NRG ONCOLOGY
RTOG 1221

RANDOMIZED PHASE II TRIAL OF TRANSORAL ENDOSCOPIC HEAD AND NECK SURGERY FOLLOWED BY RISK-BASED IMRT AND WEEKLY CISPLATIN VERSUS IMRT AND WEEKLY CISPLATIN FOR HPV NEGATIVE OROPHARYNX 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 Medical Research Foundation, Inc., and SWOG.

Study Team (8/19/14)

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NRG ONCOLOGY

RTOG 1221

RANDOMIZED PHASE II TRIAL OF TRANSORAL ENDOSCOPIC HEAD AND NECK SURGERY FOLLOWED BY RISK-BASED IMRT AND WEEKLY CISPLATIN VERSUS IMRT AND WEEKLY CISPLATIN FOR HPV NEGATIVE OROPHARYNX CANCER

Protocol Agent (10/2/13)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Supply</th>
<th>NSC #</th>
<th>IND #</th>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>Commercial</td>
<td>N/A</td>
<td>Exempt</td>
</tr>
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</table>

Participating Sites

- U.S. Only
- Canada Only
- U.S. and Canada
- Approved International Member Sites

Note: Participation in this study is limited to institutions with experienced surgeons on the Institution’s NRG Oncology staff roster who are capable and trained to perform transoral eHNS (either TLM or TORS). Participating institutions must have the surgical technology as well as all related accessories and instruments in place.

Document History

<table>
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<td>February 16, 2015</td>
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<td>August 19, 2014</td>
<td>September 2, 2014</td>
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<tr>
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<td>February 27, 2014</td>
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<tr>
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<td>October 30, 2013</td>
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NRG Oncology
1-800-227-5463, ext. 4189

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NRG ONCOLOGY

RTOG 1221

RANDOMIZED PHASE II TRIAL OF TRANSORAL ENDOSCOPIC HEAD AND NECK SURGERY FOLLOWED BY RISK-BASED IMRT AND WEEKLY CISPLATIN VERSUS IMRT AND WEEKLY CISPLATIN FOR HPV NEGATIVE OROPHARYNX CANCER

CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (8/19/14)

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office</td>
<td>See Sections 5.0 and 5.5 for instructions for the Oncology Patient Enrollment Network (OPEN).</td>
<td>Submit study data to: NRG Oncology 1818 Market Street, Suite 1600 Philadelphia, PA 19103</td>
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<tr>
<td>1818 Market Street, Suite 1100</td>
<td>Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a></td>
<td>Submit data electronically via the NRG Oncology/RTOG web site, <a href="http://www.rtog.org">www.rtog.org</a></td>
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<td>Philadelphia, PA 19103</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(for submitting regulatory documents only)</td>
<td></td>
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</table>

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](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.

**For clinical questions (i.e. patient eligibility or treatment-related):** Contact the Study PI of the Lead Protocol Organization.

**For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)** contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

**For detailed information on the regulatory and monitoring procedures for CTSU sites** please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members’ web site [https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy](https://www.ctsu.org). The CTSU Website is located at [https://www.ctsu.org](https://www.ctsu.org).
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Randomized Phase II Trial of Transoral Endoscopic Head and Neck Surgery followed by Risk-Based IMRT and Weekly Cisplatin versus IMRT and Weekly Cisplatin for HPV Negative Oropharynx Cancer

SCHEMA (2/19/14)

<table>
<thead>
<tr>
<th>T Stage</th>
<th>Arm 1: eHNS* + Neck Dissection (Experimental Arm)</th>
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<tbody>
<tr>
<td>1. T1</td>
<td>“Risk-based” post-operative Adjuvant Therapy, +/ IMRT (60 Gy) +/- Weekly cisplatin for high-risk patients with ≥ 5 metastatic nodes, extracapsular extension, or positive surgical margins on final surgical pathology</td>
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<tr>
<td>1. N1</td>
<td>IMRT (70 Gy) + Weekly cisplatin</td>
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<tr>
<th>Zubrod Performance Status</th>
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<tbody>
<tr>
<td>1. 0</td>
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<tr>
<td>2. 1</td>
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*eHNS = TLM or TORS

Institution’s Screening for p16 Prior to Randomization: Mandatory
The enrolling institution is responsible for screening (must be done at CLIA certified lab) for documentation of p16 negative. See Section 10.0 for details of retrospective central review.

