impacts the clinical relevance of this effort. Typically, QOL forms are filled out in hardcopy (paper). To provide a more convenient method of completing QOL assessments, NRG Oncology is working with VisionTree Software, Inc., San Diego, CA. VisionTree offers patients on this study the option of completing their QOL forms online from any location that has a computer with Internet access, including the patient's home, and provides reminders to patients to complete the assessments.

VisionTree has developed a tool, VisionTree Optimal Care (VTOC), a HIPAA-secure, user friendly, web-based software system (Gorgulho 2005; Gorgulho 2007; Pedroso 2006). The VTOC tool contains a web-based system for global patient and trial administration access, which allows improved compliance and accuracy of data collection, validation, and reporting. It is compliant with the Title 21, Code of Federal Regulations, Part 11 statistical process control system and provides a mobile solution for clinical trials. QOL data are collected with Microsoft Excel and PDF export of reports. VTOC also has mobile messaging and e-mail reminders. Surveys can be "pushed" to patients for completion at timed intervals (see http://www.visiontree.com for details). This technology allows consenting patients on this study to fill out their QOL forms online from any location and to receive e-mail reminders to complete assessments. E-mail reminders also can be sent to research associates (RAs) at the appropriate institutions to remind them that a QOL time point window is about to close so that a patient can be contacted to fill out QOL information on time, before it becomes "missing data".

In a pilot RTOG study (RTOG 0828), the compliance rate of patients completing QOL assessments at 6 months significantly improved using electronic technology. Based on this pilot data, NRG Oncology is offering VisionTree as an option in other studies, including this one. Patients preferring to complete hardcopy QOL assessments can do so.

For this trial, the baseline QOL forms must be completed in hardcopy at the time of enrollment. To complete subsequent QOL forms online, patients will be asked for an e-mail address that they consent to use so that e-mail reminders may be sent to them. The patient's e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g. Yahoo!, Hotmail, or AOL). Patients will receive a login card (either printed or sent via e-mail) with which to log in using the secure, web-based VTOC portal. VTOC meets all HIPAA guidelines and is encrypted (via 128-bit SSL) for the security, privacy, and confidentiality of QOL information. It is similar to the secure login commonly used when performing online banking. The login card can then be kept and maintained by the patient.

The patient's e-mail address only will be used by NRG Oncology for this purpose. Patients will be sent e-mail reminders to complete QOL forms. A typical e-mail reminder would read: "Your Quality of Life forms for the study, NRG-HN001, are now due. Please go to http://www.optimalcare.com, use your secure login, and complete the online forms. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. If you have any questions, please e-mail or call your research associate at [insert RA e-mail address] or [insert RA telephone number]. Thank you for participating in this study." The reminders will be created by NRG Oncology and placed into a study template that will be sent to patients at customized intervals (at the time points when QOL forms are due). The first reminder will be sent at the beginning of the "window" to complete a QOL form, with a second reminder halfway through the window period if the QOL forms are not yet completed at that time point. A maximum of 3 reminders will be sent for each of the 4 QOL time points (following the baseline QOL forms, which are

completed in hardcopy). After a patient has completed all forms in the VTOC portal, a dialogue box will appear that says "Thank you for completing your Quality of Life forms," and the patient will no longer receive any remaining notices for that time point. The site RA or study administrator will be informed through the VTOC "At-A-Glance" form management system when QOL forms have been completed.

Rationale for including Modified Barium Swallow (MBS) as a Measure of Swallow Safety and Efficiency

The purpose of the MBS component of this trial is to determine the long-term safety and efficiency profile of pharyngeal swallowing function two years after de-escalated therapy in patients with low-risk oropharyngeal squamous cell carcinoma (OPSCC). Participating sites are given the option to participate in this NCI NCI Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP) -funded component of the study; MBS studies are not required for all sites to participate in the main part of the study.

Videofluoroscopic swallowing evaluation (also known as the modified barium swallow [MBS] study) remains the gold-standard method to measure pathophysiology of swallowing dysfunction. MBS is widely utilized in clinical practice to measure safety and efficiency of pharyngeal bolus transport. MBS data are complementary to patient-reported outcome (PRO) data. Patients' perception of swallowing abilities are influenced by a host of factors including physical swallowing dysfunction after nonsurgical therapy (eg, radiation-associated dysphagia and stricture) alongside other confounding toxicities of therapy that make eating a less pleasant experience (eg, thick mucus, dysgeusia, xerostomia). As such, PROs can over or under-report the true level of physical impairment. MBS offers the specificity of detecting aspiration (perceived or silent) along with physical effects of therapy on swallowing biomechanics free of these competing toxicities that elevate an individual's perception of swallow dysfunction but do not carry the same risk of secondary pneumonia.

Much of our knowledge of aspiration and physiologic swallowing impairment comes from single-institution organ preservation trials that aggregate functional outcomes from HNSCC at multiple sites and report aspiration rates up to 40% in unselected post-radiated HNSCC cohorts, and in up to 80% of symptomatic patients (Eisbruch 2002, Eisbruch 2011, Logemann 2006, Caudell 2009, Hutcheson 2012, Hutcheson 2014). These data, based on findings from MBS studies, confirm that when swallowing physiology is disrupted after head and neck radiotherapy, patients have high rates of aspiration, much of which is undetected by patient report because of diminished sensory awareness. Silent aspiration has been reported in excess of 50% of patients who aspirate (Eisbruch 2002, Hutcheson 2012).

Data specific to patients with oropharyngeal primary tumors are limited but suggest still a high burden of dysphagia using traditionally prescribed doses around 70 Gy. Using prospective MBS (baseline through 2 years), Eisbruch and colleagues (2011) reported 31% of OPSCC patients with elevated occurrences of aspiration relative to baseline ≥1 year after treatment, and 22% 3-year risk of aspiration pneumonia in a trial of

chemotherapy and IMRT (70 Gy in 35 fractions, with weekly carboplatin AUC of 1 and paclitaxel 30 mg/m2) that was designed to protect dysphagia-organs-at-risk using dose constraints. MBS-detected aspiration significantly predicted pneumonia in this trial ($p=0.017$, Se 80%, Sp 60%), and silent aspiration was evident on MBS studies in 63% of patients who developed pneumonia. Pharyngeal residue on MBS studies also was significantly predictive of pneumonia after chemotherapy and IMRT ($p<0.01$) (Eisbruch 2011, Hunter 2013). Using split-field IMRT (70-72 Gy/35 fractions), >6-month aspiration rates of 8% and 10% were detected in oropharyngeal cancer patients enrolled in two single-arm phase II instititutional trials of induction chemotherapy and adaptive IMRT, respectively, at U.T.-MD Anderson Cancer Center, per prospective MBS analysis baseline through 2 years (Hutcheson 2014, Schwartz 2012). These results offer compelling support for the radiographic examination of swallowing outcomes to measure swallowing safety and efficiency as health-related endpoints cannot be fully detailed by PROs. Thus, we propose to evaluate swallowing using MBS studies at baseline and at 2 years after the end of radiotherapy as a secondary measure of functional outcomes in this trial. This will be the first prospective MBS-driven swallowing outcomes assessment after de-escalated radiotherapy in low-risk OPSCC. As the radiotherapy effect on swallowing would be expected to be lessened as compared to the traditional treatment at 70 Gy or more, this data will provide a clearer assessment of the impact of the addition of concurrent chemotherapy to a radiotherapy platform. The data will not only be important as a functional comparison of OPSCC patients treated with and without chemotherapy but will supply baseline values needed for future trial design

The optimal time point for MBS is contigent on the study question. Two MBS time points (baseline and at 2 years after end RT) were selected for the current trial in order to prioritize the understanding of baseline-adjusted, long-term swallowing recovery after de-escalated therapy. There is only limited data to date that delineates swallowing function beyond 1 year after radiotherapy. Single-institution HNSCC trials that have incorporated prospective MBS have examined MBS data at multiple intervals (typically baseline, 3-6-months, 12-months, and at 24-months after end of radiotherapy) to model trajectories of swallowing impairment. Trajectories suggest a nadir in MBS-detected swallowing function on early post-RT MBS (<6-month intervals) with partial recovery of function by 12-months and incremental improvement thereafter to 24 months. That is, most recovery of swallowing function will occur in the first year, and dysphagia events after that point can be taken to reflect chronic dysfunction that will likely persist lifelong. By 2 years, MBS analysis reflects the “new normal” swallow and the new baseline by which to benchmark any progressive functional deterioration in long-term survivorship. Progressive or late deterioriation of swallow function is possible (ie, late-radiation associated dysphagia or “late-RAD”), but emerging data suggest a much longer latency to de novo late-RAD well beyond 5 years (median latency: 8 years) making it unrealistic to attempt to capture these late events in the MBS arm of the current trial (Hutcheson 10/2015). Two-year MBS-detected swallow recovery outcomes must be obtained to set the foundation to evaluate late events in follow-up studies.

The proposed MBS centralized scoring method for MBS studies is the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST). With DIGEST, two MBS outcomes will be

rated: 1) penetration/aspiration (ie, “swallow safety”), and 2) pharyngeal residue (ie, “swallow efficiency”). These domains were selected as universal items reported in swallowing practice that have been shown to significantly predict pneumonia in patients with oropharyngeal cancers. Laryngeal penetration and aspiration represent impairments in airway protection or swallow safety, whereas pharyngeal residue represents impairment in bolus clearance or swallow efficiency. Factor analyses have established these as valid constructs of pharyngeal dysphagia in patients with head and neck cancer (Frowen 2008).

Ratings of aspiration and penetration are highly reliable (intraclass correlation coefficient: 0.80- 1.0) (Stoeckli 2003, Frowen 2008). Intraclass correlation coefficients for inter- and intra-rater reliability on the Penetration-Aspiration Scale were 0.96 and 0.95-0.97, respectively (Rosenbek 1996). Pharyngeal residue also is reliably measured as an ordinal rating (weighted kappa: 0.73 interrater, 0.85 intrarater) (Dyer 2008). A cut-point of 50% residue is widely used to represent a significant impairment in bolus transit (Eisenhuber 2002, Martin-Harris 2008, Ryu 2012). Furthermore, discriminant analyses of two-dimensional area measures suggested a threshold value of 55% residue correlates with qualitative ratings of moderate/severe residue by expert clinicians (Dyer 2008). Safety and efficiency profiles of the pharyngeal swallow using ordinal-scaled penetration/aspiration and residue scores from MBS have been mapped to the CTCAE taxonomy in a validation study that is currently concluding at U.T. MD Anderson – the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST). DIGEST ratings will be assigned to each MBS to provide a CTCAE-compatible summary grade to the pharyngeal swallow: grade 1 “mild”, grade 2 “moderate”, grade 3 “severe”, and grade 4 “life threatening” pharyngeal dysphagia.

2.5 FDG-PET/CT Imaging as a Predictive Imaging Marker for Locoregional Control and Progression-Free Survival

The purpose of studying FDG-PET/CT in the context of HN002 is to determine the predictive value of 12-14 week post therapy FDG-PET/CT for locoregional control and 2-year PFS. Patients and investigators are given the option to participate in this component of the study although PET/CT scans are not required to participate in the parent study, HN002.

The sensitivity and specificity of post-treatment FDG-PET/CT depend on the time interval between the completion of therapy and FDG-PET/CT. In a study of 26 patients, Goerres, et al. (2004) observed a sensitivity and specificity of 91% and 93%, respectively, for PET/CT scans performed as early as 6 weeks after chemoradiotherapy. However, other studies have not been able to reproduce these data (Porceddu 2005, Yao 2005) and instead suggest that PET/CT after chemoradiotherapy should not be performed before 10-12 weeks after the end of radiation treatment. By that time, most of the post-treatment inflammatory changes will have subsided, reducing the number of potentially false-positive interpretations. In general, the rate of false-positive cases declines with the interval between the end of therapy and PET/CT imaging (Lonneux 2000). The optimal timing of the first response assessment FDG-PET/CT after definitive (chemo) radiation is not precisely known, but an interval of at least 12 weeks

has generally been recommended to balance the drawbacks of imaging too early versus too late. In rare cases, early detection of residual/recurrent disease is central to successful surgical salvage if appropriate, while a demonstration of a clinical and radiographic complete response obviates the need for further unnecessary and potentially morbid interventions. A recent meta-analysis involving 51 studies and 2335 patients (Gupta 2011) estimated the sensitivity and specificity of post-treatment FDG-PET/CT at 91.9% and 86.9% for primary tumor and 90.4% and 94.3% for neck nodes, respectively, when the PET/CT was performed > 12 weeks after completion of concurrent chemoradiation therapy. Therefore, in this study, the FDG-PET/CT should be obtained at 12-14 weeks post-treatment.

A reliable imaging modality to predict long-term locoregional control can serve as a surrogate imaging biomarker to judge the effectiveness of the investigational treatment. Residual structural abnormalities seen on anatomic imaging such as CT or MRI after definitive radiotherapy may not harbor viable cancer cells (Ware 2004). FDG-PET/CT is a functional imaging assessment that detects glucose metabolism of the tissue, and it is highly sensitive in the detection of viable cancer cells due to the high metabolic rate in these cells. Several single-institution retrospective studies have shown that a negative post-radiotherapy PET/CT was highly predictive of long-term locoregional control in locally advanced head and neck cancer after chemoradiation. Yao, et al. (2009) from the University of Iowa reported 188 patients with FDG-PET/CT obtained at a median of 15 weeks after radiotherapy. Of 151 patients with a negative FDG-PET/CT at the primary site, only 2 developed locally recurrent disease, with a negative predictive value of 98.7%. Of 171 patients who had a negative PET/CT in the cervical lymphatic region, only 2 were falsely negative, with a negative predictive value of 99%. Ryan, et al. (2005) summarized the experience from Stanford University in 103 patients with 118 post-treatment PET/CTs. PET/CT results were correlated with surgical pathology and clinical outcomes, and the negative predictive value of PET was 98%. In a prospective study of 98 patients by investigators from MD Anderson Cancer Center (Moeller 2010), using a post-radiation maximum standardized uptake value (SUV_{max}) of 6.0 of the primary tumor as a cut-off, the investigators reported that the negative predictive value of FDG-PET/CT for disease-specific survival was 92%. In this study, they reported that there was no additional prognostic information of FDG-PET/CT in low-risk patients, i.e. HPV positive oropharyngeal cancer patients. However, this was assessed under conditions of standard regimens of chemoradiation. In addition, this study was under powered due to a low number of events. In this trial, 2 de-intensified regimens are being tested in p16 positive oropharyngeal cancer patients, and the predictive value of 12-14 week post therapy FDG-PET/CT for 2-year PFS is unknown when treatment intensity is reduced. Therefore, the assessment of PET/CT in this setting is novel and important.

Currently, FDG-PET/CT is commonly used for staging and assessment of treatment response in head and neck cancer. The Centers for Medicare and Medicaid services and most third party payers in USA provide reimbursement for a pre-treatment and a post-treatment FDG-PET/CT in head and neck cancer patients scheduled to receive definitive-intent radiotherapy. While PET/CT has become very accepted, practice patterns among head and neck cancer treatment centers vary somewhat in their use of PET/CT.

Therefore, obtaining a pretreatment PET/CT and a 12-14 week post therapy PET/CT is highly recommended but not required, and for this study, obtaining PET/CT is left to the discretion of the clinician, as dictated per local clinical practice, and participation in the PET/CT assessment study is highly recommended but optional on the part of the patient and the investigator.

Because of the frequent use of PET/CT in local centers, it is of interest to the study investigators to document the performance of PET/CT under "real-world" conditions. This approach may increase the future generalizability of any findings. Furthermore, based on the experience of RTOG 0522, a requirement for scanner accreditation would pose a concerning barrier to participation and produce an unacceptably low sample size. Therefore, a study-specific accreditation of PET/CT scanners of the participating institutions will not be required for participation in the PET/CT sub-study, although information will be requested on the facility where the PET/CT scans were performed. Because the PET/CT images will be centrally reviewed and scored on a qualitative basis, the impact of variations in the imaging technique should be substantially lessened. Regarding PET/CT technique, the study investigators recommend that the standard-of-care guidelines from the National Cancer Institute and ACRIN Imaging Standards for PET should be followed as closely as possible (Shankar 2006).

To provide a platform for standardizing interpretations of the PET/CT scans, the study investigators have developed a reader-based scoring system to minimize the effect of varying acquisition techniques. This ordinal scoring system (see below) will identify those patients who have complete metabolic response and those who did not have complete metabolic response, retrospectively. All of the post-treatment PET/CT images will be centrally reviewed at the end of the recruitment period and correlated with the clinical treatment outcomes.

The proposed centralized scoring system was modified from the well-validated and clinically most useful five-point scoring system for mid-therapy and post-therapy assessment for lymphoma (Deauville criteria). This scoring system has been previously validated as a collapsed three-point categorization (negative for tumor, indeterminate, positive for tumor) for head and neck FDG-PET/CT scans performed between 4 and 24 months after therapy completion (Paidpally 2013). The scoring system successfully predicted outcome in these patients and added value to the clinical assessment at the time of the scans. In addition, the five-point scoring system has been recently validated in head and neck FDG-PET/CT scans performed between five weeks and 6 months after therapy completion in 214 head and neck squamous cell carcinoma patients. There was 90%, 97.2%, 94.9% and 91.3% agreement between the readers for overall, left neck, right neck and primary tumor site response scores, respectively. The corresponding Kappa coefficients for inter-reader agreement were $k=0.70$ ($p<0.0001$), $k=0.81$ ($p<0.0001$), $k=0.69$ ($p<0.0001$), and $k=0.67$ ($p<0.0001$), respectively. The accuracy of the scoring system against a 6 month clinical follow up as the reference standard is excellent with ROC area under the curve 0.98 (95% CI 0.97-0.99; $P < 0.001$). Cox regression analysis showed a significant difference in overall survival between the patients who had a score between 1-3 (negative for tumor) and those who had a score 4 or 5 (positive for tumor)

(log-rank, P<0.0001 with a hazard ratio of 0.056 [95% CI 0.022-0.138] (Subramanian, personal communication, 2014; Marcus 2014).

Proposed Harmonization of FDG-PET/CT Ordinal Scoring and Classification of Results

The tumor response evaluation will be carried out using a 5-point ordinal scale ranging from Definite Complete Response (score 1) to Definite Residual Disease (score 5). Diffuse uptake is defined as homogeneous FDG uptake, with smooth tapering borders. Focal uptake is characterized by an abrupt drop-off of FDG activity at the boundaries of the active area.

Score 1: Definite complete metabolic response: The FDG uptake in the primary tumor or nodal sites is less than the background blood pool FDG uptake.

Score 2: Likely complete metabolic response: The FDG uptake in the primary tumor or nodal sites is greater than the background blood pool uptake but it is equal to or less than the liver FDG uptake.

Score 3: Likely inflammatory: There is diffuse FDG uptake in the primary tumor or nodal sites. This diffuse FDG uptake is greater than the liver FDG uptake and likely related to post-radiation inflammation.

Score 4: Likely residual metabolic disease: There is focal FDG uptake in the primary or nodal sites. The focal FDG uptake is greater than the liver FDG uptake.

Score 5: Definite residual metabolic disease: There is intense focal FDG uptake in the primary tumor or nodal sites. This focal FDG uptake is greater than the liver FDG uptake.

Definitions of 'Positive,' 'Negative' and 'Indeterminate' FDG Uptake and PET/CT Results

A score of 1 or 2 will be interpreted as 'Negative,' a score of 3 as 'Indeterminate,' and a score of 4 or 5 as 'Positive.' A 'Negative' result at the primary or nodal sites is defined as equal or less FDG uptake than the blood pool and liver FDG uptake. Uptake for the local blood pool reference value will be measured from the carotid or the aortic arch. The 'Indeterminate' result is defined as diffuse FDG uptake in the treatment field with intensity of the uptake greater than the liver FDG uptake. A 'Positive' result is defined as focal uptake visually greater than the background and at a higher level than the activity seen in the liver.