For this study, IMRT is mandatory and IGRT is optional (Exception: IGRT is mandatory when using reduced margins). See Section 5.0 for required pre-registration credentialing for IMRT (and for IGRT, if used for reduced margins). See Section 7.0 for details/doses of cisplatin.

Patient Population: (See Section 3.0 for Eligibility)
Squamous cell carcinoma of the oropharynx (localized to the tonsil, glossoharyngeal sulcus, and tongue-base); clinical stage III-IV; T1-2, N1-2b; not approaching within 1 cm of midline, and amenable to transoral eHNS; patient tumor must be p16 negative

Required Sample Size: 144
NRG Oncology Institution #
RTOG 1221
Case #

1. Does the patient have histologically or cytologically proven diagnosis of squamous cell carcinoma of the oropharynx, localized to the tonsil, Glossopharyngeal sulcus and tongue base within 6 weeks (42 days) of registration?

2. Is the primary tumor resectable through a transoral endoscopic head and neck surgery with anticipation of resection free margins? Resection does not require total or subtotal glossectomy or total laryngectomy. Note: Patients must (1) not have trismus, (2) not have interincisor opening less than 2.5 cm, and (3) not have poor transoral exposure of the tumor itself nor surrounding soft-tissue margins, regardless of etiology.

3. Does the patient have clinical stage III-IV; T1-2, N1-2b with tumor not approaching within 1 cm of midline, and amenable to transoral eHNS?

4. Does the patient have p16 negative by immunohistochemistry (documented by a CLIA-certified lab), defined as absent, weak, and only focal nuclear and/or cytoplasmic staining in less than 70% of the tumor cells?

5. Was a history and physical examination performed by the treating physician (Radiation Oncologist, Medical Oncologist, or Head and Neck Surgeon) within 30 days prior to registration?

6. Was there imaging of the head and neck performed (CT with contrast, PET/CT, or MRI) within 30 days prior to registration?

7. Was there a chest CT scan (with or without contrast) or PET/CT of chest (with or without contrast) performed within 30 days prior to registration?

8. Was there a Modified Barium Swallow (MBS) performed within 30 days prior to registration?

9. Was there a preoperative Mallampatti assessment performed by the Attending Surgeon within 30 days prior to registration?

10. Is the Zubrod Performance Status 0-1 within 30 days prior to registration?

11. Is the patient ≥ 18 years of age?

12. Does the patient have adequate bone marrow, hepatic, and renal function as specified in Section 3.1?

13. For women of child bearing potential, was a serum pregnancy test completed within 14 days of registration?

14. If a woman of childbearing potential or sexually active male, is the patient willing to use effective contraception throughout their participation during the treatment phase and for 42 days following completion of treatment?
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15. Did the patient provide study-specific informed consent prior to study entry?

16. Does the patient have prior invasive malignancy (except non-melanomatos skin cancer) unless disease free for a minimum of 1095 days (3 years)?

17. Did the patient have prior systemic chemotherapy for the study cancer? (prior chemotherapy for a different cancer is allowable).

18. Did the patient have prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?

19. Does the patient have any of the severe, active co-morbidities specified in Section 3.2?

20. Did the patient have a prior allergic reaction to cisplatin?

21. Does the patient have radiographic evidence of retropharyngeal metastasis?

The following questions will be asked at Study Registration:
IMRT and IGRT (if used for reduced margins) CREDENTIALING IS REQUIRED BEFORE REGISTRATION

1. Institutional person randomizing case.

2. Has the Eligibility Checklist been completed?

3. In the opinion of the investigator, is the patient eligible?

4. Date informed consent signed

5. Patient’s Initials (Last First Middle)

6. Verifying Physician

7. Patient ID

8. Date of Birth

9. Race

10. Ethnicity

11. Gender
ELIGIBILITY CHECKLIST (10/2/13)
NRG Oncology Institution #
RTOG 1221
Case #

12. Country of Residence
13. Zip Code (U.S. Residents)
14. Method of Payment
15. Any care at a VA or Military Hospital?
16. Calendar Base Date
17. Randomization date
18. Medical oncologist’s name
19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?  
20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?
21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?
22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?
24. (Y/N) Did the patient agree to participate in the quality of life component?  
   If no, provide reason:
   1. Patient refused due to illness
   2. Patient refused for other reason: specify ________________
   3. Not approved by institutional IRB
   4. Tool not available in patient’s language
   5. Other reason: specify_________________
25. Specify T stage (T1 vs. T2)
26. Specify N stage (N1 vs. N2)
27. Specify Zubrod performance status (0 vs. 1)
The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by ___________________________  Date ___________________________
1.0 INTRODUCTION