Sites that are interested in participating are encouraged to explain this component of the study to patients and obtained consent from all patients. All pre and post therapy FDG-PET/CT images for patients enrolled in this optional component will be collected. The first 3 studies from each site will be centrally reviewed as a 'live read' within 3 working days of submission of scans to IROC Imaging, to establish a training and quality assurance process that will validate the local interpretation using the 5-point scoring system. All positive and indeterminate post-therapy scans also will be centrally reviewed as 'live reads' within 3 working days of submission of the scans to IROC Imaging.

It is important to note that local sites will decide the post-therapy management and may incorporate the information from FDG-PET/CT into decision making according to these

guidelines. However, determination of PFS events will require pathologic confirmation from biopsy or surgery; and an indeterminate or positive reading on FDG-PET/CT in itself will not be considered to affect the primary endpoint **unless pathologic confirmation of persistent/residual cancer is obtained.**

Any FDG-PET/CT scan that merits an indeterminate or positive read must be followed by a mandated, short-term follow up (either focused clinical examination or another imaging study within 4 weeks).

2.6 Circulating HPV DNA as a Potential Marker for Relapse (5/24/16)

Circulating HPV DNA was detected in the blood of mouse-bearing xenografts harboring HPV positive tumors (SCC90 & Hela cells) but not in HPV negative tumors (MiaPaCa2 and SAS cells) using a PCR-based approach with either the L1 G5+/6+ primer or HPV16/18 subtype specific nested E6/E7 primers. A quantitative PCR approach using qPCR E6/7 primers was able to quantify plasma HPV DNA in 40 patients with HPV positive oropharyngeal cancer (OPC), 24 patients with HPV negative head and neck cancer (HNC), and 10 non-cancer volunteers. This approach detected circulating HPV DNA in 65% of pretreatment plasma samples from HPV positive OPC patients. None of the HPV negative HNC or non-cancer controls had detectable HPV DNA. In addition, pre-treatment plasma HPV DNA copy number correlated significantly with nodal metabolic tumor volume (assessed on FDG-PET/CT). Serial measurements in 14 patients found a rapid decline in HPV DNA, which became undetectable at completion of the chemoradiation treatment course. In 3 patients, HPV DNA had risen to a discernible level at the time of metastasis (Cao 2012).

One drawback about the traditional qPCR approach is its low sensitivity and the requirement of large amount of DNA. Recently, Newman, et al. have published on the use of "Cancer Personalized Profiling by Deep Sequencing" (Capp-Seq) as an ultrasensitive method to quantify circulating tumor (ct) DNA with broad coverage in patients with locally advanced non-small cell lung cancer (NSCLC) (Newman 2014). Capp-Seq has been shown to outperform existing methods with a mean background level of 0.0007% and a detection limit of 0.025% for SNV and < 0.01% for rearrangement. It can detect mutant or viral DNA in picograms of DNA due to its low background and high sensitivity. The researchers also showed that the ctDNA levels were highly correlated with the tumor volumes and that it could distinguish between residual disease and treatment related imaging changes in these patients. Moreover, measurement of ctDNA allowed for earlier response assessment in NSCLC than radiographic approaches. We are currently validating the Capp-Seq approach on HPV+ HNSCC using our samples, and the results are encouraging. Based on this, we would like to determine whether the levels of HPV ctDNA as measured by Capp-Seq reflects tumor burden in patients treated on this trial and whether serial measurements can be used to track response and identify patients at high risk of relapse after treatment de-intensification therapy.

Hypothesis 1: To determine whether that HPV DNA levels as measured by the Capp-Seq platform correlates with the tumor volume (GTV) in HPV positive OPC.

As mentioned above, tumor ctDNA as measured by this platform significantly correlated with the tumor volume in NSCLC. Similarly, we found that plasma HPV DNA copy number as measured by traditional qPCR approach significantly correlated with nodal classification and nodal metabolic tumor volume in patients with HPV+ oropharyngeal carcinoma. We hypothesize that Capp-Seq is more sensitive and HPV ctDNA measurements by Capp-Seq will be a better reflection of tumor burden than DNA copy from qPCR. Since all patients will undergo pre-treatment simulation with recorded GTV and have pre-treatment plasma collection, it should be straightforward to extract DNA and measure HPV DNA by Capp-Seq and qPCR and correlate with GTV.

Hypothesis 2: To determine whether the rate of HPV DNA declines during therapy by Capp-Seq and whether the measured level at the completion of radiotherapy correlates with the rate of relapse in treated patients.

Serial circulating HPV DNA was measured in 14 patients with qPCR during therapy and in all of these patients, HPV DNA declined during treatment and became undetectable after treatment. In this small study, the investigators were not able to distinguish the pattern of relapse based on these 14 patients (4 with relapse and 10 without). However, with such a small sample size and the poor sensitivity of the qPCR method, it was difficult to distinguish those with a very low detectable versus an undetectable level. In contrast, Capp-Seq was able to track the NSCLC response to chemotherapy or radiation in a few patients evaluated. We hypothesize that the Capp-Seq approach will be superior to the traditional qPCR approach in detecting very low levels of HPV DNA in the blood after completion of radiation therapy, and those with detectable levels by Capp-Seq are more likely to have persistent disease or relapse after treatment. To address this hypothesis, this study proposes to measure HPV DNA by both qPCR and Capp-Seq pre-therapy, mid-way into the course of treatment (after 20 Gy) and within 2 weeks of completion of all therapy. We will quantify the rate of HPV DNA decline measured in a short window after the first 20 Gy. The specific hypothesis that the rate of initial decline after the first 20 Gy and/or the post-treatment level reflects tumor response to therapy and can be used to predict for tumor persistence and relapse in these patients.

2.7 PI3K Pathway Activation and Its Associated Genomic Profile as Prognostic Biomarkers of HPV Related Oropharyngeal Cancer

Recent genomic studies using next-generation sequencing (NGS) technology have shown that HPV related oropharynx cancer is genetically distinct compared to HPV unrelated oropharynx cancer (Agrawal 2011; Stransky 2011). In addition, a 182-cancer gene targeted analysis showed that HPV related oropharyngeal cancer has a particularly high prevalence of the phosphotidylinositol-3-kinase (PI3K) pathway aberration through activating mutation and increased gene copy number of the PI3K catalytic subunit, PIK3CA, and PTEN loss of function, the negative regulator of PI3K (Lechner 2013). The PI3K pathway is a well-known oncogenic pathway in numerous cancers and is activated by several receptor tyrosine kinases including epidermal growth factor receptor (EGFR), a key pathway in HNSCC. Activation of PI3K initiates a signal transduction cascade that promotes cancer cell growth, survival, and metabolism through several important downstream mediators, including Akt and mTOR complex 1 (mTORC1). Akt is the

serine–threonine kinase that is directly activated in the response to PI3K and serves as a major mediator within the PI3K pathway. Further downstream of Akt is the mTORC1, which is not only under control of PI3K–Akt signaling, but also integrates many cellular inputs from hypoxia to growth factor stimulation and stress response. In addition, PTEN loss is commonly seen in HNSCC resulting in uncontrolled activation of PI3K (Okami 1998). However, these aberrations generally are not the only abnormal oncogenic pathway but co-exist with other cancer related genes within an individual oropharyngeal cancer. Therefore, evaluation of PI3K pathway aberrations as prognostic biomarkers within the genetic contexts of other cancer gene mutations such as TP53 mutation is extremely important. In this proposal, the plan is to investigate mutations and copy number changes in genes within the PI3K pathway (PIK3CA and PTEN) and 180 additional cancer related genes using NGS. Improved understanding of this pathway in a specific genetic context also may lead to development of novel therapies and/or predictive biomarkers to improve the clinical outcomes of HPV related oropharyngeal cancer patients.

Hypothesis 1: Activation of the PI3K pathway by PIK3CA activating mutation or copy number gain or PTEN loss of function mutation or copy number loss is associated with increased rates of locoregional failure in patients with HPV related oropharyngeal cancer.

Hypothesis 2: Co-existence of PI3K pathway activation and TP53 mutation (or additional oncogene mutations such as KRAS mutation) will improve the prognostic potential of PI3K pathway activation.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG web site). For radiation therapy-related eligibility questions, please contact IROC Philadelphia RT (via the contact list on the NRG web site).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception throughout the treatment phase of the trial and until at least 60 days following the last study treatment.

3.1.3 Submission of H&E and p16 slides to the NRG Oncology Biospecimen Bank for confirmation of positive immunohistochemical staining for p16 is required for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See

Sections 10 and 11.)

3.2 Eligibility Criteria (5/24/16)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Step 1: Registration

3.2.1 Pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma (including the histological variants papillary squamous cell carcinoma and basaloid squamous cell carcinoma) of the oropharynx (tonsil, base of tongue, soft palate, or oropharyngeal walls); cytologic diagnosis from a cervical lymph node is sufficient in the presence of clinical evidence of a primary tumor in the oropharynx. Clinical evidence should be documented, may consist of palpation, imaging, or endoscopic evaluation, and should be sufficient to estimate the size of the primary (for T stage).

3.2.2 Patients must have clinically or radiographically evident measurable disease at the primary site or at nodal stations. Tonsillectomy or local excision of the primary without removal of nodal disease is permitted, as is excision removing gross nodal disease but with intact primary site. Limited neck dissections retrieving ≤ 4 nodes are permitted and considered as non-therapeutic nodal excisions.

3.2.3 Immunohistochemical staining for p16 must be performed on tissue, and this tissue must be submitted for central review. Fine needle aspiration (FNA) biopsy specimens may be used as the sole diagnostic tissue if formalin-fixed paraffin-embedded cell block material is available for p16 immunohistochemistry. FNA specimens prepared with adequate p16 testing in this manner are acceptable to submit for central review. If the p16 preparation is not adequate, additional specimens will be required to establish p16 status. Centers are encouraged to contact the pathology chairs for clarification.

3.2.4 Clinical stage T1-T2, N1-N2b or T3, N0-N2b (AJCC, 7th ed.) including no distant metastases based on the following diagnostic workup:

- General history and physical examination within 56 days prior to registration;
- Fiberoptic exam with laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) within 70 days prior to registration;
- One of the following combinations of imaging is required within 56 days prior to registration:
  a) A CT scan of the neck (with contrast) and a chest CT scan (with or without contrast);
  b) **or** an MRI of the neck (with contrast) and a chest CT scan (with or without contrast);
  c) **or** a CT scan of neck (with contrast) and a PET/CT of neck and chest (with or without contrast);
  d) **or** an MRI of the neck (with contrast) and a PET/CT of neck and chest (with or without contrast).

Note: A CT scan of neck and/or a PET/CT performed for the purposes of radiation planning may serve as both staging and planning tools.

3.2.5 Patients must provide their personal smoking history prior to registration. The lifetime cumulative history cannot exceed 10 pack-years. The following formula is used to calculate the pack-years during the periods of smoking in the patient's life; the

cumulative total of the number of pack-years during each period of active smoking is the lifetime cumulative history.

Number of pack-years = [Frequency of smoking (number of cigarettes per day) × duration of cigarette smoking (years)] / 20

Note: Twenty cigarettes is considered equivalent to one pack. The effect of non-cigarette tobacco products on the survival of patients with p16-positive oropharyngeal cancers is undefined. While there are reportedly increased risks of head and neck cancer associated with sustained heavy cigar and pipe use (Wyss 2013), such sustained use of non-cigarette products is unusual and does not appear to convey added risk with synchronous cigarette smoking. Cigar and pipe tobacco consumption is therefore not included in calculating the lifetime pack-years. Marijuana consumption is likewise not considered in this calculation. There is no clear scientific evidence regarding the role of chewing tobacco-containing products in this disease, although this is possibly more concerning given the proximity of the oral cavity and oropharynx. In any case, investigators are discouraged from enrolling patients with a history of very sustained use (such as several years or more) of non-cigarette tobacco products alone.

3.2.6 Zubrod Performance Status of 0-1 within 56 days prior to registration;

3.2.7 Age ≥ 18;

3.2.8 The trial is open to both genders;

3.2.9 Adequate hematologic function within 14 days prior to registration, defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 8.0 g/dl; Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.

3.2.10 Adequate renal function within 14 days prior to registration, defined as follows:

- Serum creatinine ≤ 1.5 mg/dl or creatinine clearance (CC) ≥ 50 ml/min determined by 24-hour collection or estimated by Cockcroft-Gault formula:

$$\text{CCr male} = \frac{[(140 - \text{age}) \times (\text{wt in kg})]}{[(\text{Serum Cr mg/dl}) \times (72)]}$$

$$\text{CCr female} = 0.85 \times (\text{CrCl male})$$

3.2.11 Adequate hepatic function within 14 days prior to registration defined as follows:

- Bilirubin ≤ 2 mg/dl;
- AST or ALT ≤ 3 x the upper limit of normal.

3.2.12 Negative serum pregnancy test within 14 days prior to registration for women of childbearing potential;

3.2.13 Patients who are HIV positive but have no prior AIDS-defining illness and have CD4 cells of at least 350/mm^3 are eligible. HIV-positive patients must not have multi-drug resistant HIV infection or other concurrent AIDS-defining conditions. Patients must not be sero-positive for Hepatitis B (Hepatitis B surface antigen positive or anti-hepatitis B core antigen positive) or sero-positive for Hepatitis C (anti-Hepatitis C antibody positive). However, patients who are immune to hepatitis B (anti-Hepatitis B surface antibody positive) are eligible (e.g. patients immunized against hepatitis B).

3.2.14 The patient must provide study-specific informed consent prior to study entry, including consent for mandatory submission of tissue for required, central p16 review.

3.2.15 Patients who speak English (or read one of the languages for which a translation is available (see Section 10.2) must consent to complete the mandatory dysphagia-related patient reported instrument (MDADI). If the patient cannot understand spoken English and reads only languages not available in the MDADI translations, the patient can still participate in the trial, as this has been factored into the trial statistics. For all other patients, the MDADI is mandatory as it is included in the primary endpoint to be studied.

Step 2: Randomization

3.2.16 p16 positive by immunohistochemistry (defined as greater than 70% strong nuclear or nuclear and cytoplasmic staining of tumor cells), confirmed by central pathology review; (see Section 10.1 for details).

3.3 Ineligibility Criteria (5/24/16)

Patients with one or more of the following conditions are NOT eligible for this study.

Step 1: Registration

3.3.1 Cancers considered to be from an oral cavity site (oral tongue, floor mouth, alveolar ridge, buccal or lip), or the nasopharynx, hypopharynx, or larynx, even if p16 positive, or histologies of adenosquamous, verrucous, or spindle cell carcinomas;

3.3.2 Carcinoma of the neck of unknown primary site origin (even if p16 positive);

3.3.3 Radiographically matted nodes, defined as 3 abutting nodes with loss of the intervening fat plane;

3.3.4 Supraclavicular nodes, defined as nodes visualized on the same axial imaging slice as the clavicle;

3.3.5 Definitive clinical or radiologic evidence of metastatic disease or adenopathy below the clavicles;

3.3.6 Gross total excision of both primary and nodal disease with curative intent; this includes tonsillectomy, local excision of primary site, and nodal excision that removes all clinically and radiographically evident disease. In other words, to participate in this protocol, the patient must have clinically or radiographically evident gross disease for which disease response can be assessed.

3.3.7 Patients with simultaneous primary cancers or separate bilateral primary tumor sites are excluded with the exception of patients with bilateral tonsil cancers;

3.3.8 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 1095 days (3 years) (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.3.9 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;

3.3.10 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.3.11 Severe, active co-morbidity defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Transmural myocardial infarction within the last 6 months;

- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration;
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol other than those requested in Section 3.2.10.
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition with immune compromise greater than that noted in Section 3.1.13; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.3.12 Pregnancy; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.3.13 Prior allergic reaction to cisplatin.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW UP (5/24/16)

PRE-TREATMENT ASSESSMENTS

Assessments	Prior to Registration-Step 1 Registration (calendar days)	Prior to Treatment (calendar days)
History/physical with height & weight	56	
Fiberoptic exam with laryngopharyngoscopy (see note below)	70	
Imaging: (see note below) • CT with contrast of neck and CT of chest +/- contrast; • Or MRI with contrast of neck and CT of chest +/- contrast; • Or CT with contrast of neck and PET/CT of neck and chest +/- contrast; • Or MRI with contrast of neck and PET/CT of neck and chest +/- contrast	56	

Patient's smoking history	X	
Zubrod Performance Status	56	
CBC/differential	14	
Bilirubin, AST or ALT	14	
Serum creatinine or creatinine clearance	14	
Serum pregnancy test, if applicable	14	
Na, K, Cl, glucose, Ca, Mg, and albumin (see note below)		28
Dental assessment (see note below)		28
Audiogram		112 (16 weeks)
Swallowing assessment (see note below)		28
MDADI		Required: 28
PSS-HN, CCI, Work Status		Required
EKG		Recommended for Arm 1 patients: 70 days (10 weeks)
Whole body PET/CT (see note below)		Recommended: 70 days (10 weeks)
Nutritional evaluation (see note below)		Recommended: 28
QOL: UW-QoL, if patient consents		Prior to start of protocol-specific treatment
Biospecimen Collection for Central Review and for Banking		See Section 10.1 for details
Modified Barium Swallow, if patient consents		Prior to start of protocol-specific treatment

Notes for Pre-Treatment Assessments (table above)

- The fiberoptic exam with laryngopharyngoscopy can be done by the treating surgeon, medical oncologist, or radiation oncologist with experience in endoscopic examinations of cancer patients.
- Patients with an initial magnesium < 0.5 mmol/L (1.2 mg/dl) may receive corrective magnesium supplementation but should continue to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) at the investigator's discretion.
- The protocol-specific dental assessment is by a physician or designee (such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist) to assess number of teeth and overall dental health with management; see guidelines at www.ctsu.org on the NRG-HN002 protocol page.
- The protocol-specific swallowing assessment is a single question completed by the physician and/or research associate to describe the consistencies of foodstuff that the

patient is able to swallow.

- The MDADI is a required PRO (if the patient can comprehend spoken English or read one of the validated language translations) and it is completed by the patient.
- The EKG is recommended for Arm 1 patients (RT + cisplatin).
- "Whole body" PET/CT may be limited to neck and chest. Note: Diagnostic quality CT scan of neck with contrast and/or PET/CT performed for radiation planning may serve as both staging and planning tools. Centers that wish to participate in the PET/CT correlative study component should refer to guidelines for submitting these images and their associated data (see Section 10.3).
- Nutritional evaluation to include the physician's evaluation for placement of prophylactic gastrostomy or other type of feeding tube; note: The decision to place a feeding tube should be individualized and is not mandated. Investigators may consider a number of factors including: prior weight loss, current nutritional status, size and location of the primary tumor (impacting high dose target volume), availability of feeding tube placement services, availability of speech and swallowing specialists, dietician counseling, and social support. Feeding tubes may be placed after start of treatment at the discretion of the clinical team. If a tube is placed, the site will document on the appropriate case report form (see Section 12.1) if the tube was placed prophylactically (as a preventative measure) or therapeutically (because of nutritional compromise or other clinical indications). It is highly recommended as part of the standard of care that all patients, but particularly those who require feeding tubes, be provided with professional swallowing evaluations and counseling before, during, and after treatment.
- Quality of Life:
  - Patients are **required** to complete the MDADI at pre-treatment as this assessment is needed for the primary objective of the trial.
  - Patients who consent to participate in the optional QOL study will complete the UW-QoL.
  - The Performance Status Scale for Head and Neck (PSS-HN), Charlson Comorbidity Index (CCI), and Work Status questions are **required and are completed by the investigator and/or research associate.**
  - Patients who consent to participate in the quality of life (QOL) component of this study have the option of completing QOL forms online from any location, including home, via VisionTree Optimal Care (VTOC). Patients without e-mail or Internet access are still able to participate in the QOL component of the study by completing hardcopy (paper) forms. Indeed, at any time, any patient may choose to fill out their QOL form using the hardcopy form.

    If the patient wishes to complete QOL assessments online, the patient must have an e-mail address that they consent to use for this purpose. Patients' e-mail addresses are necessary so that e-mail reminders may be sent to them to remind them to fill out QOL forms that are due. The patient's e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g.,Yahoo!, Hotmail, or AOL). **Note: The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link https://rtog.optimalcare.com - medical team. RA login information will be provided by VTOC after the patient is randomized to the**

study. The patient's VTOC account must be set up within 14 days after randomization.

ASSESSMENTS DURING TREATMENT (5/24/16)

Assessments	Weekly during Treatment	As Clinically Indicated
Brief history	X	X
Physical examination	X	X
Zubrod Performance Status	X	
CBC/differential	Arm 1: Weekly Arm 2: At Weeks 3 and 5	
Serum creatinine or creatinine clearance	Arm 1: Weekly Arm 2: At Weeks 3 and 5	
Na, K, Cl, glucose, Ca, Mg, and albumin	Arm 1: Weekly Arm 2: At Weeks 3 and 5	
Bilirubin, AST or ALT	At Weeks 3 and 5	
Whole body PET/CT		X
CT or MRI or PET/CT of neck, with contrast		X
Biopsy		If suspicion of tumor recurrence
Adverse Event Evaluation	X	X
QOL: MDADI	Mandatory at completion of radiation	
QOL: UW-Qol	For patients who consent: At completion of radiation	
QOL: PSS-HN, Work Status questions	Required: Completed by the investigator and/or research associate at completion of radiation	
Biospecimen Collection for Banking	For patients who consent: After at least 20 Gy RT has been given but before 28 Gy RT has been given	

ASSESSMENTS IN FOLLOW UP (5/24/16)

Assessments	At 1 Month Post-treatment	q3 mos. from end of RT for 2 yrs; q6 mos. for 3 yrs; then annually	As Clinically Indicated
Brief history, physical examination, and laryngopharyngoscopy	X	X	
Zubrod Performance Status	X	X	
CBC/differential	X		
Na, K, Cl, glucose, Ca, Mg, and albumin	X		
Total bilirubin; AST or ALT	X		
Optional imaging study, if patient consents: FDG-PET/CT (see note below)		12-14 weeks post-therapy	
Chest CT or PET/CT		At 6 mos post-RT, then annually for 2 years	After 3 years, as clinically indicated
CT or MRI of the neck with contrast		Initial post-treatment scan at 3 months is required; recommended at other time points if disease progression is suspected by treating physician	
PET/CT of neck		Initial post-treatment scan at 3 months is recommended; may be substituted for CT or MRI only if the CT component is performed with contrast as a diagnostic quality imaging study	

Biopsy			If suspicion of tumor recurrence
Adverse Event Evaluation	X	X	X
Nutrition/Feeding Tube Evaluation			X
Dental Assessment		At 12, 24, 60, and 120 mos. from end of treatment	
QOL: MDADI	Mandatory at 6, 12, and 24 months from end of radiation		
QOL: UW-Qol	For patients who consent: At 6, 12, and 24 mos. from end of radiation		
QOL: PSS-HN	Required: Completed by the investigator and/or research associate at 6, 12, and 24 mos. from end of radiation		
QOL: Work Status questions	Required: Completed by the investigator and/or research associate at 6, 12, and 24 mos. from end of radiation		
Biospecimen Collection for Banking	For patients who consent: No earlier than 2 weeks and up to 1 month after the completion of treatment		
Modified Barium Swallow, if patient consents	24 months +/- 3 months from end of radiation		

Notes for Assessments in Follow Up (table above)

- A brief history & physical examination by a Radiation or Medical Oncologist or an ENT or Head & Neck Surgeon, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure), must be done at 1 and 3 months from the end of radiation treatment, then every 3 months through year 2, every 6 months for 3 years, then annually.
- The initial post-radiation imaging evaluation at 3 months after the completion of radiotherapy is required. The imaging can be contrast-enhanced CT of the neck, MRI of the neck with contrast, PET/CT of the head and neck with contrast and including diagnostic quality imaging of the neck, or "whole body" PET/CT (minimum neck and chest) with contrast and including diagnostic quality imaging of the neck based on the preference of the treating clinician. Centers that wish to participate in the PET/CT correlative study component should refer to guidelines for submitting these images and associated data (see Section 10.3).
- Radiographic imaging (CT, MRI, or PET/CT as appropriate) at follow-up time points is highly recommended if disease progression is suspected by the treating physician. If performed, radiographic imaging to evaluate the patient for both local-regional recurrence and distant metastases is highly recommended (see Section 5.7).
- Chest imaging: A chest CT +/- contrast or a PET/CT including the chest is required once per year for a total of 3 image sets, then may be performed as clinically indicated.
- Optional imaging study: A post-therapy FDG-PET/CT scan is highly recommended at 12-14 weeks post-therapy for assessment of response to therapy. If the patient consents to participate, the site is required to submit the patient's post-treatment PET/CT scan; see Section 10.3 for details.
- Biopsy of any lesion(s) suspicious for tumor recurrence is recommended as clinically indicated.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

Intensity-modulated radiation therapy (IMRT) is required, although non-IMRT techniques may be used to treat the low neck, if it is the institution's practice. For IMRT planning, margin expansions will be set at 0.5 cm from GTV to the high dose CTVs. Sites will have the option to use an additional 0.3 or 0.5 cm to the PTV, depending on the frequency of IGRT.

If PTV margins of 0.3 cm are used, daily IGRT usage is required, and IGRT credentialing is required. If using 0.5 cm PTV margins, a minimum of weekly IGRT is required and imaging alignment must be approved by the attending physician on the first day of treatment and weekly thereafter. IGRT credentialing is not required for 0.5 cm PTV margin expansion.

5.1 Chemotherapy (5/24/16)

Protocol treatment must begin within 14 days after randomization.

5.1.1 Arm 1 Patients: Low-dose Intravenous Cisplatin Administration Concurrent with Radiation

Cisplatin: 40 mg/m^2/day, weekly during radiation treatment, for a maximum of 6 doses.

Dose should be based on actual body weight. Treatment may be administered before or after radiotherapy. The first cisplatin infusion should be started within 24 hours before or after the first scheduled radiation therapy administration.

No concurrent cisplatin will be administered after the final week of radiation, but the final dose of cisplatin may be administered following the last dose of radiation if it is administered within the same calendar week. **Cisplatin should be administered on Mondays or Tuesdays to maximize overlap of daily radiation with cisplatin exposure**. Administration on Wednesday prior to that day's radiation dose is acceptable but not preferred. Investigators should strive to administer cisplatin on the same day each week but variance of 1 day is acceptable for vacations, holidays, etc. If radiation treatments are held for toxicity, cisplatin dosing should also be held. If cisplatin is held for toxicity, then the dose will not be made up.

5.1.2 Low-dose Cisplatin Concurrent with Radiation Administration Guidelines

High dose cisplatin is highly emetogenic. While this protocol is using more frequent dosing of cisplatin that is considered moderately emetogenic, investigators should be prepared to use aggressive prophylactic antiemetics and hydration. Many institutions will have standard guidelines for the administration of cisplatin at the doses used in this study. **For purposes of this protocol, individual investigators may use these local guidelines for cisplatin administration. One possible approach is outlined below.** These guidelines may need to be modified based on local guidelines and patient related factors (e.g. the substitution of normal saline in diabetic patients). Similarly, the anti-emetic regimen is to be determined by the local investigator, although one possible approach is outlined below.

- *Low-dose Cisplatin anti-emetic administration guidelines*: 5-HT3 antagonists and decadron should be given (e.g. ondansetron 16 mg PO prior to cisplatin and 8 mg PO up to 3 times daily on days 2 and 3 following cisplatin weekly and dexamethasone x 3 days starting prior to the cisplatin dose weekly, 12 mg on day 1 and 8 mg on days 2 and 3 each week OR palonosetron 0.25 mgs IV and decadron 12 mgs prior to cisplatin. Use of other anti-nausea meds such as aprepitant, metoclopramide, or prochlorperazine is left to the discretion of the investigator.
- *Low-dose Cisplatin pre-hydration guidelines*: Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin should be given. Mannitol 12.5 gm IV immediately prior to cisplatin may be given. Use of mannitol is left to the discretion of the investigator.
- *Low-dose Cisplatin administration*: Standard administration is cisplatin, 40 mg/m^2 over 30-60 minutes IV in 250 cc NS. Infusion rate not to exceed 2 mgs per min. See Section 6.0 for dose modifications. See above discussion on scheduling and number of doses concurrent with radiation.
- *Low-dose Cisplatin post-hydration guidelines*: Following the end of the cisplatin administration, an additional liter of D5½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2 hours. On the second and third day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS. The amount of pre- and post-hydration is left to the discretion of the investigator.

5.2 Radiation Therapy (5/24/16)

Protocol treatment must begin within 14 days after randomization.

All patients will receive 60 Gy delivered in 30 fractions of 2 Gy. Full details of radiation dose prescriptions are provided in Section 5.2.7.

Unilateral radiation will be permitted in selected patients; see Section 5.2.4.

5.2.1 Treatment Technology

All patients will be managed with IMRT delivered with megavoltage photons. A matched AP or AP-PA field with larynx block may be utilized to manage the low neck as described in Section 5.2.4. All institutions must be credentialed for IMRT if not already done. Treatment verification is required and required frequency of IGRT depends on the use of PTV margins (see Section 5 and 5.2.13).

5.2.2 Immobilization and Simulation

Patients will be treated supine and must have a secure head and neck immobilization (e.g. aquaplast mask) made prior to the treatment planning CT scan.

The treatment planning CT scan should be performed with IV contrast unless contraindicated, obtained in the immobilization device and in the treatment position with a slice thickness of 3 mm or less.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-up

A diagnostic CT or MRI for structure delineation is recommended. These may be fused to the planning CT scans to facilitate target and structure definition. When available FDG

PET/CT images may also be fused to the planning CT data set.

5.2.4 Definition of Target Volumes and Margins

All specified target volumes and organs-at-risk (OAR) will be contoured on the planning CT scan data sets and named according to the nomenclature described below. For the purposes of contouring, MRI and PET images, if available and clinically indicated, may be fused with the planning CT data set. Target volumes and OARs will be labeled according to published guidelines (Santanam 2012).

Gross Tumor Volume (GTV)

The GTV represents clinically or radiographically grossly involved regions of primary tumor or involved nodes designated GTVp_6000 and GTVn_6000 respectively. These volumes are defined based on physical exam and review of available imaging. FDG-PET may assist in GTV identification but specific GTV border delineation should not rely exclusively on PET signal given the known variable association between gross tumor extent and PET signal cutoff. For purposes of dose evaluation GTVp and GTVn will be labeled GTVp_6000 and GTVn_6000.

Post-Biopsy GTV

Patients undergoing gross total excision of both primary and gross nodal disease with curative intent are not eligible for this study (see Section 3.3.6). Patients undergoing diagnostic procedures at the primary site, such as simple/diagnostic tonsillectomy or excisional biopsy, are eligible but are not considered to have had an oncologically therapeutic surgical procedure even in the absence of clinically or radiologically appreciable gross residual disease at the primary site. As such, these patients require full radiation dose (60 Gy) to be delivered to a volume immediately adjacent to the tissues removed at the time of the biopsy. For purposes of planning, this volume will be labeled GTVp and it should be defined relative to the extent of disease prior to removal. This GTVp may be defined by fusion of pre-biopsy imaging studies (CT, MRI) with the planning CT data set. The gross primary tumor on the pre-biopsy imaging may be projected on the planning CT and defined as the intersection with the residual tissues. If there is not such an intersection or the residual tissues lie in a different anatomic orientation post-biopsy, the GTVp may be defined as a 5 mm expansion into the residual tissues circumferential to the area of the biopsy. In the event that pre-biopsy imaging is not available the GTVp must be defined relative to the clinical exam of the biopsy site and normal anatomic landmarks. For instance, in the specific case of tonsillectomy the GTVp will include, at a minimum, the tonsillar bed to include anterior and posterior tonsillar pillars up to the level of the soft palate and inferiorly to the pharyngoepiglottic fold; the GTVp should be expanded superiorly or inferiorly if the pre-biopsy tumor extended past these landmarks. A CTV_6000 and CTV_5400 are then defined for this GTVp according to methods defined below.

Nodal Definitions

- Grossly Positive Nodes (GTVn_6000) are defined as those greater than 1.5 cm in long axis and/or > 1 cm in short axis, a cluster of 3 or more borderline size nodes, radiographic evidence of extracapsular extension (ECE), or a node of any size with evidence of necrosis. Smaller nodes may be determined to be gross disease

objects depending on clinical suspicion (based on proximity to the primary site or other involved nodes) or demonstration of significant uptake of FDG on PET scanning.

- Extracapsular extension (ECE): is defined as radiographic evidence of irregular borders and/or perinodal fat stranding, invasion of adjacent structures, or both. Any areas of potential involvement should be included within the GTV. Clinicians are highly encouraged to request radiologist review if the determination is unclear.
- Matted Nodes: Three or more abutting nodes with loss of the intervening fat planes. Patients with matted nodes should not participate in this trial (see exclusion criteria, Section 3.3).

Clinical Target Volume (CTV)

- CTVs are defined and contoured in relation to the targets they are intended to encompass and the dose they are intended to receive. For gross targets (GTVs), the CTVs are defined by 3D isotropic expansions that should then be limited by potential barriers to tumor spread such as air cavities, external contours and bony or fascial planes through which tumor spread is not possible or apparent. Similarly CTVs may be expanded beyond the limits defined in this protocol in order to cover areas deemed at risk of tumor extension (e.g. neck musculature invaded by nodal disease, or pterygoid regions of infratemporal fossa in superiorly extending tonsilar cancers). For nodal regions of potential microscopic involvement CTVs are defined according to normal anatomic landmarks (Gregoire 2014).
- **CTV_6000: Primary Tumor and Involved Nodes**
  A CTV_6000 will be defined for primary tumor and involved nodes as a 0.5 cm isotropic expansion of the GTVs defined for these structures. When defined for nodes, the CTV_6000 should be suffixed as CTVn_6000 to distinguish this from the primary, CTVp_6000, for the purposes of plan evaluation. CTV_6000 is the sum of CTVp_6000 and CTVn_6000.
- **CTV_5400: High-Risk Subclinical Sites**
  High-risk subclinical sites are defined as: i) areas of potential subclinical tumor infiltration beyond the primary site CTVp_6000 and ii) the first echelon node levels to the primary site irrespective of gross nodal involvement and all node levels containing gross nodes. In the event of a node excision (≤ 4 per protocol) that occurred at time of diagnosis, the node levels that contained grossly involved adenopathy should be included in CTV_5400, even if there is no residual post excision adenopathy.

  A CTV_5400 will be defined for these sites and include the following:
  i) 1.0 cm isotropic expansion of GTVp_6000 , which is an 0.5cm expansion on the CTVp_6000.
  ii) 1st echelon node levels based on standard anatomic definitions. In most cases 1st echelon would be ipsilateral level II, but in cases of midline primary site involvement this should include bilateral level II. In cases with soft palate or posterior pharyngeal wall involvement this should include the

lateral retropharyngeal lymph nodes.

iii) All node levels containing a CTVn_6000 that has been assigned to involved nodes (all grossly involved nodal levels).

iv) Other high-risk subclinical sites may include nodes < 1cm not thought to harbor gross disease yet thought to be at risk of containing more than subclinical disease based on their location relative to the primary site. In such cases of clinical concern that do not meet the above criteria, a 0.5cm expansion on these nodes can be added to the CTV_5400 at the discretion of the treating clinician.

- **CTV_4800: Node Levels at Risk of Microscopic Spread**
  A CTV_4800 will be defined to treat node levels without evidence of gross disease yet at risk of microscopic spread and not contained in CTV_5400. These levels are defined anatomically according to published Intergroup consensus guidelines (Gregoire 2014). The levels to be treated will depend on the site and extent of the primary tumor and any grossly involved lymph nodes and are indicated in Table 5.2.4A.
- **CTV_4400: Low Neck Nodes at Risk of Microscopic Spread**
  For patients with no low neck nodal involvement, a matched AP or AP-PA field with larynx block may be utilized to manage the low neck. Under this scenario, CTV_4800 will not include the low neck, but rather CTV_4400 will be defined by contouring the prescription iso-dose line of the AP or AP-PA field. For centers that use IMRT for the low neck, the low neck nodes at risk of microscopic spread will be included CTV_4800.

Table 5.2.4A: Nodal Levels to Receive Prophylactic Microscopic Dose–(4800 cGy)

CTV_4800*	Ipsilateral Neck	Contralateral Neck**
N0-1 (in level II – IV)	• Ib (for primary oral cavity extension), • II-IV • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate	• II-IV • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate
N2a-b	• Ib,II,III,IV,V,RP	• II-IV • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate

*Applies to neck levels not included in CTV_5400.
** The contralateral neck may be omitted according to guidelines defined below.

- **Contralateral Neck**

It is recognized that the evidence as to the efficacy and safety of a unilateral neck radiotherapy approach within specific patient groups is largely retrospective, yet increasingly compelling evidence has led some centers to consider unilateral radiotherapy standard practice for selected patients while others continue to treat in a bilateral fashion. Unfortunately, the data for patients with selected N2b or lateralized tongue base cancers is less well defined in the literature than that for N0-N2a tonsillar cancer, and additionally, substantial disparities in opinions remain related to the effect of extracapsular extension (Vergeer 2010; Yeung 2012, Geropantas 2013, Lynch 2013). It also can be difficult to define the number of involved nodes, since it may vary depending on whether the site uses CT, MRI or PET/CT for initial staging. Based on these considerations, the study team has concluded that the use of unilateral radiation techniques should remain optional, in deference to the established practice and clinical judgment of the enrolling investigator, but have defined 3 groups of patients with respect to neck irradiation.

Unilateral radiotherapy is recommended (see guidelines below) if it is the institution's established practice, if the primary tumor originates in the tonsil, and is well-lateralized, with less than 1 cm of involvement of the soft palate or base of tongue, no posterior pharyngeal wall involvement, and with minimal nodal disease burden (N0-N2a) as assessed by clinical exam and staging radiology studies. For patients who share these characteristics but have N2b nodal disease confined to ipsilateral level 2 of the neck, unilateral radiotherapy is optional. Due to the imperative to maintain high PFS for this trial and the lack of prospectively collected data on this controversial subject, for patients with characteristics that fall outside these categorizations, bilateral treatment is required.

- **Groups of Patients with Regard to Unilateral or Bilateral Neck Irradiation**
  Group 1: Unilateral treatment is recommended.
  T1 to T3 tonsil primaries with < 1cm clinical or radiographic extension into tongue base and/or palate, no posterior pharyngeal wall extension, N0-N2a (no ECE)

  Group 2: Unilateral treatment is optional.
  T1 to T3 tonsil primaries with < 1cm clinical or radiographic extension into tongue base and/or palate, no posterior pharyngeal wall extension, N2b (no ECE) with involved adenopathy confined to ipsilateral level 2 of the neck

  Group 3: Bilateral treatment is mandatory.
  Tongue base, palate or posterior pharyngeal wall primaries or tonsil primaries with >1cm soft palate and/or tongue base extension or any posterior pharyngeal wall extension; patients with any ECE or with involved adenopathy outside of ipsilateral level 2 of the neck

  Prior to individual patient randomization, oncologists will declare their intention to treat unilaterally or bilaterally, which will serve as a stratification factor (Unilateral vs. Bilateral) ensuring balance between the 2 study arms. Exploratory analyses adjusted for unilateral vs. bilateral radiotherapy will be conducted when

the results are available.

- **Management of the Low Neck (levels III, IV, V)**
  Treatment of the uninvolved low neck may be achieved with a single IMRT plan encompassing the whole neck along with the primary site. Alternatively the low neck may be treated with AP or AP-PA fields, with a midline block to shield larynx and spinal cord, junctioned isocentrically with the IMRT volumes at the plane of the isocenter. This may only be done in cases without gross nodes in the low neck and if the match is >1 cm clear of gross nodal disease and primary site superiorly. The dose for the low neck volumes managed with this technique will be 2 Gy per fraction prescribed to 3 cm depth to a total dose of 44 Gy in 22 once daily fractions.