1.1 The Impact of Human Papillomavirus (HPV)

Recently, Ang, et al. have highlighted the significant impact HPV status has on the epidemiology of oropharyngeal carcinoma (OPC) (Ang, 2011). RTOG 0129 provided strong evidence that HPV status is an independent prognostic factor for overall survival (OS) and progression-free survival (PFS) among patients with squamous-cell OPC. In this study, 64% of OPC patients were found to have HPV positive (+) tumors, as measured by in-situ hybridization for the HPV subtype 16. The presence of HPV DNA correlated well with p16 expression (kappa = 0.80; 95% CI, 0.73 to 0.87). For this reason, p16 IHC (immunohistochemistry) was used as a surrogate biomarker for HPV status in OPC.

Patients with HPV-positive tumors had significantly increased OS as well as PFS. Furthermore, after adjusting for demographics, T stage, N stage, and smoking, patients with HPV+ OPC had a 58% reduction in the risk of death and a 51% reduction in risk of progression or death. RTOG 1016 is now underway to determine whether treatment can be de-intensified for these HPV+ OPC patients. Perhaps a more pressing concern is the dismal outcome for these “high-risk” HPV- OPC patients. Even when treated up front with primary radiation therapy and cisplatin, HPV- patients have substantially diminished outcomes, both in terms of locoregional control (LRC) and OS. In RTOG 0129 (Ang 2011), patients with HPV- tumors had a 25.1% reduction in OS at 3 years (57.1% vs. 82.4%) when compared to patients with HPV+ tumors. Local-regional relapse at 3 years was 21% higher in patients with HPV- tumors; 35.1% (95% C.I.: 26.4–43.8) versus 13.6% (95% C.I.: 8.9–18.3) for HPV+ tumors (p<0.001). These poor outcomes for HPV- patients are remarkable given the gradual trend toward increasing intensification of treatment with altered fractionation schema (Brizel 1998), concurrent chemoradiation (Forastiere 2003; Forastiere 2006), multi-drug induction chemotherapy (Posner 2007), and targeted molecular therapies (Bonner 2006). It seems that for these HPV- patients, simply altering the method of radiation delivery and the dosing and/or types of concurrent chemotherapy is not sufficient to improve oncologic outcomes. A completely new approach may be needed.

“Surgical Intensification”

One approach to intensity treatment would be to operate on these high-risk, HPV- OPC patients up front. In the past, surgical resection of OPC was typically permissible through disfiguring incisions and often mandibulotomy (Holsinger 2007; Sugarbaker 1946; Ward 1951) with significant post-operative functional deficits. Recently, “endoscopic” head and neck surgery (eHNS) has emerged (Holsinger 2010), evolving naturally around a common transoral route of exposure: incorporating minimally invasive techniques, with transoral laser CO2 microsurgery (TLM) (Jäckel 2005) and transoral robotic surgery (TORS) (Weinstein 2009).

Compared to “open” head and neck surgery, eHNS of the oropharynx is performed with no external incisions and never required mandibulotomy or transmandibular access. This approach can be considered “inside-out” surgery in that incisions take place starting from the mucosal (inner) surface and extend outward but without external skin incision. Using a laser and microscope (TLM) or the da Vinci® Robotic Surgical System (Intuitive Surgical Inc., Sunnyvale, CA), a complete resection of the index oropharyngeal tumor is performed with an oncologic margin. While both rely on a minimally invasive approach through the mouth, there are some significant differences in eHNS technique.

TLM is an endoscopic surgical technique performed under direct laryngoscopy, with suspension/fixation and the use of an operating microscope, microsurgical instruments, and a carbon dioxide (CO2) laser. The wavelength of the CO2 is 10,600 nm, which has a peak energy absorption that is ideal for water, the most common component of human soft-tissues. Water absorbs CO2 laser energy and tissues are vaporized, with little thermal energy dispersed to surrounding neurovascular structures and surrounding soft tissues. TLM is an adaptive surgical technique, relying on the surgeon’s understanding of the three-dimensional anatomy of the tumor’s extent and surrounding anatomy. First described in 1972, TLM has a robust literature,
though few multicenter experiences have been published, and no prospective coordinated clinical trial has been performed.