Table 5.2.4B: Clinical Target Volume Nomenclature and Description.
All volumes are to be treated using IMRT in 30 fractions except CTV_4400 in 22 fractions given to the low neck when applicable. **Note**: All structures marked as **Required** in the table below must be contoured, and labeled as listed under "Standard Name" for digital RT data submission. All structures marked as **Required if applicable** must be contoured and labeled as listed under "Standard Name" for digital data submission **IF** they are applicable to the patient's plan. Resubmission of data is necessary when labeling of structures does not conform to the DICOM Standard Name listed.

Standard Name	Description	Detailed Specification
GTVp_6000	GTV to receive 60 Gy at the primary site **Required**	Equivalent to GTVp as defined above
GTVn_6000	GTV to receive 60 Gy at involved nodes **Required**	Equivalent to GTVn as defined above
CTVp_6000	CTV to receive 60 Gy at the primary site **Required**	0.5 cm isotropic expansion of GTVp_6000 limited by potential anatomic barriers to tumor spread such as air cavities, external contours and bony or fascial planes through which tumor spread is not possible or apparent
CTVn_6000	CTV to receive 60 Gy at involved nodes **Required**	0.5 cm isotropic expansion of GTVn_6000 limited by potential anatomic barriers to tumor spread such as air cavities, external contours and bony or fascial planes through which tumor spread is not possible or apparent
CTV_6000	CTV to receive 60Gy **Required**	Sum of CTVp_6000 and CTVn_6000
CTV_5400	CTV to receive 54 Gy at high risk volume at the	i) 1.0 cm expansion of GTVp_6000, which is an 0.5cm

	primary site and applicable node levels **Required**	expansion on the CTVp_6000 ii) First echelon nodes (unilateral or bilateral) iii) node levels containing involved nodes iv) 0.5 cm expansion on nodes < 1 cm thought to be at risk of containing more than subclinical disease.
CTV_4800	CTV to receive 48 Gy to right and/or left neck regions at risk of microscopic disease **Required if applicable**	Defined anatomically according to consensus guidelines (Gregoire 2014). The levels to be treated will depend in the site and extent of the primary tumor and any grossly involved lymph nodes. See table 5.2.4A for specifics
CTV_4400	CTV to receive 44Gy to low neck regions at risk of microscopic disease **Required if applicable**	Option for lower neck volumes (levels III, IV,V) treated with non IMRT techniques and midline sparing junctioned >1cm clear of gross disease, defined as prescription isodose line of the AP or AP-PA field used to treat these volumes

See Table 5.2.6 for corresponding PTV descriptions.

5.2.5 Definition of Organs at Risk

Note: All structures marked as **Required** in the table below must be labeled as listed under "Standard Name" for digital RT data submission. Resubmission of data is necessary when labeling of structures does not conform to the DICOM Standard Name listed.

Table 5.2.5: Organ at Risk Nomenclature

For detailed descriptions see below.

OAR Standard Name	Description
SpinalCord	Spinal cord **Required**
SpinalCord_05	PRV = 5 mm expansion on spinal cord **Required**
BrainStem	Brain stem **Required**
BrainStem_03	PRV= 3 mm expansion on brainstem **Required**
Lips	Lips

	Required
OralCavity	Oral cavity **Required**
Parotid_R	Right parotid gland **Required**
Parotid_L	Left parotid gland **Required**
Submandibula_R	Right submandibular gland **Required, if applicable**
Submandibula_L	Left submandibular gland **Required, if applicable**
Pharynx	Non-treated pharynx **Required**
Esophagus_Up	Cervical esophagus **Required**
Larynx	Larynx **Required**
Mandible	Mandible **Required**
NonPTV	Unspecified tissue, External minus all PTVs **Required**
External	External border of the patient **Required**

- **Spinal Cord**: The cord begins at the cranial-cervical junction (ie, the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The spinal cord must be contoured at least 1 cm below the lowest extent of the neck PTVs. The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined as: SpinalCord_05 = cord + 5 mm in each dimension.
- **Brain Stem**: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined as: BrainStem_03 = brainstem + 3 mm in each dimension.
- **Lips**: The definition of lips is self-explanatory.
- **Oral Cavity**: The oral cavity will be defined as a composite structure posterior to lips consisting of the anterior ½ to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and superiorly the palate, and inferiorly to the plane containing the tip of the mandible.
- **Parotid Glands**: Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan.
- **Submandibular Glands**: Submandibular glands will be defined in their entirety based on treatment planning CT scans.

- **Pharynx**: This will be defined as the pharyngeal wall plus adjacent constrictor muscles deemed not to require treatment (external to PTVs). This extends from the superior constrictor region (level of the inferior pterygoid plates) to the cricopharyngeal inlet (level of the posterior cricoid cartilage).
- **Esophagus**: This will be defined as the cervical (upper) esophagus, a tubular structure that starts at the bottom of pharynx (cricopharyngeal inlet) and extends to the thoracic inlet.
- **Larynx**: This will be defined as the glottic and supraglottic larynx, including the tip of the epiglottis, the aryepiglottic folds, arytenoids, false cords, and true cords, bounded by the thyroid cartilage laterally, anteriorly including the anterior edge of the pre-epiglottic fat, and posteriorly bounded by the anterior edge of the pharyngeal wall or the posterior edge of the arytenoid and/or cricoid cartilage.
- **Mandible**: This includes the entire bony structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.
- **Unspecified Tissue Outside the Targets (NonPTV)**: This will be defined as tissue located between the skull base and thoracic inlet external to all PTVs and defined normal stuctures within the external contour of the patient.

5.2.6 Planning Target Volumes

All CTVs will have associated PTVs which represent the volumes to which radiation dose will be prescribed, delivered and evaluated. The PTVs are isotropic expansions of the CTVs to account for internal motion and residual set-up error.

PTVs are defined as either a 3 mm or 5 mm expansion of the CTV in all planes, depending on the frequency of IGRT (see Sections 5 and 5.2.13).

The simple isotropic expansion of CTVs to create PTVs will result in dosimetric challenges in 2 instances:

i. when the CTV expansion results in a PTV that overlaps a critical OAR or its PRV, hence dose delivered to this PTV will exceed the acceptable dose limits for the OAR;
ii. and when the CTV expansion results in PTVs extending beyond the patient external contour, making PTV dose calculation and evaluation unreliable.

The PTVs may be modified in the following situations:

1) When a PTV overlaps a critical OAR (spinal cord and/or brainstem) and its associated PRV, the PTV should be modified to exclude the PRV so as to limit the dose delivered to the PRV within constraints defined in table 5.2.10.
2) The PTVs should be constrained 5 mm within the external contour. For situations where gross disease is external to the external contour (disease at or through the skin surface), the use of 5 mm tissue equivalent material (bolus) is required, and no PTV constraint should be used underneath the bolus.

Table 5.2.6: Planning Target Volume Nomenclature and Description

All to be treated in 30 fractions except PTV_4400 in 22 fractions. For CTV descriptions see Table 5.2.4B. **Note**: All structures marked as **Required** in the table below must be contoured and labeled as listed under "Standard Name" for digital RT data submission. All structures marked as **Required if applicable** must be contoured and labeled as listed under "Standard Name" for digital data submission **IF** they are applicable to the patient's plan. Resubmission of data is necessary when labeling of structures does not conform to the DICOM Standard Name listed.

Standard Name	Description	Detailed Description
PTVp_6000	PTV to receive 60Gy at the primary site **Required**	3-5mm expansion of CTVp_6000
PTVn_6000	PTV to receive 60 Gy at involved nodes **Required**	3-5mm expansion of CTVn_6000
PTV_6000	PTV to receive 60 Gy **Required**	Sum of PTVp_6000 and PTVn_6000
PTV_5400	PTV to receive 54 Gy at the primary site and applicable node levels **Required**	3-5mm expansion of CTV_5400
PTV_4800	PTV to receive 48 Gy in neck **Required if applicable**	3-5mm expansion of CTV_4800
PTV_4400	PTV to receive 44 Gy at lower neck (non IMRT) **Required if applicable**	CTV_4400*

*No expansion from CTV_4400 to PTV_4400.

5.2.7 Dose Prescription

The prescribed radiotherapy dose to gross disease for all patients will be 60 Gy delivered in 30 fractions of 2 Gy. For Arm 1, radiotherapy will be delivered once daily, 5 fractions per week Monday to Friday for 30 consecutive treatment days (6 weeks), with weekly concurrent cisplatin at 40 mg/m^2.

For Arm 2, the radiotherapy will be delivered alone (without the addition of chemotherapy) in an accelerated schedule over 5 weeks, which requires delivery of 6 fractions per week. The sixth fraction can be delivered either on a Saturday or as a second daily fraction, with at least a 6 hour interfraction interval if 2 fractions are given on one of the weekdays.

Target volumes will be similar in both arms and for both, the primary tumor and involved nodes will receive 60 Gy (2 Gy per fraction for 30 fractions), high-risk subclinical sites will receive 54 Gy (1.8 Gy per fraction for 30 fractions) and nodal regions at risk of microscopic spread will receive 48 Gy (1.6 Gy per fraction for 30 fractions). If the low neck is treated with non-IMRT technique, 44 Gy (in 22 fractions) will be prescribed to a

point of 3 cm depth. Unilateral radiation will be permitted in selected patients; see Section 5.2.4.

Doses prescribed are indicated in Table 5.2.7 below. All PTVs are to be treated concurrently within a single IMRT plan of 30 fractions. If the low neck is treated with non-IMRT techniques to 44 Gy in 22 fractions once daily fractions will commence simultaneously and be delivered concurrently with the IMRT plan.

Table 5.2.7: Doses Prescribed to PTVs

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Dose specification technique**
PTV_6000	60	2.0	30	Covering ≥ 95% of PTV_6000
PTV_5400	54	1.8	30	Covering ≥ 95% of PTV_5400
PTV_4800	48	1.6	30	Covering ≥ 95% of PTV_4800
PTV_4400	44	2.0	22	100% at 3 cm

5.2.8 Treatment Planning Priorities and Instructions

IMRT Dose Prescription to PTVs

Doses are prescribed to PTVs as outlined in Table 5.2.7. The treatment goal is that 95% of the volume of all PTVs must receive the prescribed dose with a minimum dose (defined as dose to 99% of PTVs) greater than 93% of the prescription dose and a maximum dose (defined as dose encompassing 0.03 cc of the PTV) less than 110-115% of the highest prescription dose.

It is recognized that portions of PTVs close to the skin or critical PRVs (spinal cord and brainstem) may receive significantly less than the prescription doses. This is acceptable in these regions as long as cold spots within these PTVs do not exist within the GTV. In cases of PTVs close to skin, tissue equivalent bolus must be utilized to ensure adequate dose.

It is also recognized that PTVs abutting or enclosing higher dose PTVs will have regions of maximum dose that may exceed their prescribed dose in order to achieve acceptable minimal doses to the higher dose PTVs which are considered a higher priority target.

Prioritization for IMRT Planning

1. Spinal Cord
2. Brainstem
3. PTV_6000
4. PTV_5400

5. PTV_4800 and PTV_4400
6. a. Parotid gland contralateral to primary tumor site
   b. Larynx
7. a. Pharynx
   b. Contralateral submandibular
8. a. Oral Cavity
   b. Lips
   c. Esophagus
9. a. Parotid gland ipsilateral to primary tumor site
   b. Mandible
10. Unspecified tissue outside the targets

5.2.9 Doses to Normal Structure

Dose limitations to normal stuctures are described below. For the critical structures of spinal cord and brainstem these are mandatory. For other structures recommended limits are provided, but the doses delivered should always be as low as reasonably achievable without compromising doses to PTVs.

- **Spinal Cord***:* The PRV for spinal cord (SpinalCord_05) should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the spinal cord PRV should be given the highest priority.
- **Brainstem**: The PRV for brainstem (BrainStem_03) should not exceed 50 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the BrainStem_03 should be given less priority than the SpinalCord_05, but more than the critical structures listed below.
- **Lips***:* Reduce the dose as much as possible. The mean dose should be < 20 Gy.
- **Oral Cavity***:* Reduce the dose as much as possible. The mean dose should be < 32 Gy for the oral cavity. Efforts should also be made to avoid hot spots (> 60 Gy) within the non-involved oral cavity.
- **Parotid Glands**: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 26 Gy but efforts should be made to reduce this further if possible without compromising dose to PTVs.
- **Contralateral submandibular gland**: If contralateral level Ib is not a target, aim to reduce mean contralateral submandibular gland to < 39 Gy.
- **Pharynx:** Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the Pharynx exceeds 50 Gy; 2) Mean dose < 40 Gy; 3) No more than 15% of the Pharynx exceeds 60 Gy.
- **Esophagus**: Reduce the dose as much as possible; recommended (but not mandatory) treatment goal: mean dose < 30 Gy.
- **Larynx***:* Reduce the dose as much as possible. The larynx mean dose is recommended to be ≤ 35 Gy if whole-neck IMRT is used.
- **Mandible***:* Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 63 Gy.
- **Unspecified Tissue Outside the Targets (NonPTV)**: No more than 1cc of unspecified tissue outside the targets can receive ≥ 63Gy .

5.2.10 Dose Compliance Criteria **(4/29/15)**

The compliance criteria listed in Table 5.2.10 will be used to evaluate each case. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended to avoid protocol deviation.

Table 5.2.10: Planning Target Volume and Critical OAR Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter*	Per Protocol Dose (Gy)	Variation Acceptable
PTV_6000	$D_{95\%}$*(Gy)	60	> 60 and ≤ 63
	$D_{99\%}$(Gy)	≥ 55.8	≥ 54
	D_{max}**(Gy)	≤ 66	≤ 69
CTV_6000	$V_{60\ Gy}$ (%)	≥ 99 %	95 to 99 %
PTV_5400	$D_{95\%}$*(Gy) $D_{99\%}$(Gy)	≥ 54 ≥ 50.2	≥ 51.3 ≥ 48
CTV_5400	$V_{54\ Gy}$ (%)	≥99 %	95 to 99 %
PTV_4800	$D_{95\%}$*(Gy) $D_{99\%}$(Gy)	≥ 48 ≥ 44.6	≥ 44 ≥ 43.2
CTV_4800	$V_{48\ Gy}$ (%)	99 %	95 to 99 %
SpinalCord_05	D_{max}**(Gy)	≤48	≤50
Spinal Cord	D_{max}**(Gy)	≤45	≤48
BrainStem_03	D_{max}**(Gy)	≤ 50	≤52

A **Deviation Unacceptable** will be scored when the Variation Acceptable limits are not met.

*$D_{95\%}$(Gy) = dose to 95% of volume
**Dmax = maximum dose to 0.03 cc of the volume

Recommended dose acceptance criteria for other normal tissue,
but not to be used for plan score

Structure	**Recommended dose acceptance criteria**
Parotid	Mean dose to one parotid ≤ 26 Gy
Larynx	Mean dose ≤ 35 Gy
Pharynx	Mean dose ≤ 40 Gy
Submandibula_R Or Submandibula_L (contralateral)	Mean Dose ≤ 39 Gy
OralCavity (excluding PTV's)	Mean dose ≤ 32 Gy
Esophagus_Up	Mean dose ≤ 30 Gy
NonPTV	D1cc < 63 Gy
Mandible	D0.03cc < 63 Gy

5.2.11 Delivery Compliance Criteria

Protocol treatment must begin within 14 days of randomization. Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should not exceed 3 treatment days at a time and 5 treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding 2 treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

Given the importance of timeliness of treatment delivery in this study, it is strongly recommended that patients receive twice-daily treatments with a minimum 6-hour inter-fraction interval to compensate for missed days including holidays and those for toxicity or illness once sufficiently recovered with the goal of keeping the overall treatment time within the limits defined in Table 5.2.11.

Table 5.2.11: Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	Deviation Unacceptable
Overall Treatment time Six week arm	<45 days	46-50 days	>50 days without a medically appropriate indication for delay
Overall Treatment time Five week arm	<37 days	38-42 days	>42 days without a medically appropriate indication for delay
Interruptions (without medical indication)	0-2 days	2-4 days	>4 days

5.2.12 Dose Calculations

The primary data set for dose calculation is CT. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density. The dose grid size should be ≤ 3 mm in all directions, which means that the CT slice thickness should be ≤ 3 mm.

Dose calculation algorithms have been credentialed by IROC Houston. To find whether your commercial treatment planning system has been credentialed by IROC Houston, please see the list from the following website: (http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf).

Any other dose calculation algorithms not listed on the web site must be credentialed by IROC Houston prior to the use for this study.

5.2.13 Daily Treatment Localization/IGRT

Daily image guidance (IGRT) of IMRT is required if PTV margins of 0.3 cm are used, and IGRT credentialing is also required. (Section 8.3). **Note**: Sites that have been approved for head and neck IGRT credentialing will not have to repeat IGRT credentialing for this study.

If using PTV margins of 0.5 cm, a minimum of weekly IGRT will be required, and the imaging alignment must be approved by the attending physician on the first day of treatment and weekly thereafter. IGRT credentialing is not required for 0.5 cm PTV margin expansion.

IGRT may be achieved using any one of more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac;
- Linear-accelerator mounted kV and MV conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy);

- Other mechanism, after discussion with the Radiation Oncology Co-Chair and/or Medical Physics Co-chair.

The institution's procedure to register the treatment day imaging dataset with the reference dataset should comply with the following recommendations:

- Region-of-interest (ROI) or "clip box" for fusion should be set to encompass the high dose PTV and adjacent spinal cord;
- If the fusion software allows the user to create an irregular ROI (e.g. ExacTrac), treatment room objects seen on in-room X-rays should be excluded from the registration;
- Both manual (e.g. based on bony anatomy) and automatic (e.g. based on mutual information) types of registration can be used; the result of the fusion must be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable surgical clips and soft tissue structures (e.g. optic nerves and/or optic chiasm);
- Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are less than 2.5 mm (this typically corresponds to one half of the usual PRV margin), the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 2.5 mm). If one or more corrections are 2.5-5 mm, adjustment is necessary prior to treatment; however, reimaging is not mandatory. If one or more of the corrections are larger than 5 mm, the imaging must be repeated in addition to performing table/positioning adjustments.

Management of Radiation Dose to the Patient from IGRT

NRG Oncology is concerned about the estimated doses given from IGRT, and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by avoiding the use of this technology to make small changes in patient positioning that are within the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g. requiring frequent corrections that are larger than the PTV margins). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

5.2.14 Replanning

In cases of weight loss > 10% or substantial shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask be adjusted or re-made in order to preserve adequate immobilization, and that a repeated simulation CT be performed to assess the dose distributions in the current anatomy. Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same as those used for the initial plan and not adjusted in cases of disease regression, except to respect clear anatomic barriers such as skin or fascial or muscle planes initially uninvolved by disease. The new CT dataset should be used for IGRT image registration when the patient's shape changes significantly.

5.2.15 Radiation Therapy Adverse Events **(5/24/16)**

Grade 3-4 (CTCAE, v. 4) therapy-induced mucositis and/or dysphagia, which are

enhanced by cisplatin, are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy to decide on the use of a prophylactic gastrostomy (PEG) tube placement is recommended, but in the absence of significant pretreatment dysphagia and associated weight loss of < 10% body weight the insertion of a prophylactic PEG is not recommended. If done the placement of a feeding tube should be recorded, as should proportion of use of a feeding tube during and after treatment (e.g. greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to the dental recommendations provided in Appendix I, "Dental Assessment and Management Document), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

5.3 Surgery

Surgery is expected to play only a limited role in the favorable risk HPV-associated cancers included in this study. Locoregional progression is expected in <10% of patients. The role of neck dissection has been declining in recent years, in part due to a high rate of negative specimens when planned neck dissections are performed in cancers of the oropharynx.

5.3.1 Post-Treatment Imaging/Timing

While centers are allowed to follow their institutional policies in conducting earlier post-treatment imaging evaluations, the major initial post-radiation imaging evaluation for the purposes of this study is required at 12-14 weeks after the completion of radiotherapy with diagnostic quality, contrast-enhanced CT or MRI of the neck. PET/CT may be conducted in this timeframe as well, based on the preference of treating clinicians, but does not substitute for the mandatory anatomic imaging. The required diagnostic CT may be performed as part of the integrated PET/CT but only if the CT is considered diagnostic quality and is contrast enhanced. PET/CT may facilitate pre-and post-treatment evaluation of metabolic response and the need for post-treatment neck dissection. Centers that are participating in the PET/CT correlative study component should refer to section 10.3 for guidelines on submitting the PET/CT images. If physical examination and imaging suggest residual disease at the primary site, a biopsy will be performed to confirm residual disease; otherwise, patients will undergo serial follow up. Annual chest imaging is required to a maximum of 3 annual imaging sets and thereafter should be performed based on clinical judgment.

5.3.2 Post-Treatment Surgical Salvage of Residual Disease

Treatment of residual disease at the primary site will be determined by the treating clinicians and the clinical situation, and surgical resection, re-irradiation, chemotherapy, or palliative care will be done. If the primary site is cleared of residual disease yet residual disease at the cervical nodal basin is strongly suggested by imaging/clinical evaluation, then selective neck dissection will be performed unless a cytologic sampling

(biopsy) of the node is negative. Post-treatment "planned" neck dissection will be defined as being performed for residual disease and within 20 weeks (140 days) of completion of radiotherapy. Positive neck specimens removed within 140 days will be considered part of the initial treatment plan and not considered as failures of initial management; positive specimens upon neck dissection beyond 140 days will be considered regional failures. Note that this is relaxed from the traditional definition of 105 days (15 weeks) in order to permit resolution of HPV-associated adenopathy, which is commonly cystic and may have a somewhat slower regression rate. Such post-treatment consolidation neck dissections will encompass only the areas (typically only levels 2 and 3) initially involved in the side of the neck in question. The extent of neck dissections performed for nodal recurrence, nodal progression, or salvage of disease at the primary ultimately will be determined by the treating surgeon. In the case of negative PET/CT in patients who did not achieve clinical or CT/MRI-based radiological nodal CR, a minimum of careful clinical examination is required at 3 months, and further imaging is highly recommended, such as follow-up imaging every 3-4 months for at least 24 months, as well as careful recording of the clinical dimensions of the residual abnormality.

5.4 Imaging

See Section 10.3 for details of the optional FDG-PET/CT correlative study.

5.5 General Concomitant Medication and Supportive Care Guidelines

5.5.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication. These may include analgesics, antiemetics, topical mouth rinses, skin creams/ointments, etc. In general, HIV-positive patients who are on a stable Highly Active Anti-Retroviral Therapy (HAART) regimen should continue HAART while receiving chemotherapy. However, for patients who are newly diagnosed with HIV but with laboratory parameters meeting the eligibility criteria, it is preferable to defer initiation of HAART until after chemotherapy is completed. HAART regimens containing zidovudine and stavudine should be avoided during chemotherapy due to concerns for overlapping toxicity with chemotherapy. In addition, the protease inhibitor atazanavir (RayatazTM) can cause a physiologically unimportant hyper-hyperbilirubinemia; however, in the setting of chemotherapy, some experts suggest switching that drug for another equally effective one. If HAART is withheld during chemotherapy, it should be resumed promptly after conclusion of the last cycle of chemotherapy.

5.5.2 Prohibited Therapies

The use of amifostine or palifermin as a radioprotectant is not allowed. The use of granulocyte colony stimulating factor or erythropoietin is not allowed. Transfusion is to be performed at the discretion of the treating physician. Any exceptions must be approved by the Principal Investigator, Dr. Yom, or the Medical Oncology Co-Chairs, Drs. Gillison and Gibson.

5.5.3 Participation in Other Trials

Patients may not participate in other clinical trials that are intended to treat the diagnosed oropharyngeal cancer or intended to reduce toxicity of therapy.

5.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.7 Measurement of Response/Progression

- Response versus "Tumor Clearance" versus Cancer Progression
  Response and confirmation of local (primary site) or regional (neck) "tumor clearance" are not endpoints in this study. Clinical or radiographic evidence of progressive local-regional disease beyond 20 weeks should be documented in the clinical record and ideally confirmed by local or regional biopsy, neck dissection, or salvage surgery. CT or MRI (of head and neck region, with Chest CT), or PET/CT (including chest anatomy) may be used as radiographic evaluation of overall cancer status. The primary, neck and chest portions of the scans should be evaluated and reported separately. The CT portion of a PET/CT may serve as sufficient radiographic evaluation of the chest. If CT or MRI is used for evaluation of the head and neck region, CT of chest will be needed to rule out distant disease or second primaries at the designated evaluation intervals.
- Local or Regional Progression
  Local (primary site) or regional (neck) progression is defined as clinical or radiographic evidence of progressive disease at the primary site or neck. The location of progressive disease should be separately distinguished (local vs. neck) to document the precise pattern of failure if possible. Progression of local or regional disease should be confirmed by biopsy when possible but may be clinically assessed and documented in the clinical record at the judgment of the treating clinicians. Suspicion of disease progression exclusively on the basis of indeterminate or positive PET/CT scan must be pathologically confirmed.
- Distant Metastasis
  Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise.
- Second Primary Neoplasm
  Tumor reappearing with the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

6. TREATMENT MODIFICATIONS/MANAGEMENT (5/24/16)

6.1 Chemotherapy Dose Modifications (20-DEC-2017)

Note: If adverse events prevent the administration of chemotherapy, the patient may continue to receive radiation therapy.

6.1.1 Cisplatin Dose Modifications During Concurrent Radiation

Note: Substitution of carboplatin for cisplatin during adverse events is NOT allowed.

Patients will be examined and graded for subjective/objective evidence of developing toxicity weekly according to CTCAE, v. 4 while receiving concurrent cisplatin with radiotherapy.

Treatment interruptions are allowed if there is symptomatic mucositis or skin reaction that, in the judgment of the clinician, warrants a break. For chemotherapy-attributable AEs requiring a break in treatment, resumption of concurrent cisplatin may begin when AEs have recovered to the levels specified below. Chemotherapy should be discontinued in the event of more than 2 events requiring dose reduction (e.g. if grade 3 or greater non-hematologic or hematologic event occurs at the reduced dose of cisplatin, at 23 mg/m^2/week.

If an AE does not resolve to the levels specified in the sections below prior to the calendar week of the last radiation treatment (See Section 5.1 for details concerning parameters for timing of last allowable concurrent cisplatin dose), then chemotherapy should be discontinued.

There will be no dose re-escalation for concurrent cisplatin.

Chemotherapy dosage modifications are based upon lab values obtained prior to cisplatin and interim non-hematologic toxicities during the week prior to a particular cisplatin dose.

The dose modifications for cisplatin (below) are intended to be permanent (i.e., if the patient's dose is reduced to dose level -1, it remains at the reduced dose level).

6.1.2 Cisplatin Dose Modifications for Hematologic Adverse Events during Concurrent Radiation

Starting Dose	Dose Level -1	Dose Level -2
40 mg/m^2	30 mg/m^2	23 mg/m^2

Chemotherapy must not be administered until the ANC is $\geq$ 1,000 mm^3 and platelets are $\geq$ 75,000 mm^3. If not, delay 7 days. Cisplatin should be held every week until the above ANC and platelet parameters are met. Dose reductions when cisplatin is resumed after delay for low ANC or platelets will be as follows, based upon counts at time cisplatin was held.

ANC		Platelets	Reduction
< 1000 mm3	or	< 75,000	One dose level

Note: **Hematologic growth factors for neutropenia or anemia are not allowed during concurrent cisplatin and radiation treatment.**

Neutropenic Fever: Grade 3 (CTCAE, v 4) neutropenic fever (ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C [101 degrees F] or a sustained temperature of ≥ 38 degrees C [100.4 degrees F] for more than 1 hour) is an expected potential complication of concurrent chemotherapy and radiotherapy or chemotherapy alone. If neutropenic fever is noted, the chemotherapy dose reduction will be determined by the weekly blood counts. See above.

6.1.3 Cisplatin Dose Modifications for Non-Hematologic Adverse Events during Concurrent Radiation

Renal Adverse Events: Dose will be modified based on the serum creatinine prior to each cisplatin dose. If the serum creatinine is ≤ 1.5 mg/dL, creatinine clearance is not necessary for treatment with full dose. If the serum creatinine is > 1.5 mg/dL, a creatinine clearance should be obtained by urine collection or nomogram calculation (valid only if serum creatinine is not changing rapidly).

Cisplatin must not be administered until creatinine is ≤ 1.5 or creatinine clearance ≥ 50. Once the creatinine has met the above parameters, cisplatin may be restarted with the below modifications based on the creatinine at the time the cisplatin was held: In general, cisplatin should be held for weekly intervals (rather than restarting cisplatin later in the same week that a dose limiting AE is seen).

Cisplatin dose modifications for creatinine during concurrent radiation			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction
≤ 1.5	or	≥ 50	No change
> 1.5	and	40-49	One dose level
		< 40	Hold drug

Neurologic (neuropathy) Adverse Events:

Grade (CTCAE, v. 4)	Dose Reduction
0-1	None
2	One dose level
3-4	Hold drug

Ototoxicity: Should patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. A neurologic deficit should be distinguished from a conductive loss from obstruction of the Eustachian tube leading to a middle ear effusion. Because no AE scale, including the CTCAE, v. 4, has been validated in terms of correlation with clinically relevant hearing loss, there are no protocol mandates requiring dose reduction

for audiogram-determined sensorineural hearing loss without an analogous clinical high grade (> grade 2) hearing loss. However, for clinical grade 3 or higher hearing loss, cisplatin should be held and for grade 2 clinical hearing loss, one dose level reduction should be implemented.

All Other Non-Hematologic Adverse Events Attributable to Cisplatin during Concurrent Radiation: For all other non-hematologic adverse events in which toxicity is ≥ grade 2 (CTCAE v. 4), investigators are advised to evaluate and manage correctable issues promptly to prevent worsening of toxicity. For these events in which toxicity is ≥ grade 3, investigators should hold cisplatin, with weekly re-evaluation until AE grade falls to 0-1, then restart cisplatin at one lower dose level. Note: Grade 3 mucositis is commonly experienced by head and neck cancer patients; the investigator generally would not hold the cisplatin dosing in this case, unless there is unusual concern for progression to grade 4 mucositis.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP web site at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via r the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613)

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to NRG Oncology at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once Internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.1 Adverse Events (AE)

Definition of an 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 (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. ; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.2 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.2 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.2. **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.4 CTEP-AERS Expedited Reporting Requirements (4/29/15)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting

System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once Internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **the NRG Oncology dedicated SAE FAX, 215-717-0990.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS as "expedited reporting NOT required" must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the "NOT Required" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 13.2).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Commercial Agent within 30 Days of the Last Administration of the Commercial Agent. [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting

Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent: The following are protocol specific exceptions to expedited reporting via CTEP-AERS. Report the following AEs in an expedited manner only if they exceed the grade in parentheses next to the AE: nausea (grade 3), vomiting (grade 3), diarrhea (grade 3), dehydration (grade 3), lymphocyte count decreased (grade 4), and mucositis (grade 3). Routine adverse event reporting on the case report form fulfills safety reporting requirements for these events at the aforementioned grades.

8. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES (20-DEC-2017)

Access requirements for OPEN, Medidata Rave, and TRIAD: Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account.

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	✔	✔		

Documentation Required	IVR	NPIVR	AP	A
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

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

8.1 CTSU Registration Procedures (20-DEC-2017)

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

IRB Approval

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.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents

Site registration forms may be downloaded from the NRG-HN002 protocol page located on the CTSU members' web site.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- 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 NRG Oncology link to expand, then select trial protocol #
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for NRG-HN002 site registration:

- IRB Approval Letter (for sites not participating via the NCI CIRB; 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)
- IRB/REB Approved Informed Consent (English and native language versions*****)
  ***Note**: Institutions must provide certification/verification of IRB/REB consent translation to NRG Headquarters (described below).
- IRB/REB registration number renewal information as appropriate.
- CTSU RT Facilities Inventory Form NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

8.2 Submitting Regulatory Documents (20-DEC-2017)

Submit completed forms along with a copy of your IRB Approval and Informed Consent 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 1100
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.

8.2.1 Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU web site.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Non-English Speaking Canadian and International Institutions:

*Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

8.2.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

In addition to the requirements above, Canadian institutions must also complete the following documents to the CTSU Regulatory Office via the Regulatory Submission Portal:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form;
- Qualified Investigator Undertaking Form;
- Research Ethics Board Attestation Form;
- Attestation memo for participation in FDG-PET/CT imaging.

8.2.3 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS

*For institutions that **do not have an approved LOI** for this protocol:*

International sites must submit an LOI to NRG Headquarters to receive approval to participate in this trial. (For more details, see http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx.

*For institutions that **have an approved LOI** for this protocol:*

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

8.3 RT-Specific Pre-registration Requirements

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, Imaging and Radiation Oncology Core (IROC) Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

RT Credentialing Requirements	**Web Link for Procedures and Instructions: http://irochouston.mdanderson.org**	
	Treatment Modality	
	IMRT	**Key Information**
Facility Questionnaire	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center web site (http://irochouston.mdanderson.org).
Knowledge Assessment	N/A	
Benchmark Cases	N/A	

Phantom Irradiation	X	An IMRT H&N phantom study provided by the IROC QA Center Houston must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Tomotherapy and Cyberknife treatment delivery modalities must be credentialed individually.
IGRT Verification Study	X	The institution must submit a sample of verification images showing their ability to reproducibly register daily IGRT information with a planning CT dataset (i.e. the GTV falls within the CT simulation defined PTV). The patient ("as if patient") used for this study must have a target (or mock target) in the H&N region. The information submitted must include 2 IGRT datasets (from 2 treatment fractions) for a single patient. This information with a spreadsheet (the spreadsheet is available on the IROC Houston web site: http://irochouston.mdanderson.org.
Pre-Treatment Review	N/A	
Institution		IROC Houston will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

8.3.1 Digital RT Data Submission to NRG Oncology Using TRIAD

TRIAD is the image exchange application used by the NRG. TRIAD provides sites participating in NRG clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to the beginning of Section 4 for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG website Core Lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

8.4 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.4.1 Oncology Patient Enrollment Network (OPEN)

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. All site staff (NRG 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' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- See beginning of Section 4 for information on obtaining a CTEP-IAM account.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the NRG, you must have an equivalent 'Registrar' role on the NRG roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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 located on the CTSU members' web site 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.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: websupport@acr.org or call the NRG

Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

9. DRUG INFORMATION

9.1 Investigational Study Agent

Not applicable for this study.

9.2 Commercial Agent: Cisplatin

Adverse Events: Sites must refer to the package insert for detailed pharmacologic and safety information.

9.2.1 Availability/Supply

Please see Section 5.1 for administration instructions. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

10. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

10.1 Biomarkers (5/24/16)

Institutions must screen patients, whose tumors must be p16 positive by immunohistochemistry (IHC) in order to be eligible for the trial using a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Then the institution must submit one H&E slide and one p16 IHC slide to the NRG Oncology Biospecimen Bank for central review prior to randomization (see the table below). **Note**: A rigorous laboratory accreditation process similar to the U.S. CLIA certification, such as the provincial accreditation status offered by the Ontario Laboratory Accreditation (OLA) Program in Canada, the College of American Pathologists (CAP), or an equivalent accreditation in other countries, is acceptable.

Central review will be conducted with rapid turnaround (1-2 business days from receipt of the slides) coordinated by Dr. Richard Jordan at the NRG Oncology Biospecimen Bank. Specifics of type and source of p16 antibody and testing method will be requested (although not required) at the time of specimen submission. Every effort should be made to obtain and submit this information at the time of specimen transmission, in order to ensure the fastest possible resolution should there be any questions about staining technique.

Note: Due to potential delays in customs, Canadian sites will be permitted to submit an Aperio digital image of the H&E and p16 stained slide for remote central review by Dr. Jordan. Prior approval for this must be obtained from the NRG Biospecimen Bank. In cases in which Dr. Jordan determines that the image quality or staining is inadequate, the site will be required to send the original slides to the Biospecimen Bank directly.

H&E stained slides will be used to confirm presence of tumor in the sample and to aid in assay interpretation. Interpretation of each p16 immunostained slide will be performed

using the H-score method described by Jordan, et al. (2012) that has been validated as a reliable, reproducible, and accurate method to score p16 in squamous cell carcinoma of the head and neck. The primary reviewer will be the Pathology Co-Chair, Richard Jordan, DDS, PhD, with secondary analysis by the Pathology Co-Chair, Christina Kong, MD. p16 IHC will be scored as evaluable if strong and diffuse positivity was observed in the tissue mounted on each slide. The highest intensity of p16 staining present in the tumor will be scored on an ordinal score of 0-3, relative to the intensity of the positive (score 3) and negative (score 0). The percent of tumor staining at the highest intensity also will be estimated within 5% increments. The H score is derived from the cross product of the intensity score (0 to 3), and the percent of tumor staining at the highest intensity (0-100%). An optimal H-score cut-point of 60 on a scale of 0-300 yields an average sensitivity of 91.6% and specificity of 90.4% for HR-HPV oncogene expression and thus an H-score cut-point of 60 indicates that a tumor with diffuse low-intensity nuclear and cytoplasmic p16 staining in the majority of the tumor is a true positive (Jordan 2012). High agreement on inter-rater interpretation has been reported (Schlecht 2011, Thavaraj 2011), indicating the familiarity of pathologists with interpretation of IHC assays. Similarly, comparable assay performance for p16 to that observed here has also been previously reported (Schlecht 2011, Thavaraj 2011). The most common p16 monoclonal antibody in use is E6H4 (CINtec). Other acceptable p16 antibody types include 16P04 and JC8. If a different p16 antibody is used, discussion with the Pathology Co-Chairs is strongly encouraged.

In cases in which a major discrepancy arises between the primary evaluator and the central reviewer (Dr. Jordan), the p16 stained slide and the associated probe and testing specifics will be sent to a secondary central reviewer, Dr. C. Kong at Stanford University, to resolve the disagreement. If p16 staining cannot be established as positive through the central review process, the patient is not considered eligible.

Ship all biospecimens for central review and banking for this trial to:
NRG Oncology Biospecimen Bank—San Francisco
2340 Sutter Street, Room S341 (Box 1800)
University of California San Francisco
San Francisco, CA 94115
415-476-7864; NRGBB@ucsf.edu

See the tables below for mandatory and optional specimen collection.

See further details of specimen collection/processing/shipping on the RTOG/NRG Oncology web site,
http://www.rtog.org/LinkClick.aspx?fileticket=1SFlEVxSui4%3d&tabid=281.

Mandatory: Specimen Collection for Central p16 Confirmation
The specimens are being collected for confirmation by central review (see Section 10). Institutions must screen patients, who must be p16 positive by immunohistochemistry in order to be eligible for the trial.

- Required Forms: ST form and pathology reports with accession number and p16 staining result; any other personal health information (PHI) should be redacted.
- Shipping costs: Submitting site pays cost of shipping.
- Results: Dr. Richard Jordan, NRG Oncology Biospecimen Bank, or Dr. Christina Kong, Pathology Co-Chair, will report to NRG Oncology.
- Residual Material: p16 slides will be retained unless return is requested by the submitting site.

For questions, contact:
NRG Oncology Biospecimen Bank;NRGBB@ucsf.edu; 415-476-7864/FAX 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
One H&E slide One p16 stained IHC slide	Pre-Treatment	Enrolling institution, using a CLIA certified laboratory, screens patient with p16 testing by IHC (must be positive). Then Biospecimen Bank does central review prior to randomization.	Slides shipped ambient

Optional Study #1: Circulating HPV DNA as a Potential Marker for Relapse

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified in the protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

Specimens are being collected to determine whether a novel method for detecting tumor-derived DNA is superior to qPCR in the detection of circulating HPV DNA in the blood (see Section 2.6 for further details).