On the other hand, robotic head and neck surgery was approved for use by the FDA in 2009. Transoral robotic head and neck surgery is performed using 3 arms, which are placed within the patient’s mouth but controlled by a surgeon sitting at a remote console, in a “master-slave” configuration. After placing a suitable oral retractor, the endoscope or camera is introduced into the pharynx followed by 2 other arms carrying interchangeable 5 mm wide working instruments. The surgeon is provided with an endoscopically derived 3-dimensional visual display that is collocated with control handles that direct movements of the robot’s instruments inside the patient’s body. Standard surgical instruments, including tissue forceps, an electrocautery spatula, or carbon dioxide and Thulium laser (Desai 2008; Solares 2007) are then used to perform an en-bloc resection of the oropharyngeal tumor.

While the first paper on robotic surgery for OPC was published in 2005, there is little prospective literature examining the role of TORS within the multidisciplinary paradigm.

Both techniques have in common an outstanding highly magnified view of the tumor, which allows confident resection of various tumor invaginations that are not often visualized with standard surgical techniques. While numerous retrospective single-institution reports and a few important multicenter trials have generated significant enthusiasm for implementing eHNS into the multidisciplinary approach, there is little prospective clinical evidence to support its use. Recently, Ridge and Adelstein hosted an NCI-sponsored, R13-funded Clinical Trials Planning Meeting to discuss the role of transoral endoscopic surgery for the treatment of OPC.

At present, there is no surgical cooperative group to host and administer prospective clinical trials in head and neck surgery, and thus, there is no track record for participation in clinical research. Thus, a comparative phase III clinical trial comparing primary radiation-based approach versus surgical intensification up front is not feasible.

For this reason, we propose a randomized phase II trial comparing radiation with a concurrent cisplatin-based chemotherapy approach versus transoral eHNS with neck dissection and risk-based adjuvant therapy.

1.2 Why It’s Important to Study Transoral Endoscopic Head and Neck Surgery (eHNS) in A Prospective Randomized Clinical Trial


Advocates for eHNS (TLM and TORS) for oncologic surgery cite excellent functional results and argue that eHNS “deintensifies” the long-term toxicity that is sometimes associated with a primary radiation-based approach for OPC. Skeptics of TORS and TLM are wary of this approach, citing concerns about the relatively “close” margins and the high rate of postoperative radiation therapy required after eHNS. However, due to the sigmoidal shape of the normal tissue complication probability curve (NTCP), treatment with a postoperative dose (60 Gy) rather than a definitive dose (70 Gy) combined with an IMRT technique that is optimized to spare adjacent organs at risk may significantly reduce the risk of damaging critical normal tissue for the group of patients who require adjuvant therapy.

Despite a surge in interest in eHNS by surgeons, there is no “level-A” evidence-based clinical data to support its use. Granted, surgery followed by radiation therapy is a time-honored paradigm—perhaps the first such approach to oropharyngeal cancer, dating back to the early- and mid-20th century (Sugarbaker 1946; Ward 1951). However, eHNS is a significant technological advance in surgical technique, akin to the difference between conventional two and
three-dimensional conformal radiotherapy (3D-CRT) versus IMRT. Nonetheless, this surgical approach, including the impact of margins and the role of postoperative radiation therapy following TORS and TLM must be carefully studied, ideally in the setting of a prospective multicenter clinical trial. While there is clinical equipoise for the use of eHNS within the surgical community, at a recent multidisciplinary R13-funded Clinical Trials Planning Meeting, support for a randomized phase II trial comparing standard therapy to eHNS was proposed.

Such a trial would be the first comparison of “new” minimally invasive surgery (+/- adjuvant therapy) versus definitive nonsurgical treatment for high-risk HPV-negative oropharyngeal carcinoma, somewhat analogous to the VA larynx trial. In contrast, however, it is the addition of this type of surgery (and subsequent lower dose IMRT if required) that is postulated to be “organ preserving” (swallowing function) compared with definitive full dose radiation or chemoradiotherapy. Thus, head and neck toxicity, quality of life (QOL) short and long term, and speech/swallowing measurement and analysis are important secondary objectives.