- Required Form: ST form
- Biospecimen Kits: Available from the NRG Oncology Biospecimen Bank
- Shipping days: Monday-Wednesday (U.S. sites); Monday-Tuesday (Canada and Non-North American).
- Shipping costs: Return labels are provided for frozen biospecimens only.

For questions, contact:
NRG Oncology Biospecimen Bank;NRGBB@ucsf.edu; 415-476-7864/FAX 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Plasma: 5-10 mL of anticoagulated whole blood from two EDTA tubes #1 and #2 (purple/ lavender top) and centrifuge	1) Pre-treatment; 2) During the treatment, obtained after 20Gy RT but before 28 Gy; 3) No earlier than 2 weeks and up to 1 month after the completion of treatment	Frozen plasma samples containing 1 mL per aliquot in 1 mL cryovials (5-10) **Need plasma from two tubes**	Plasma sent frozen on dry ice via overnight carrier

Optional Study #2: PI3K Pathway Activation and Its Associated Genomic Profile as Prognostic Biomarkers of HPV Related Oropharyngeal Cancer

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified in the protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

Specimens are being collected to study the PI3K pathway (see Section 2.7 for further details).

- Required Forms: ST form and pathology reports to confirm the diagnosis
- Biospecimen Kits: Available from the NRG Oncology Biospecimen Bank.
- Shipping days: Frozen specimens: Monday-Wednesday (U.S. sites); Monday-Tuesday (Canada and Non-North American). FFPE: No restriction.
- Shipping costs: Return labels are provided for frozen biospecimens only.

For questions, contact:
NRG Oncology Biospecimen Bank
415-476-7864/FAX 415-476-5271
NRGBB@ucsf.edu

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide (can be the same one submitted for central review)	Slide shipped ambient
A corresponding paraffin-embedded tissue block or 2 mm punch block of the primary tumor taken before initiation of treatment	Pre-treatment	Paraffin-embedded tissue block or punch block (with punch block H&E). If site is unable to provide the block or punch, then 10 unstained tumor slides (cut at 5 micron) is an acceptable alternative	Block or unstained slides shipped ambient (ship with a cold pack during hot weather)
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #3	Pre-treatment; **note**: If site missed this collection time point they may collect whole blood for	Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (3-5)	Whole blood sent frozen on dry ice via overnight carrier

(purple/lavender top) and mix	DNA at a later time point but must note this on the ST Form.		

10.2 Quality of Life (5/24/16)

Completion of the MD Anderson Dysphagia Inventory-Head and Neck (MDADI-HN)is **mandatory**, as the MDADI is being used to assess the primary objective of the trial. Patients who speak English (or read one of the languages for which a translation is available; see below) are required to complete the MDADI assessments. If the patient does not understand spoken English and only reads languages not available in the validated MDADI translations, the patient can still participate in the trial, as this has been factored into the trial statistics; however, reasons for not completing this required component should be clearly documented.

Patients must be offered the opportunity to consent to the optional quality of life component. If the patient consents to participate, the site is required to administer the University of Washington Quality of Life Questionnaire, version 4 (UW-QoLv.4) at baseline, completion of radiation therapy, and at 6, 12 and 24 months from the end of radiation. Sites are not permitted to delete the quality of life component from the protocol or from the sample consent.

Optional Online Completion of QOL Assessments

Patients who consent to participate in the quality of life (QOL) component of this study have the option of completing QOL forms online from any location, including home, via VisionTree Optimal Care (VTOC). The baseline QOL forms must be completed in hardcopy at the time of enrollment, but all subsequent QOL forms can be completed by the patient online. Patients without e-mail or Internet access can participate in the QOL component of the study by completing hardcopy (paper) forms. Indeed, at any time, any patient may choose to fill out their QOL form using the hardcopy form. The QOL forms completed via VTOC are identical to the hardcopy forms; this technology does not add to or change the QOL assessments in this study.

Following completion of baseline QOL forms, if the patient wishes to complete any of the subsequent QOL assessments online, the patient must have an e-mail address that they consent to use for this purpose. Patients' e-mail addresses are necessary so that e-mail reminders may be sent to them to remind them to fill out QOL forms that are due. The patient's e-mail address also will be used for password-protected access to VisionTree Optimal Care (VTOC), Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g.,Yahoo!, Hotmail, or AOL).

VTOC will send patients e-mail reminders to complete QOL forms. The first reminder will be sent at the beginning of the window for completion of the form, with a second reminder sent halfway through the window, if the form has not yet been completed. A maximum of 3 reminders will be sent for each of the 4 QOL assessment time points (subsequent to the baseline assessments). After the patient has completed all forms, a dialogue box will appear thanking the patient for completing the QOL form(s), and the patient will no longer receive reminders for that time point.

Site Research Associates (RAs) will receive training in the use of VTOC via NRG Oncology webinars and educational sessions. **Note: The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link https://rtog.optimalcare.com - medical team. RA login information will be provided by VTOC after the patient is randomized to the study. The patient's VTOC account must be set up within 14 days after randomization.** The RA or study administrator will be informed via the VTOC "At a Glance" form management system when QOL forms have been completed or when the window for a particular form has closed. If the site RA receives a notice that forms have not been completed, she or he will contact the patient to remind the patient to fill out the QOL form or inquire why the forms have not been completed. The RA will complete the cover page for each form that was not completed (either via VTOC or in hardcopy) and will submit the cover page (see Section 12).

The Performance Status Scale for Head and Neck Cancer (PSS-HN and the Work Status questions will be completed by the investigator and/or research associate at the following time points: at baseline, at completion of radiation therapy, and at 6, 12 and 24 months from the end of radiation. The Charlson Comorbidity Index (CCI) will be completed by the investigator and/or research associate at baseline only.

<u>The MD Anderson Dysphagia Inventory-Head and Neck (MDADI-HN)</u>
The MDADI will be the primary tool to assess swallowing-related QOL. The MDADI is a 20-item PRO instrument, scored on a scale from 1 to 5 (lowest to highest), consisting of global, emotional, functional, and physical subscales. The questionnaire can be completed by the patient in 5-10 minutes and is available in English, Spanish, Brazilian, and Portugese. The MDADI is the first validated self-administered questionnaire designed to measure the impact of dysphagia on the health-related QOL (HRQOL) of patients with head and neck cancer. Scores range from 0 (extremely low functioning) to 100 (high functioning). The score is further divided into a global score question, six

emotional quotient questions (score range 6–30), five functional quotient questions (score range 5–25) and eight physical quotient questions (score range 8–40).

The University of Washington Quality of Life Questionnaire, version 4 (UW-QoLv.4)
The UW-Qolv.4 will be used as a secondary tool to assess general QOL. Hassan and Weymuller of the University of Washington, Seattle, developed the University of Washington Quality of Life Questionnaire and first published in 1993 (Hassan). It has been validated and widely used since. This questionnaire was designed specifically to address problems incurred by head and neck cancer patients. The first scale consists of 20 questions on head and neck cancer symptoms that generate scores for 4 domains or dimensions of quality of life; communication, eating, pain, and emotional well-being. Global symptoms, disability attributable to head and neck cancer, and response to treatment also are assessed (Terrell 1998). It is a validated instrument that is available in English. In the original UW-QoLv.4 relevant domains were identified: Eating (6 items), Communication (4 items), Pain (4 items), and Emotion (6 items). Each had an internal consistency (Cronbach α value) of greater than 0.80. Construct validity was demonstrated by moderate correlations with SF-12 Physical and Mental component scores (r=0.43-0.60). Test-retest reliability for each domain demonstrated strong reliability between the 2 time points. Correlations were strong for each individual question, ranging from 0.53 to 0.93 (Terrell 1997). The questionnaire was tested on 75 head and neck cancer patients and was compared to 2 established tools, the Karnofsky Performance Scale (KPS) and the Sickness Impact Profile (SIP), for validity, acceptability, reliability, and responsiveness. The scores of the UW-QoLv.4 correlated well with the KPS and Sickness Impact Profile, indicating validity. The test-retest reliability coefficient was 0.95 (Hassan 1993). Normative data have previously been published (Lin 2003, Terrell 1997).

The UW-QoLv. 4 has undergone several improvements. Version 3 included 10 domain-specific questions focusing on physical symptoms, physical functioning, and social function. Specifically, the items address pain, appearance, activity level, recreation, swallowing, chewing, speech, shoulder function, taste, and saliva production. The most current version, Version 4, includes 2 additional questions about emotional function; the 2 specific questions address depression and anxiety (Weymuller 2001, Roges 2002). In addition to domain-specific items, both versions also include 4 generic QOL questions:

- What is your overall quality of life ('Global QOL')?;
- What is your *health-related* quality of life ("Global HR-QOL")?
- How has your health-related quality of life changed ("Transitional HRQOL", "Incremental HR-QOL")?
- Free text response to describe quality of life ("Open-ended QOL"). Patients have used this question as an opportunity to describe their QOL in their own words or in drawings.

The additional items of mood and anxiety have been tested against the Center for Epidemiology Studies Depression Scale (CES-D) and the Hospital Anxiety Depression Scale (HADS). The UW-QOLv.4 mood correlated with the scores and "case-ness" categories of the HADS depression and CES-D scales, whereas the UW-QOLv.4 anxiety correlated with the scores and "case-ness" of the HADS anxiety. Questions on mood and

anxiety can help identify significant psychological morbidity, taking a score of less than 75 for UW-QOLv.4 mood and less than 70 for UW-QOLv.4 anxiety (Rogers 2006).

Scoring of the UW-QoLv.4 can be found at http://depts.washington.edu/otoweb/research/head_neck_cancer/uw_qol_scoring_instructions.pdf.

Each of the domain-specific items is scored from 0 (worst QOL) to 100 (best QOL). The 'composite' score is created by averaging the scores from the 10 (version 3) or 12 (version 4) items. The 4 generic questions in the composite scoring are not included, because they represent different constructs. It is recommended that the questions on global QOL, global HR-QOL and transitional HR-QOL items be used independently as they provide different and useful perspectives from the composite score. Scoring of individual domain items range from 0 (worst QOL) to 100 (best QOL) for each item. Intermediate scores depend on the number of responses to each question: On 3 point items, scores are 0, 50, and 100. On 4 point items, scores are 0, 33, 67, and 100. On 5 point items, scores of 0, 25, 50, 75, and 100. For clarity, the scoring sheets list specific scores for each item response. The scoring sheet should not be used as the questionnaire.

The Performance Status Scale for Head and Neck Cancer (PSS-HN)
The PSS-HN will be an exploratory tool to compare clinician ratings of swallowing function between arms. The PSS-HN is a clinician-rated instrument consisting of 3 subscales: normalcy of diet, public eating, and understandability of speech. The PSS-HN has been psychometrically validated (List 1990) and recommended by the National Comprehensive Cancer Network for measurement of swallowing and speech performance in patients with head and neck cancer. The tool is used in an unstructured interview format. It is not a PRO; hence, investigators or research associates can complete it quickly without adding to patient burden.

Charlson Comorbidity Index (CCI)
Classically, head and neck cancer patients have a high burden of comorbidity, related in part to risk behaviors of smoking and alcohol use. In the HPV positive population, pre-existing comorbidities are expected to be lower compared to the HPV negative head and neck cancer population. The CCI (Charlson 1987) will be collected by chart extraction once at baseline to characterize the study cohort and assess comparability between the treatment arms. It is not a PRO; hence, it can be completed by investigators or research associates without adding to patient burden.

Employment/Work Status and Return to Work after Radiotherapy
An exploratory objective will be to determine the impact of radiotherapy de-escalation in HPV positive oropharyngeal cancer on the patient's work status before and after treatment. Descriptive statistics will be used to assess work status before and after treatment. Work status will be tested for associations with concurrent chemotherapy use, age, gender, marital status, education level, tumor factors and health related quality of life using the UW-QoLv.4.

The following questions regarding work status will be completed by the investigator and/or research associate on a case report form.

At Baseline and Follow Up
Q1. Which if the following best describes the patient's current work status?
(Select all that apply)
1 Currently working in at least one FULL time job
2 Currently working in at least one PART time job
3 Not working outside of the home
4 Student, full-time
5 Student, part-time
6 Not employed
7 On disability
8 On sick leave
9 Retired
10 Other, please specify_____
11 Don't know

Q2. How many hours a week does the patient work? ____ hours

Q3. Which of the following best describes the patient's primary income?
1 Salaried annual
2 Wages hourly
3 Self employed
4 Other specify _____

Method of payment (for health care received)
1. Private insurance
2. Medicare
3. Medicare and Private Insurance
4. Medicaid
5. Medicaid and Medicare
6. Military or Veterans sponsored
7. Self-Pay (No Insurance)
8. No means of payment
9. Unknown

10.3 FDG-PET/CT Imaging (5/24/16)

Patients must be offered the opportunity to consent to the optional FDG-PET/CT imaging. If the patient consents to participate, the site is required to submit the patient's post-treatment PET/CT scan and associated information, as specified in Section 10.3.3. Sites are not permitted to delete the imaging component from the protocol; however, it is acceptable for sites in Canada to remove the optional PET/CT scan from the sample consent if the site does not plan to participate in this component.

A post-therapy FDG-PET/CT scan is highly recommended at 12-14 weeks post-therapy

for assessment of response to therapy (see Section 2.5 for rationale and hypothesis). This scan is required for the patient to participate in this substudy.

If the patient's pre-therapy FDG-PET/CT scan is available, institutions are highly encouraged to submit this scan as well (see Section 10.3.3 below for details of submission).

10.3.1 Recommended FDG-PET/CT Imaging Sequence and Details

- Serum glucose must be measured (ideally within 1 hour of FDG administration).
- If the serum glucose concentration is found to be > 200 mg/dL, the study should be rescheduled. The referring physician or primary physician will be contacted to optimize blood glucose control.
- It is recommended that the PET/CT scan begin 60 minutes +/- 10 minutes after FDG injection.
- It is recommended that patients be imaged from the orbits through the upper thigh.
- A dedicated head and neck imaging acquisition (orbits to upper thorax) with the patient's arms down is recommended given the higher sensitivity of this exam. The remainder of the body is to be scanned with the patient's arms raised over the patient's head. If patients cannot tolerate these positions for the PET/CT scan, investigators can use different patient positioning.
- A low-dose CT scan is required for attenuation correction and anatomical localization of findings in the PET scan.
- The acquisition parameters for the dedicated head and neck CT, low-dose CT scan must be approximately as follows: kV = 120; effective mAs = 90-150 (patient dependent, auto current modification acceptable); gantry rotation time < 0.5 sec; maximum reconstructed slice width = 2.5 mm (overlap acceptable); standard reconstruction algorithm, maximum reconstruction diameter = 30 cm; and without iodinated contrast.
- The acquisition parameters for the low-dose CT scan for attenuation correction must be approximately as follows: kV = 120; effective mAs = 30–80 (patient dependent, auto current modification acceptable); gantry rotation time < 0.5 sec; maximum reconstructed width = 3–5 mm without overlap; standard reconstruction algorithm, minimum reconstruction diameter = outer arm to outer arm; and without iodinated contrast.
- The axial field of view of the CT scan for attenuation correction will range from the mid thighs to the base of the skull. Arm positioning will be the same as for the PET scan (see above).
- The CT scan will be performed during the patient's normal breathing. No respiratory gating is needed.
- After the CT scan, a PET scan covering the same axial field of view will be performed. This scan will start at the upper thighs. The number of bed positions and the acquisition time per bed position will be scanner specific. Typical parameters are 6 bed positions and an acquisition of 2 to 5 minutes per bed position. The dedicated head and neck PET/CT will typically follow the body exam. Two bed positions will often suffice for orbits to upper thorax (top of aortic arch), and acquisitions must be at a minimum of 6 minutes per bed position and be reconstructed into a 30 cm field of view (FOV) with a 256 x 256 matrix.

- Additional diagnostic-quality CT of the neck may be performed with contrast if needed to fulfill requirements for anatomic post-treatment imaging.

10.3.2 FDG-PET/CT Image Reconstruction

The PET/CT data will be corrected for dead time, scatter, randoms, and attenuation using standard algorithms provided by the scanner manufacturers. For the dedicated head and neck views, a post-filter with a full-width at half maximum (FWHM) in the range of 5 mm is recommended.

10.3.3 Submission of FDG-PET/CT Image and Site Read

- Following the completion of PET/CT imaging at the site, the institution will submit images in DICOM format via TRIAD to IROC Imaging; see Section 8.3.1 for details regarding TRIAD.
- Institutions must submit a case report form (CRF) for each PET/CT image in which a site reader characterizes the patient's therapy response using the 5-point scale outlined in Section 2.5 (i.e. the local site read).

10.3.4 FDG-PET/CT Central Image Evaluation

- Rapid review process: For the first 3 patient cases with post-treatment PET/CT imaging submitted by an enrolling center, these images will be evaluated with central rapid review by the Imaging Co-Chairs to ensure consistency in the application of the scoring system and provide feedback to the local site, if advisable. Subsequently, central rapid review only will be conducted based on CRFs indicating an indeterminate or positive read by the local site.
- For study purposes, PET/CT images will be retroactively interpreted by an NRG Oncology Imaging Core Panel (NRGICP) of expert PET/CT readers who will have no involvement or knowledge of the participant's clinical care and who will be blinded to the participant's diagnosis, local PET/CT scan results, and clinical history. No NRGICP readers can be site investigators at the site producing the PET/CT scans and local site reads (characterization of patient response). NRGICP readers will be shown a group of 10 cases for training purposes. Feedback on each of these training cases will be provided prior to reading the HN002 patients' PET/CT scans.
- NRGICP readers will be provided with a case report form (CRF) that details—in a standardized manner—basic patient demographics that include age, gender, height, and weight. Readers will be instructed to characterize the therapy response using the 5-point scale outlined in Section 2.5.
- Each PET/CT scan will be evaluated independently by 3 NRGICP PET/CT readers.

10.4 Determining the Extent of Dysphagia using the Modified Barium Swallow (5/24/16)

10.4.1. Long-term swallowing outcomes will be measured at selected sites using modified barium swallow (MBS) studies according to the assessment schedule in Section 4 (baseline and 24 months ± 3 months after the end of radiotherapy) and the instructions provided in the Modified Barium Swallow Study Form.

Participating institutions must complete the the MBS Credentialing Checklist prior to enrolling patients on this substudy and must follow the instructions for the MBS and submission of the MBS video in Appendix II. Facilities unable to participate in the MBS assessments may still enroll patients on the main study, NRG-HN002, without participating in the swallowing evaluations.

11. MODALITY REVIEWS

11.1 Radiation Therapy Quality Assurance Reviews

The Principal Investigator, Sue S. Yom, MD, PhD, and the Radiation Oncology Co-Chairs, Jimmy J. Caudell, MD, PhD, and John Waldron, MD, will perform RT Quality Assurance Reviews after cases enrolled have been received at IROC Philadelphia RT. The RTQA reviews will be ongoing, and will be facilitated by IROC Philadelphia RT.

The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of radiotherapy treatment data as specified in Section 12.2. The scoring mechanism is: Per Protocol, Variation Acceptable, and Deviation Unacceptable.

11.2 Drug Quality Assurance Reviews

The Medical Oncology Co-Chairs, Maura Gillison, MD, PhD, and Michael Gibson, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 13. The scoring mechanism is: Per Protocol/Acceptable Variation, Unacceptable Deviation, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Drs. Gillison and Gibson will perform a Quality Assurance Review after NRG Headquarters has received complete data for the first 20 cases enrolled. Drs. Gillison and Gibson will perform the next review after NRG Headquarters has received complete data for the next 20 cases enrolled. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

12. DATA AND RECORDS (5/24/16)

12.1 Data Management/Collection (20-DEC-2017)

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). 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.
Each person responsible for data entry must be on the NRG roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. 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. Once an account is activated, eLearning modules will be available for Rave RDC instructions. 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 also will 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 www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7.0 for information about expedited and routine reporting.

For reporting of secondary cancers or other report forms available in Rave:
Indicate form for reporting in Rave, timeframes, add if loading of the pathology report is required.