Prospective head-to-head comparative data regarding function after both treatment modalities is lacking. Finally, the proposed randomized phase II trial would have an important impact on future trials, setting the stage for a larger randomized phase III comparative trial. Normative baseline data regarding margin status, functional outcomes +/- adjuvant therapy must first be obtained. Our trial provides such an opportunity to collect these data and to define the endpoints to be studied and the statistical power to perform future phase III clinical trials.

1.3 Feasibility of an HPV-negative Trial

The poor outcome for patients with HPV-negative OPC still does not obviate the need to determine the feasibility of accrual to a clinical trial for this population. Chaturvedi, et al. (2011) have recently reviewed the population-level incidence of HPV-positive OPC using the Surveillance, Epidemiology, and End Results (SEER) database. From 1988 to 2004, HPV-positive OPC increased by 225% (95% CI, 208% to 242%; from 0.8 per 100,000 to 2.6 per 100,000), while the incidence for HPV-negative cancers declined by 50% (95% CI, 47% to 53%; from 2.0 per 100,000 to 1.0 per 100,000). While this study shows a dramatic decline in HPV-negative OPC, the exact incidence of the disease remains unknown. According to the American Cancer Society, there will be an estimated 52,140 new cases of laryngeal, oral and pharyngeal cancers. (Table 1)

From these data, one must further estimate what proportion of the patients with “Oral Cavity and Pharynx” cancer has oropharyngeal cancer, per se. In this schema, “oral cavity” tumors (per AJCC designation) likely are found in the “mouth” and “other oral cavity”, as shown above. Oropharyngeal cancers are most likely included in the “tongue” and “pharynx” subcategories (highlighted in grey below). In RTOG 0129, the incidence of HPV-negative tumors was approximately 40% of the total population. Using this ratio, we calculated the total number of estimated patients with HPV-negative (HPV-) versus HPV-positive (HPV+) tumors (Table 2 below).
Table 2

<table>
<thead>
<tr>
<th>Head and Neck Cancers</th>
<th>Total</th>
<th>HPV-</th>
<th>HPV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx</td>
<td>12,740</td>
<td>10,192</td>
<td>2,548</td>
</tr>
<tr>
<td>OC/P: mouth</td>
<td>11,510</td>
<td>9,208</td>
<td>2,302</td>
</tr>
<tr>
<td>OC/P: other</td>
<td>2,250</td>
<td>1,800</td>
<td>450</td>
</tr>
<tr>
<td>OC/P: tongue</td>
<td>12,060</td>
<td>4,342</td>
<td>7,718</td>
</tr>
<tr>
<td>OC/P: pharynx</td>
<td>13,580</td>
<td>4,889</td>
<td>8,691</td>
</tr>
<tr>
<td>(Oropharyngeal Cancer)</td>
<td>(25,640)</td>
<td>(9,231)</td>
<td>(16,409)</td>
</tr>
<tr>
<td>Total</td>
<td>52,140</td>
<td>30,431</td>
<td>21,709</td>
</tr>
</tbody>
</table>

While these numbers represent an estimation of the study population, HPV-negative OPC still may account for nearly 10,000 new cases per year, confirming the feasibility of accruing to an HPV-negative study. When combined with other laryngeal and oral cavity cases (where HPV might be associated with as little as 10-20% of cases), HPV-negative tumors still account for most new cases of head and neck cancers in the United States. Thus, we feel that prospective clinical investigation for this population would significantly impact public health.

1.4 RTOG 1221 Trial Design and Rationale (2/19/14)

This is a randomized phase II, 2-arm trial. The control group will be treated with once daily IMRT to 70 Gy in 35 fractions with concurrent weekly cisplatin chemotherapy. This will be compared to patients treated first with eHNS and neck dissection (experimental arm).

For the experimental arm, patients would first undergo transoral resection via eHNS and subsequent neck dissection. A formal selective or modified radical neck dissection, level II-IV, will be performed in all cases. Numbering and/or nomenclature will be standardized using “Neck Dissection Guide”. Resection of levels II-IV is required, with levels I and/or V electively dissected at the discretion of the attending surgeon. The neck dissection must be oriented by the surgeon or sectioned in order to identify levels of lymph nodes encompassed in the dissection.