Summary of Data Submission

Folder	Form/Item
Registration via the OPEN System	• ***Subject Enrollment Form***
Enrollment When pushed into RAVE there will be 5 forms representing registration	• ***Step Information*** • ***Treatment Assignment Form*** • ***Demography*** • ***Eligibility Checklist Form*** • ***Eligibility Checklist 2 Form***
p 16 CRF	• ***p 16 CRF- to be completed prior to Step II registration***
Baseline	• ***Work Up*** • ***Lab Results Baseline*** • ***Patient History Form*** *(formerly known as the A5)* • ***Protocol Specified AE Form*** • ***MDADI Coversheet*** • ***MDADI- if questionnaire completed = 'yes'***

	• ***CCI*** • ***PSS-HN Coversheet*** • ***PSS-HN- if questionnaire completed = 'yes'*** • ***Work Status***
RT Upload	• ***Digital Data****-(Refer to section 12.3)*
End of RT	• ***RT Administration*** • ***RT Treatment-****if was radiation therapy given = 'yes'* • ***Protocol Specific RT Form-****if was radiation therapy given = 'yes'* • ***Cisplatin (Arm 1 only)*** • ***Supportive Care*** • ***Hospitalization*** • ***Follow-up Head and Neck*** • ***Protocol Specified AE Form*** • ***Other Adverse Event Forms****– if new or continuing adverse events = 'yes'* • ***MDADI Coversheet*** • ***MDADI- if questionnaire completed = 'yes'*** • ***PSS-HN Coversheet*** • ***PSS-HN- if questionnaire completed = 'yes'*** • ***Work Status***
Concurrent Labs	• ***Lab Units Pre-Rx, week 1-6*** *(During Treatment Labs)* • ***Lab Results Follow Up*** *(During Treatment Labs)*
MONTH 1 (Post RT) Arm 1 & 2 MONTH 3 (Post RT) Arm 1 & 2 MONTH 6 (Post RT) Arm 1 & 2 MONTH 9 (Post RT) Arm 1 & 2 MONTH 12 (Post RT) Arm 1 & 2 MONTH 15 (Post RT) Arm 1 & 2 MONTH 18 (Post RT) Arm 1 & 2 MONTH 21 (Post RT) Arm 1 & 2 MONTH 24 (Post RT) Arm 1 & 2 MONTH 30 (Post RT) Arm 1 & 2 MONTH 36 (Post RT) Arm 1 & 2	• ***Patient Contacted*** • ***Follow-up-*** *if Patient able to be Contacted ='yes'* • ***Follow-up Head and Neck*** *-if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer= 'yes'* • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form-*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death- –*** *if Patient's Vital Status = 'dead'* • ***Salvage surgery-*** *if salvage surgery= 'yes'*

MONTH 42 (Post RT) Arm 1 & 2 MONTH 48 (Post RT) Arm 1 & 2 MONTH 54 (Post RT) Arm 1 & 2 MONTH 60 (Post RT) Arm 1 & 2 Year 6-15 Arm 1 & 2	• ***MDADI Coversheet**** • ***MDADI- if questionnaire completed = 'yes'**** • ***PSS-HN Coversheet**** • ***PSS-HN- If questionnaire completed = 'yes'**** • ***Work Status**** ** These quality of life forms will appear in Month 6 (Post RT), Month 12 (Post RT) and Month 24 (Post RT)*
Source Documentation Upload	• ***Source Documentation Upload-*** *used by site in the event that source documentation needs to be uploaded to HQ*
FDG-PET/CT Imaging Image submission forms will appear in the following folders if the patient has consented to the Optional Imaging Study. ***(Note: Institutions will submit images in DICOM format via TRIAD to IROC Imaging, refer to section 8.4.1.)*** • Baseline • Month 3 (Post RT) Arm 1 & 2	• ***Scan submission*** • ***SOC imaging form*** • ***Site Interpretation of PET/CT **** ** This form only appears if the Scan submission form is submitted and 'Was the Site Interpretation form completed' was answered as YES.*
Quality of Life Coversheets will appear in the following folders if the patient has consented to the Quality of Life Component: **<u>UW-QOL</u>** • Baseline • Completion of RT • 6 months from end of RT • 12 months from end of RT • 24 months from end of RT •	• ***UW QOL Coversheet*** • ***UW-QOL**** **These quality of life forms only appear if the corresponding cover page is submitted and 'Was the patient questionnaire completed' was answered as YES.*
MBS CRF will appear in the following folders if the patient has consented to the modified barium swallowing study:	• ***MBS***

• Baseline • Month 24	

12.3 Digital Data Submission Requirements (20-DEC-2017)

Summary of Dosimetry Digital Data Submission

Submit Digital RT Data via TRIAD; see Section 8.3.1 for TRIAD account access and installation instructions. **Item**		**Due**
Arm 1 and Arm 2		
DICOM Items	DICOM CT Image	**Within 1 week of start of RT**
	DICOM Structure	
	DICOM Dose	
	DICOM RT Plan	
All required structures must be labeled per the tables in Section 5.2		
HN002 DVH Analysis Worksheet to be submitted via TRIAD with RT Digital Data listed above is located on the CTSU web site, www.ctsu.org, on the NRG-HN002 protocol page.		
Upon submission of the digital data via TRIAD, complete an online **Digital Data Submission Information Form (DDSI):** https://www.irocqa.org/Resources/TRIAD-for-RT-QA		
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.		

12.4 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

13.1.1 Stratification

Patients will be stratified by radiotherapy planning (Unilateral vs. Bilateral), based on the investigator's decision to place the patient into one of the two groups described in Section 5.2 and the investigator's pre-randomization declaration of the type of treatment that will be used (Unilateral vs. Bilateral).

13.1.2 Randomization

Patients will be randomized to each arm using a randomized permuted blocked design.

13.1.3 Total Accrual

296 patients

13.2 Study Endpoints

13.2.1 Primary Endpoint

Progression-free survival (PFS) at 2 years

13.2.2 Secondary Endpoints

- Local-regional failure at 6 months and 2 years;
- Distant metastasis at 6 months and 2 years;
- Overall survival at 6 months and 2 years;
- Acute toxicities (≥ grade 3, CTCAE, v. 4) at the end of radiation therapy and at 1 and 6 months;
- Late toxicities at (≥ grade 3, CTCAE, v. 4) 1 and 2 years;
- Patient-reported swallowing outcomes at 6 months and 1 and 2 years;
- Post-treatment FDG-PET/CT;
- Translational research.

13.3 Primary Objectives Study Design

13.3.1 Primary Hypothesis and Endpoints

For patients with p16 positive, locoregionally advanced oropharyngeal cancer who have a smoking history of ≤10 pack-years, a program of reduced-dose radiation therapy (given either in combination with concurrent radiosensitizing cisplatin or in modestly accelerated fractionation) will achieve a 2-year progression-free survival (PFS) rate of ≥ 85%, without unacceptable swallowing toxicity.

13.3.2 Definitions of Primary Endpoints and How These Will Be Analyzed

Progression free survival is defined as from time of randomization to local- regional failure, distant metastasis, or deaths due to any causes. PFS rates will be estimated for all treatment arms using the Kaplan-Meier method (1958). One sample binomial test will be used to test the 2-year PFS for each arm. Multivariate analysis will be performed using the Cox proportional hazards model.

13.3.3 Sample Size and Power Calculations:

The estimated 2-year PFS for this population is 91% based on the eligible population of patients on the 2 arms of 0522 (N=65 available patients) at this time. If the 2-year PFS is less than 85%, we will consider it unacceptable. So, the null hypothesis for this study is: Neither arm achieves a 2-year progression-free survival (PFS) rate of ≥ 85%. The alternative hypothesis is: One or both arms result in a 2-year progression-free survival (PFS) rate of > 91%. With one-sided type I error rate of 10% and 80% power, we would need 140 analyzable patients per arm.

All head and neck cancer trials must account for post-randomization attrition. In RTOG 1016, patients were not randomized for the following reasons: 5.3% not p16 positive; 5.2% patient refusal; 1.2% physician preference; 0.4% disease progression; 0.4% failure to submit tissue assay; and 2.5% for other reasons. In addition, 3.5% of patients were determined ineligible after randomization and 0.5% were randomized but did not receive any protocol therapy.

For this trial, since p16 is tested prior to registration, we anticipate lower loss due to lack of tissue or improper p16 determination, since that should be better controlled through

central review prior to randomization. p16 positive patients may be preference-sensitive about the arm to which they are randomized. Thus, we estimate there will be 5% loss of patients due to the reasons of “not p16 positive" and "patient refusal” pre-randomization in this study.

The stated sample size for NRG-HN002 must be adequate to provide an analyzable cohort of 280 patients. Assuming 5% loss post-randomization, we must enroll 296 patients to be randomized. We project a total pre-randomization loss of 10% for potential withdrawal of consent related to physician or patient refusal, not p16 positive, or progression of disease, failure to submit tissue assay, and other reasons, so we expect to enroll 328 patients to get the required number of patients to be randomized.

The rationale for the <85% unacceptable rate for 2-year PFS is as follows: The estimated 2-year PFS for this group of selected patients with p16 positive tumors is 91%, based on estimates derived from patients in RTOG 0522. If we set an unacceptable rate of 88% (3% difference from the expected outcome), the trial would require 500 analyzable patients per arm (1000 analyzable patients total) to conduct this phase II study. This was deemed less feasible based on the required number of patients and cost. If we set an unacceptable rate of 86% (5% difference from the expected outcome), then the trial would require 200 analyzable patients per arm (400 analyzable patients total). The number of patients required is more feasible but is still quite large for a 3-arm phase II study, in order to achieve only a 1% difference from 85%. If we set an unacceptable rate of 85% (6% difference from the expected outcome), then the trial would require 140 analyzable patients per arm (280 analyzable patients total). At this time, based on the projected rate of accrual, this was considered the most feasible scenario to accomplish in a reasonable timeframe and forms the basis of the current proposal.

13.4 Study Monitoring of Primary Objectives

Planned Interim Safety Analysis with Early Stopping Rules

At 6 months, the estimated PFS for the eligible group of patients from RTOG 0522 is 94%. With 95% two-sided confidence and a lower limit of 85% PFS, we plan to enroll 40 analyzable patients for each arm to be followed for 6 months. After these patients have been enrolled and followed for 6 months, the interim analysis will take place. The stopping rule corresponds to a number of 6 or more progressions within the first 40 patients at 6 months of follow up.

The interim analysis time will be 1.56 years from the start of the study (6 months for site IRB approval, 0.56 years for accrual, 6-month follow up). If 1 arm has more than specified number of progressions, then we will suspend the arm and a panel review will be called to decide on next steps, including closing accrual to the arm. The trial will continue to accrue during that 6 month observation period, after 40 patients/arm have been enrolled, until adequate follow up is obtained for interim analysis.

With the 2-arm design, the expected number of PFS events serving as a cut off among the 140 analyzable patients is 15 or fewer events on each arm to reject the null hypothesis and the cut off number of events for the interim analysis is 6 among the 40 analyzable

patients.

Monitoring of Study Progress for Quality of Life
NRG Oncology will prepare reports twice a year to follow compliance with required quality of life data collection. Data that is missing will be requested from enrolling institutions at each reporting time point. Further corrective action may be taken by the Study Chairs if an institution is noted to have >30% non-compliance with quality of life data collection.

Routine Interim Analysis to Monitor Study Progress
Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. These reports will contain information about the accrual rate, pretreatment characteristics of patients accrued, and the frequency and severity of adverse events.

Interim Analysis for the DMC
The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

13.5 Accrual Considerations

13.5.1 Accrual Rate
The accrual rate is estimated to be 15 patients per month.

13.5.2 Accrual Goal
The total sample size is 296 patients.

13.5.3 Study Duration
Trial accrual is projected to take 1.94 years. Allowing 6 months for site IRB approval and 2 years of follow up, the trial is estimated to take a total of 4.5 years.

13.5.4 Estimated Duration for Completion of Primary Endpoint:
Trial accrual is projected to take 1.94 years. Allowing 6 months for site IRB approval and 2 years of follow up, the trial is estimated to take a total of 4.5 years.

13.6 Secondary/Correlative Elements

13.6.1 How Secondary Endpoints Will Be Analyzed
For the secondary endpoints listed in Section 13.2.2, OS rates will be estimated using the Kaplan-Meier method (1958) and the failure rates for the experimental treatment will be compared against the control using a log rank test. The cumulative incidence method will be used to estimate locoregional and distant failure rates and the failure rates for the experimental treatment will be compared against the control using a failure specific log rank test. Failure for local-regional failure and distant metastasis endpoints is as follows:

First event	Local-regional failure	Distant metastasis
None	Censored	Censored
Local-regional progression or recurrence	Failure	Competing risk
Distant metastasis	Competing risk	Failure
Death due to study cancer or unknown	Failure	Competing risk

causes		
Death due to any other reason	Competing risk	Competing risk
Salvage surgery of primary with tumor present/unknown	Failure	Competing risk
Salvage neck dissection with tumor present/unknown, > 20 weeks from end of RT	Failure	Competing risk

Multivariate analysis will be performed using the Cox proportional hazards model.

Rates of Adverse Events (≥ grade 3, CTCAE, v. 4) for acute and late toxicities will be estimated using a binomial distribution along with their associated 95% confidence intervals and will be compared using Fisher's exact test between the 2 treatment arms.

13.6.2 Quality of Life (QOL)

The primary QOL endpoint will measure the mean individual change in total MDADI score at 1 year from baseline with the goal of detecting a ≥ 5 point difference between the 2 arms.

In the table below, we have outlined our decision making process of interpreting the phase II data with regards to PFS and QOL in order to proceed to a future phase III trial. PFS will be the primary decision making endpoint, with QOL using the comparison of mean change in MDADI score in each arm from baseline to inform the subsequent choice of one or more arms to proceed to a phase III trial.

If a PFS of ≥ 85% is not reached for any of the arms, regardless of the QOL outcome, none of the therapy regimens will move forward to a phase III study.

If 1 or both of the arms reach ≥ 85% PFS, the swallowing-related QOL endpoint of 1 year mean total MDADI score must be clinically acceptable of ≥ 60, in order to move forward into a phase III trial. That is, if the MDADI results for an arm are not clinically acceptable (mean total MDADI score at 1 year < 60), then that arm will not proceed to phase III testing, regardless of PFS results.

PFS	Long-term Swallowing-Related QOL (MDADI at 1 year)	Decision Algorithm
Only one arm achieves ≥ 85% PFS	Arm selected on the basis of PFS, *and* without unacceptable dysphagia as measured by MDADI. MDADI results for the "superior" arm must be clinically acceptable (mean total MDADI score at 1	The arm meeting the PFS cutoff with acceptable swallowing outcome, measured by mean total MDADI results of ≥ 60 at 1 year, proceeds to phase III; will be compared to other approaches, such as primary surgery or 70 Gy + concomitant

	year ≥ 60)	cisplatin chemotherapy
Two arms achieve ≥ 85% PFS; one statistically superior	Arm selected on the basis of PFS, *and* without unacceptable dysphagia as measured by MDADI. MDADI results for the "superior" arm must be clinically acceptable (mean total MDADI score at 1 year ≥ 60)	The arm with statistically superior PFS and acceptable swallowing outcome, measured by mean total MDADI of ≥ 60 at 1 year, results proceeds to phase III; will be compared to other approaches, such as primary surgery or 70 Gy + concomitant cisplatin chemotherapy
Two arms achieve ≥ 85% PFS; statistically not different	One arm is deemed "inferior" only if (1) its MDADI mean change score from baseline to 1 year shows a statistically significantly difference from the other arm; (2) a between-arms difference of at least 5 points is observed; and (3) the "inferior" arm shows a within-group decline of 5 points or more from baseline *and* MDADI results are clinically acceptable for the "superior" arm (mean total MDADI score at 1 year ≥ 60)	The arm with "superior" QOL proceeds to phase III; will be compared to other approaches, such as primary surgery or 70 Gy + concomitant cisplatin chemotherapy
Two arms achieve ≥ 85% PFS; statistically not different	Any conditions other than those described in the row above (e.g. no difference in harm is demonstrated between arms), and MDADI results are clinically acceptable for both arms (mean total MDADI score at 1 year ≥ 60)	Both arms move to phase III*

*If PFS and QOL are both acceptable and comparable, and neither arm has MDADI results that can be deemed "inferior" or "clinically unacceptable," then both arms may move forward for further testing in a phase II or III trial.

If PFS goals are met by both arms, and the MDADI results are stable or improved in one or both arms, then decision making will proceed as follows. If the MDADI data shows:

- Stability or improvement in 1 arm at 1 year from baseline, and the other arm shows a within-group decline of 5 points or more from baseline, then the arm which shows stability or improvement will proceed to a phase III.

- Stability or improvement in 1 arm at 1 year from baseline, and the other arm shows a within-group decline of less than 5 points from baseline, and there is at least a 5 point difference between arms which is statistically different, the better arm will proceed to a phase III.
- Stability or improvement in 1 arm at 1 year from baseline, and the other arm shows a within-group decline of less than 5 points from baseline, and there is less than a 5 point difference between arms or the difference between arms is not statistically different, both arms will proceed to a phase III.
- Improvement or stability in both arms, with or without a statistical difference, then both will be considered for a phase III study.

The table below shows statistical power for detecting potential PFS differences between 2 arms. For example, if the 2 arms have 2-year PFS of 85% and 92.5%, based on a two-sided log rank test (hypothesis generating) with a type I error rate of 0.1/0.2 and 140 analyzable patients in each arm, we will have 84%/91% power.

	85%	87.5%	90%	92.5%	95%	97.5%
85%		20%/32%	51%/65%	84%/91%	98%/99%	>99%/99%
87.5%			22%/27%	57%/56%	90%/84%	>99%/99%
90%				25%/38%	67%/79%	96%/98%
92.5%					31%/44%	82%/90%
95%						43%/58%

With an effect size of 0.333, an expected mean change in individual MDADI score between the 2 arms of ≥ 5 (and SD estimated to be between 15 [Gillespie 2004]) at 1 year from completion of radiation, and a two-sided, two-sample independent t-test (hypothesis generating) with alphas of 0.2, the table below shows statistical power for various rates of attrition (including 12% from French-speaking Canadian sites); for example, we will have 80% power to detect a 5 point difference for MDADI scores between 2 arms. If PFS is better for one arm but not significant, then this difference between the arms in the mean change in MDADI scores will be used to select the best arm for phase III.

	Effect size = 0.333
All cases (n=280)	93%
40% attrition (n=168)	80%
50% attrition (n=140)	75%

The mean summary score of the MDADI, PSS-HN, and CCI and the MDADI subscales including the physical, functional, and emotional domains will be determined. The mean change from baseline at each time point will be summarized using mean and standard deviations for each arm. Mean score and mean change from baseline will be compared between the arms using a two-sample t test. If data normality assumptions are not met,

the Wilcoxon rank sum test will be used to test the hypothesis. Mean change from baseline will be tested using an omnibus F test followed by individual comparisons of change scores at different time points within each treatment group. The same analysis will be conducted for between group comparisons at each time point. Overall trends for the MDADI scores and subscale scores could be modeled using the general linear mixed-effect model. This model will be used to compare the differences of scores over time between the 2 arms and to compute least squares mean and SEs, including clinical variables and treatment by visit interaction terms. The model also allows for adjustments using stratification variables (unilateral vs. bilateral radiotherapy) and other covariates of interest. The use of general linear mixed modeling allows flexibility in analyzing data with missing responses. To handle poor compliance and missing data, efforts will be made to minimize attrition due to avoidable factors. To assess the missing data mechanism, we will compare possible differences between patients who dropped out of the study against those who remained in the study with respect to imbalance factors such as treatment, baseline scores, clinical, and demographic data. We will undertake sensitivity analyses to investigate reasons for missingness (e.g. by drop-out), considering various factors as mentioned earlier. A logistic regression model will be used to summarize number of missing data and to test if the dropout process is missing completely at random (MCAR). Analysis of complete cases and cases with multiple imputations for missing observations (before death or progression) will be done to check robustness of the main results. Correlation between MDADI and dysphagia as well as other variables will be calculated using Spearman's correlation coefficient and the corresponding p values will be reported. Correlation between categorical measures will be summarized by odds ratios, chi square tests, and associated measures. Adjusted correlation may be derived from ANCOVA models or derived directly using nonparametric ANOVA models if normality assumption is violated. If comparison to historical control is needed, a one-sample t test will be utilized. Binary endpoints will be compared using Fisher's exact test.