For lateralized lesions of the tongue-base, tonsillar region, and glosopharyngeal sulcus, patients will undergo ipsilateral selective or modified radical neck dissection of levels II-IV. For patients with N1 neck and SCC of the tongue-base discovered to approach on final pathology to within 1 cm of the midline, it is recommended that a contralateral neck dissection be performed, also of levels II-IV. For ipsilateral and contralateral lymphadenectomy, level I-b and V may be electively dissected at the discretion of the attending surgeon, but is not required. A minimum of 20 lymph nodes per dissected side of the neck is required and is subject to quality assurance review. Furthermore, the type of neck dissection will be recorded by the surgeon (e.g. selective, modified radical neck dissection, sparing or sacrifice of the accessory nerve).

Risk-based postoperative adjuvant therapy will be guided by pathological findings in the primary tumor and cervical nodes. Thus, risk-based in this context refers to radiation therapy alone vs. concurrent chemoradiation therapy, personalizing the treatment of adjuvant therapy. In other words, postoperative adjuvant treatment will vary according to the “risk” associated with the pathological findings:

Post-operative Indication for Concurrent Chemoradiation

Patients with 5 or more metastatic cervical nodes, positive margins or extracapsular extension (ECE) in cervical nodes will receive postoperative cisplatin, 40 mg/m² IV on days 1, 8, 15, 22, 29, and 36, for a total of 6 weekly doses concurrent with IMRT (60 Gy at 2 Gy in 30 fractions over 6 weeks). Patients with involved surgical margins or ECS also will receive a 6 Gy boost at 2 Gy per fraction to the area of the positive margin or ECS.
Post-operative Indication for Radiation Only
Patients with “close” margins, lymphovascular (LVI) or perineural invasion (PNI), >1 metastatic lymph nodes will receive IMRT (60 Gy at 2 Gy) in 30 fractions over 6 weeks. Subclinical regions at risk for microscopic disease (e.g., contralateral hemineck, when indicated) will receive 54 Gy (1.8 Gy/fraction, using integrated boost technique).

Post-operative Indication for Treatment of the Contralateral Neck
For lateralized tonsillar tumors with < 1 cm invasion of the soft palate or BOT and p-1 node involvement in the ipsilateral neck dissection, IMRT treatment can be confined mainly to the tonsillar fossa and ipsilateral neck without contralateral neck treatment. Irradiation of the contralateral neck is controversial for patients with an N2B classification; in fact, many institutions no longer do so. Treatment of the contralateral neck in these cases is allowed, but is not required.

No Indication for Post-operative Radiation Therapy
It is possible that some patients on the experimental arm will not receive any post-operative radiation therapy. However, the RTOG 1221 team estimates that this population would account for less than 10% of the surgical (experimental) arm. With pathologic rather than clinical staging of the neck, some necks may be “downstaged” from N2b or N1 to N0. With margins >3 mm, no perineural spread or lymphovascular spread, and no nodal metastasis, this patient would not require post-operative RT. Specifically, for patients with negative margins, no adverse features, such as LVI or PNI, pathologic T1-2 tumor, and N0 neck, no adjuvant therapy would be required.

For the control arm, IMRT (70 Gy) with concurrent weekly cisplatin will be given. For patients with T1-2 lateralized tonsil tumors with < 1 cm invasion into the soft palate, no invasion of BOT, and N1 neck involvement, unilateral neck IMRT can be used. Irradiation of the contralateral neck is controversial for some tongue-base cancers or patients with N2B classification. Treatment of the contralateral neck in these cases is allowed, but is not required. Although T1N1 and T2N1 patients were excluded from many of the trials that established chemotherapy as the standard of care for non-surgical management in locally advanced H&N cancer, these trials were performed before prognostic significance of HPV status was established. In light of this new understanding, these stage III patients do poorly and will receive IMRT with concurrent chemotherapy in this trial.

For patients with residual neck disease after concurrent chemoradiation, neck dissection will be performed. Normal tissue sparing will be specified with the aim of sparing organs at risk (OARs), including those at risk for developing dysphagia, such as the larynx, oral cavity, and pharyngeal constrictors for the IMRT plan (Schwartz 2010, Caudell 2010). Weekly cisplatin will be administered during IMRT at a dose of 40 mg/m² IV on days 1, 8, 15, 22, 29, 36, and 43 for a total of 7 weekly doses with 70 Gy.