13.6.3 FDG-PET/CT Imaging as a Predictive Imaging Marker for Locoregional Control and Progression-Free Survival

Primary endpoint: Determine the Negative Predictive Value (NPV) of FDG-PET/CT, performed at 12-14 weeks post-therapy, for locoregionally advanced oropharyngeal cancer treated with (chemo) radiation therapy for PFS at 2 years.

Of the 280 evaluable patients, we anticipate that 140-180 (approximately one half to two thirds) of them will undergo 12-14 weeks post-therapy PET/CT. We assume that approximately 75-80% of total available FDG-PET/CT scans will be negative, 11-12% positive, and 8-14% indeterminate.

NPV is then the proportion of PET-negative patients that remain progression-free at 2 years. The power is calculated to reject the null hypothesis of <90% and an alternative hypothesis of 95% using a one-sided binomial test at a significance level of 0.10. With a total of 140 available scans, which indicates 105-112 PET-negative patients, the statistical power is 76-77% and if the total number of scans is 180 and 135-144 PET-negative patients, we will have 83-85% power to reject the null hypothesis regarding the

negative predictive value.

13.6.4 HPV DNA As a Potential Marker for Relapse

For Hypothesis 1, with a two-sided type error rate of 5% and based on chi-squared test for proportions, we have greater than 99% power to detect HPV DNA detection rate of 65% and 95% between the 2 groups (n=140 in each arm). The rate of detection for each group will be summarized based on binomial distributions and a 95%CI will be provided.

For Hypothesis 2, correlation between HPV DNA copy number and the nodal metabolic volume (nMTV) will be calculated using Spearman's correlation coefficient and R2, and the corresponding 95%CI will be provided.

For Hypothesis 3, first, with a two-sided type error rate of 5% and based on paired t test for means, we have 99% power to detect HPV DNA rate decline of 0.375 (effect size) within each arm (n=140). The HPV DNA rate for each group will be summarized using means and standard deviations.

For Hypothesis 3, second, assuming 5%, 6%, 7%, 8% LRF for two-year PFS of 91%, 89%, 87% and 85%, the following tables show statistical power for detecting various hazard ratios. For example, if the variance for HPV DNA is 15 and the two-year PFS is 89%, then we will have 80% power to detect a hazard ratio of 1.20 with 3 arms combined. Univariable and multivariable cause specific analysis will be performed using the Cox proportional hazards model for rate of relapse. Potential covariates evaluated for the multivariate models would be treatment, age, Zubrod performance status, T-stage, N-stage, smoking history, other risk behaviors.

Statistical power to detect various hazard ratios, continuous variable, 2 arms combined 2-year PFS 91%, 14 locoregional failure events, 2-sided 0.05

	Hazard Ratio				
Variance	1.01	1.05	1.10	1.15	1.20
5	0.03	0.06	0.12	0.21	0.33
10	0.03	0.08	0.20	0.37	0.57
15	0.03	0.10	0.28	0.52	0.75
20	0.03	0.12	0.35	0.64	0.86
25	0.03	0.14	0.42	0.74	0.92

Statistical power to detect various hazard ratios, continuous variable, 2 arms combined 2-year PFS 89%, 17 locoregional failure events, 2-sided 0.05

	Hazard Ratio				
Variance	1.01	1.05	1.10	1.15	1.20
5	0.03	0.06	0.13	0.25	0.39
10	0.03	0.09	0.23	0.44	0.66
15	0.03	0.11	0.33	0.60	0.82

	Hazard Ratio				
Variance	1.01	1.05	1.10	1.15	1.20
20	0.03	0.14	0.41	0.73	0.91
25	0.03	0.17	0.50	0.82	0.96

Statistical power to detect various hazard ratios, continuous variable, 2 arms combined 2-year PFS 87%, 20 locoregional failure events, 2-sided 0.05

	Hazard Ratio				
Variance	1.01	1.05	1.10	1.15	1.20
5	0.03	0.07	0.15	0.28	0.44
10	0.03	0.10	0.27	0.50	0.73
15	0.03	0.13	0.37	0.67	0.88
20	0.03	0.16	0.47	0.79	0.95
25	0.04	0.19	0.56	0.87	0.98

Statistical power to detect various hazard ratios, continuous variable, 2 arms combined 2-year PFS 85%, 22 locoregional failure events, 2-sided 0.05

	Hazard Ratio				
Variance	1.01	1.05	1.10	1.15	1.20
5	0.03	0.07	0.16	0.31	0.48
10	0.03	0.10	0.29	0.54	0.77
15	0.03	0.14	0.40	0.71	0.91
20	0.03	0.17	0.51	0.83	0.96
25	0.04	0.20	0.60	0.90	0.98

PI3K Pathway Activation and Its Associated Genomic Profile as Prognostic Biomarkers of HPV Related Oropharyngeal Cancer

The predictive and prognostic potential for these proposed biomarkers may become scientifically obsolete or the assay technology may evolve over time, making the technology outlined in the current protocol obsolete when the study is finished. As such, no marker assays will be reviewed on the collected specimens other than those required for patient selection (i.e. p16 immunohistochemistry). When sufficient information is available from the parent study, a full correlative study protocol for the marker studies detailing the scientific hypothesis, research plan, assay methods for each biomarker, and a complete statistical section (with adequate power justification and analysis plan) will be submitted and subjected to CTEP review in accordance with the National Clinical Trials Network (NCTN) policies.

13.6.5 Determining the Extent of Long-Term Dysphagia Using MBS **(5/24/16)**

Primary endpoint: Determine the risk of grade ≥3 MBS-detected dysphagia 2-years after de-escalated IMRT.

Of the 90 evaluable patients, we anticipate that 63-72 (approximately 20-30% attrition) will complete the 2 year MBS. We expect <20% of patients will have DIGEST grade ≥3 (severe) MBS-detected dysphagia at 2 years. No life threatening dysphagia (DIGEST grade 4) is expected.

Exploratory analyses of MBS arm will include:

- Concordance/discordance of perceived dysphagia (per PRO instrument – MDADI) with MBS detected dysphagia (per DIGEST)
- Develop predictive model for DIGEST grade ≥3 MBS detected dysphagia 2 years after de-escalated radiotherapy per age, tumor characteristics, treatment parameters (including use of concurrent chemotherapy), early toxicity profiles (clinician and provider graded)

13.7 Gender/Ethnicity/Race Distribution

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	9	10
Not Hispanic or Latino	28	258	286
Ethnic Category: Total of all subjects	29	267	**296**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	1	1
Asian	1	0	1
Black or African American	2	12	14
Native Hawaiian or other Pacific Islander	0	1	1
White	26	253	279
Racial Category: Total of all subjects	29	267	**296**

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APPENDIX I: DENTAL TOOTH COUNT AND DENTAL MANAGEMENT (5/24/16)

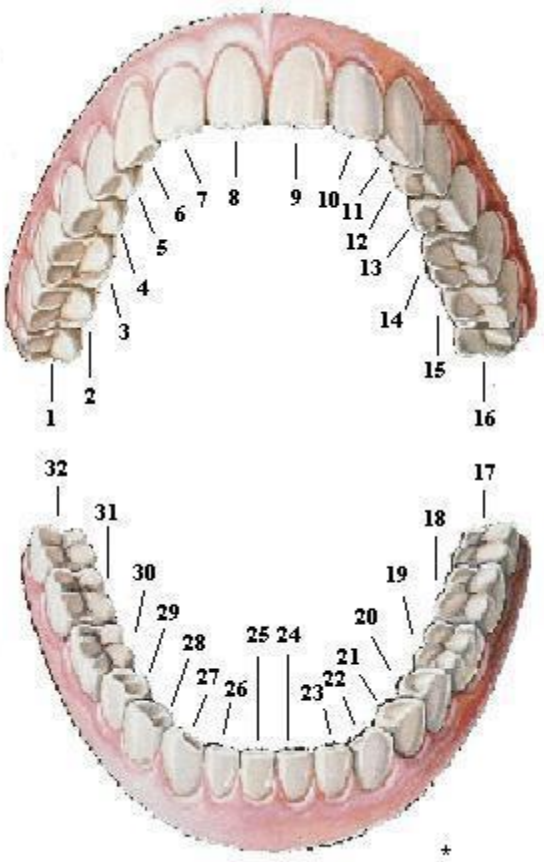
Dental Tooth Count Diagram

Use the diagram below as a guide to count the number of native teeth in place, not including full or partial dentures or bridges.

The exact location of teeth does not need to be recorded, only the total number of native teeth in place (attached to bone in mandible or maxilla) on the day of evaluation.

This exam should be completed by a physician or designee, such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist.

Date of evaluation: Total number of native teeth in place (0-32):



APPENDIX I (Continued)

Dental Effects Health Scale

0 Normal: Edentulous, with no gingival disease; native teeth in place with gingiva in excellent condition.

1 Mild changes/good dental health: mild periodontal inflammation-routine cleaning indicated; < 5 restorations indicated; no extractions indicated.

2 Moderate/fair dental health: moderate periodontal inflammation; deep periodontal cleaning indicated; 6 or more restorations indicated; less than full mouth extractions indicated.

3 Severe changes in dental health: widespread periodontal disease with extensive procedure/surgery indicated; full mouth extractions indicated.

4 Life-threatening dental condition: extensive abscess, extensive soft issue or bone infection, sepsis; urgent intervention indicated.

APPENDIX I (Continued)

Management of Dental Problems in Irradiated Patients

Goals for a dental care program include:
1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures
The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

- Group 1: Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

- Group 2: Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

  Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

- Group 3: Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth that are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

- Group 4: Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth

If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results

In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay

Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth

Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments. Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections

Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis

The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including: impairment of normal metabolism, increased susceptibility to infection and severely limited repair process. Bone necrosis occurs most often after dental or oral surgery in patients who have been previously radiated. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX II: INSTRUCTIONS AND FORMS FOR THE MODIFIED BARIUM SWALLOW (MBS) SUBSTUDY (5/24/16)

Prior to enrolling patients to this substudy, sites must complete the NRG-HN002 MBS Credentialing Checklist (see below). The institution will e-mail the completed form to Martha Portwood, MPH, mportwood@mdanderson and will receive a letter of instruction confirming that the site is approved to enroll patients in the substudy. Institutions should allow adequate processing time (10-14 days) before enrolling the first patient on this substudy.

Facilities must use a standardized contrast medium (Varibar® thin liquid and pudding contrast, Bracco Diagnostics, Inc. Princeton, NJ, or comparable in Canadian centers) and digitally record MBS studies (30 frames/second, although a minimum of 15 frames/second is acceptable if this is made clear at the time of credentialing). DIGEST grades will be assigned by the site Speech-Language Pathologist conducting the MBS study and reported by research staff on the Modified Barium Swallow Study Form as: 0 “normal”, 1 “mild”, 2 “moderate”, 3 “severe”, or 4 “life threatening”.

Participating sites are required to perform MBS studies as specified on the Modified Barium Swallow Study Form (below) and then upload the MBS video to the TRIAD (Transfer of Images and Data) application, as specified below, for central review and scoring. The percent of patients with scores of 0, 1, 2, 3, and 4 dysphagia per MBS will be compared at baseline and 24 months (+/- 3 months) from end of radiation.

Questions related to conduct of MBS studies can be directed to:
Martha Portwood, MPH
University of Texas MD Anderson Cancer Center
Phone: 713-792-6364
E-mail: mportwood@mdanderson.org

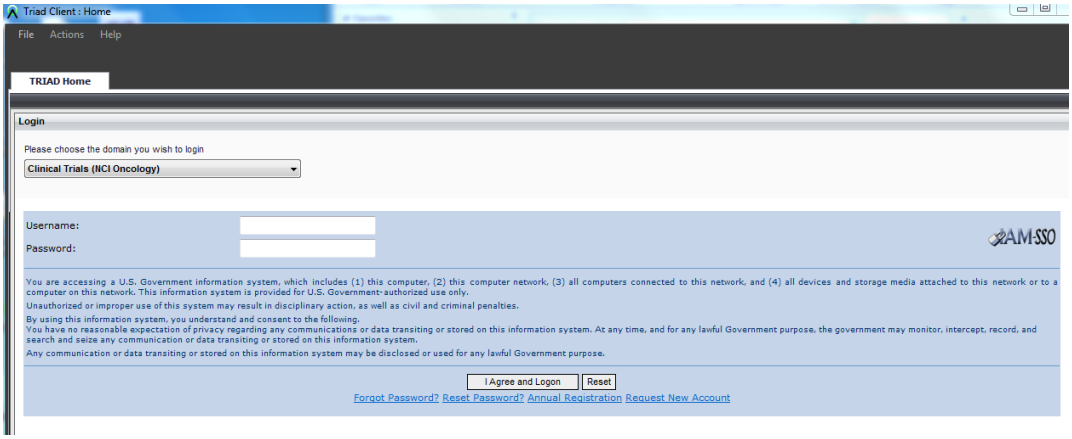
Kate Hutcheson, PhD
University of Texas MD Anderson Cancer Center
Phone: 713-792-6513
Email: karnold@mdanderson.org

Jan S. Lewin, PhD
University of Texas MD Anderson Cancer Center
Phone: 713-792-5309
Email: jlewin@mdanderson.org

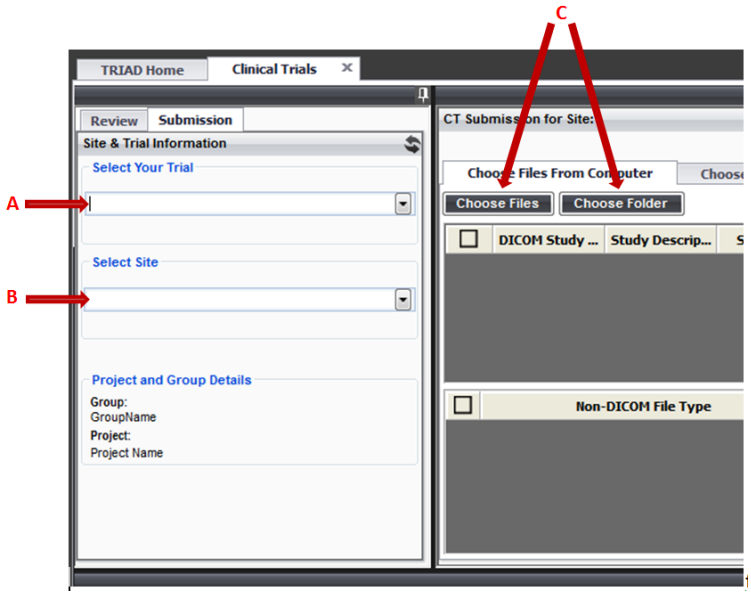
APPENDIX II (Continued)

Instructions for Submission of MBS Videos to TRIAD

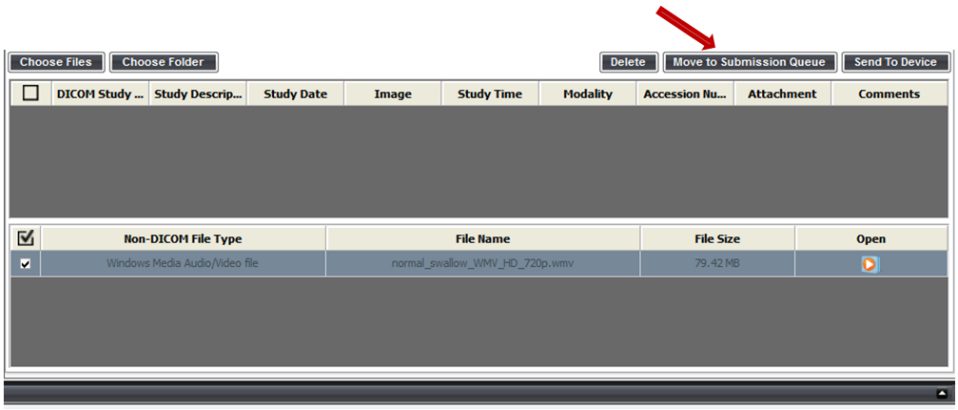
1) Download and install TRIAD 4 via https://triadinstall.acr.org/triadclient/
2) Launch TRIAD, click the dropdown to select Clinical Trials (NCI Oncology). Login using your CTEP ID and password (see Section 8 for access requirements for OPEN, Medidata Rave, and TRIAD).



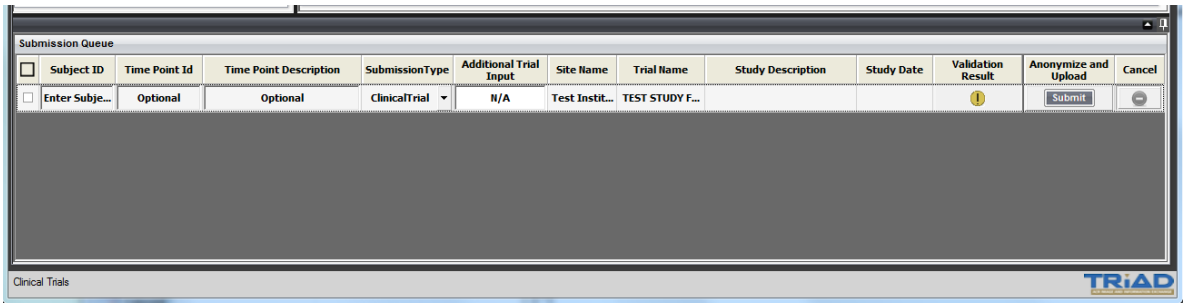
3) To begin file submission:
   A. Select the HN002 Trial from the ***Trial*** dropdown.
   B. Select your Hospital from the ***Site*** dropdown.
   C. Once these options are selected, select ***Import Folder*** (to select a group of video files), or ***Import Files*** (to import an individual video file).



4) Your selected file(s) will appear in the preview screen for review. Select ***Move to Submission Queue*** to move your files to the submission queue.



5) To complete, enter subject information (Subject ID, Time Point ID, Time Point Description, Submission Type, etc.), then select ***Submit***.



APPENDIX II (Continued)

Instructions and Forms for the Modified Barium Swallow (MBS) Substudy

Modified Barium Swallow (MBS) Credentialing Checklist

This checklist must be completed by the institution before patients can be enrolled to the MBS substudy of NRG-HN002.

1. Please provide the following data specific to your site regarding conduct of modified barium swallow (MBS) studies to evaluate swallowing disorders.

   a) Number of speech/language pathologists at your institution who perform MBS studies:_____

   b) Average number of 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:_____

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

   If no, specify frame rate used at your facility (note: 15 to 30 permitted): _____

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

   YES NO

   If no, specify the recording system used:_____

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

   YES NO

   If no, specify the standardized contrast medium used:_____

5. If no, can you access Varibar contrast agents for MBS studies conducted for this substudy?

   YES NO

Signature of Institution Speech/Language Pathologist_____

Printed Name of Speech/Language Pathologist_____

Institution Name_____

Site NRG number/CTEP ID Number_____

APPENDIX II (Continued)

Instructions and Forms for the Modified Barium Swallow (MBS) Substudy

Institution Contact Person_____

Institution Contact Person's phone and fax numbers_____

Institution Contact Person's e-mail address_____

Name and e-mail address of person uploading MBS video

_____

E-mail the completed checklist to Martha Portwood, MPH, at mportwood@mdanderson.org.

After review and approval of the form by the Swallowing Outcomes Co-Chair, Jan S. Lewin, PhD, the CRA will receive a letter of instruction confirming that the site is approved to enroll patients in this substudy.

[redacted]

APPENDIX II (Continued)

Instructions and Forms for the Modified Barium Swallow (MBS) Substudy

[redacted]