Rationales for Exclusion of T3-4 and N2c Tumors
Transoral minimally invasive, endoscopic head and neck surgery provides a surgical alternative to the time-honored transfacial transmandibular “composite resection.” However, the da Vinci Surgical System is currently approved by the FDA for tumors staged T1-2. Therefore, the inclusion of T3 and T4a tumors is not warranted at this time. T4a tumors are described as invading the “larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.” As such, these tumors are not resectable via transoral eHNS and therefore are excluded from this trial.

Similarly, patients with N2c lymphatic disease will be excluded, to minimize the morbidity of routinely dissecting both necks. Cross sectional imaging of the neck will be required for quality control and staging and to assess our exploratory 2” objective of evaluating extracapsular extension of disease, as discussed below. Thus, any patient with equivocal findings in the contralateral disease will be excluded from this study. However, the local team evaluating this patient for RTOG 1221 may within the standard of care provide histologic evidence ruling out N2c disease and confirming N2b disease with ultrasound-guided FNA, as part of the standard of care.
1.5 Translational Research

Note: The following correlative studies are proposed as outlined below; however, these proposed studies require the results of the parent study. Specifically, the number of events for the 2 clinical endpoints, DFS and OS, which are necessary to carry out a realistic statistical power justification, cannot be ascertained until the parent study is completed. Therefore, no marker assays will be conducted on the collected specimens other than those required for patient enrollment (i.e., p16). When sufficient information is available from the parent study, a full correlative study document for the marker studies will be submitted to and reviewed by CTEP.

1.5.1 The Role of PI3K/PTEN/mTOR Pathway in Local-Regional Recurrence of HPV-Negative Oropharyngeal Carcinoma

The phosphotidylinositol-3-kinase (PI3K) pathway is a well-known oncogenic pathway in numerous cancers and activated by several receptor tyrosine kinases including epidermal growth factor receptor (EGFR), a key pathway in head and neck squamous cell carcinoma (HNSCC). PI3K activation 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. Activating mutation of the PI3K catalytic subunit, PIK3CA, is seen in approximately 5% of HNSCC (Agrawal 2011; Stransky 2011). In addition, PTEN loss of function, the negative regulator of PI3K, is seen in approximately 40% of HNSCC resulting in uncontrolled activation of PI3K (Okami 1998). Thus, the PI3K/mTOR pathway may serve as a critical biomarker in the management of HPV-negative OPC while its role in this disease is poorly understood. Improved understanding of this pathway potentially serves as an important therapeutic target to improve clinical outcomes in HPV-negative HNC patients. We hypothesize that PI3K/mTOR pathway deregulation is a poor prognostic marker in HPV-negative HNSCC, and the deregulation is defined as: (a) loss of PTEN and activation of p70S6K determined by immunohistochemistry; and (b) PIK3CA activating mutations determined by tumor DNA sequencing.

1.5.2 Genomic Profile of Distant Metastasis

Recent whole exome sequencing data showed that the HPV-negative tumors are genetically complex with several mutations compared to HPV-positive tumors (Agrawal 2011; Stransky 2011). While the mutations are profiled, their biological and clinical contributions to distant metastasis and prognosis are unknown. One hundred ninety-six cancer genes with known mutations, translocations, amplifications, and deletions will be assessed, and these genetic abnormalities will be correlated with the clinical outcomes. We hypothesize that a set of genetic abnormalities will be delineated as a genomic profile of distant metastasis or poor prognosis.

The genetic abnormalities of 196 cancer genes will be determined in one experiment of exon capture-based next generation sequencing by Illumina platform. The DNA will be obtained from tumors and whole blood, and the sequences will be compared between the tumor DNA and normal DNA from whole blood.

1.5.3 Inflammatory Cytokine Profile and Toxicity

TGF-beta polymorphism and high levels of inflammatory cytokines such as plasma TGF-β1 have been associated with increased risk of radiation-induced lung toxicity suggesting that inflammatory/ immunomodulatory cytokines may play an important role in developing acute and chronic toxicities (Zhao, 2009). Therefore, examining the correlation among the TGF-beta polymorphism, inflammatory cytokine levels in plasma and/or serum and radiation-induced toxicities which may result from acute and chronic inflammation and fibrosis can potentially provide a biomarker to identify patients at risk of chronic radiation-induced toxicities. The cytokine profile results will be correlated with functional measures determined in PROs and QOL studies described in Sections 1.6 and 11.3. Early identification of the patients at risk of toxicities may benefit from early supportive intervention.
Measuring Toxicity, Patient-Reported Outcomes (PROs), and Quality of Life (QOL)

Oropharyngeal dysphagia after surgery and chemoradiation therapy can have a significant impact on QOL. Patient-reported outcomes (PROs) directly measure the patient’s perception of symptom burden and daily health status from the treatment of their disease and its impact on their health related QOL without bias from the clinician (Basch 2009; Bruner 2007; Trotti 2007). Multiple factors are thought to contribute to the severity of oropharyngeal dysphagia, including multimodality therapy (surgery, RT, chemotherapy), total radiation dose, dosimetry to OARs including the larynx, oral cavity, and pharyngeal constrictors, as well as intrinsic patient radiosensitivity and susceptibility to fibrosis.

The oral cavity, oropharynx, larynx, and the pharyngeal constrictors are thought to be the organs at risk for injury leading to swallowing dysfunction. By evaluating how differences in the treatment arms affect swallowing function, we can then evaluate how swallowing dysfunction affects QOL. 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 using the MD Anderson Dysphagia Inventory-Head and Neck (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 postoperative period with recovery of scores observed at last follow up. Poor swallowing function on any subscale was defined before surgery as a MDADI score less than 60 or after surgery as a decrease from pre-operative baseline scores by more than 20 points at the last follow up. These values were chosen as being clinically significant decline in a patient’s swallowing ability. Factors which predicted poorer physical MDADI outcomes included nodal status (p=0.049), less than 12 months follow up (p=0.01), and preoperative physical scores of less than 100 (p=0.01). However, only the preoperative physical MDADI score was significant on multivariate analysis. Postoperative chemotherapy predicted gastrostomy tube dependence for greater than 3 months on multivariate analysis (p=0.01).

In another study by Iseli, et al. (2009), mean global scores dropped from 75 to 65 after eHNS using TORs for carcinomas of the oropharynx, larynx, and hypopharynx. However, these studies did not employ standardized follow-up times for MDADI administration resulting in varied times of administration, which may affect the MDADI scores. In a cross-sectional study in patients with stage III/IV head and neck squamous cell carcinoma (Gillespie 2004), MDADI was administered to patients at least 12 months after treatment. Patients receiving primary chemoradiation for oropharyngeal primaries demonstrated significantly better scores on the emotional (p=0.03) and functional (p=0.02) subscales of the MDADI than patients receiving surgery and postoperative 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. These studies show that the MDADI is responsive in terms of the ability to detect a clinically important change in the patient population to be studied.

In the setting of eHNS, preliminary single institutional data regarding minimally invasive eHNS using TORs suggests favorable QOL outcomes after eHNS. Leonhardt, et al (2012), demonstrated that patients after TORs and adjuvant RT had a temporary decrease in several QOL domains at 6 months; however, they returned to near to baseline function, including swallowing function in all patients using the short form (SF)-8 and the Performance Status Scale Questionnaire. Other single institutional series (Hurtuk 2012) have shown decrease from baseline immediately after surgery in speech, eating, aesthetic, social, and overall QOL domains, using the Head and Neck Cancer Inventory (HNCI); however, at 1 year, the health-related QOL (HRQOL) in the aesthetic, social, and overall QOL domains were high, whereas speech and eating domains were in the intermediate domain. Eating function and attitude in the HNCI was the only variable not returning to the high domain, likely secondary to excision causing dysphagia. However, in a matched-pair study by El-Deiry, et al (2005), a comparison of QOL outcomes using...
the HNCI at 12 months in patients with advanced head and neck cancer treated with surgery and postoperative RT and concurrent chemoradiation showed the head and neck-specific domain scores (higher scores representing better outcomes) in the chemoradiation group compared to the surgery and postoperative RT group were eating, 37.8 vs. 40.8 ($P = .69$); speech, 65.1 vs. 56.0 ($P = .23$); aesthetics, 80.3 vs. 69.2 ($P = .14$); and social disruption, 69.7 vs. 70.6 ($P = .90$). Although overall HRQOL was 64.0 with the surgery group and 55.0 in the chemoradiation group, this did not reach statistical significance ($P = .142$). Limitations of such series include the small sample size, single institutional series, and lack of randomization such that the evaluation of the impact of eHNS with postoperative IMRT (+/- chemotherapy) versus primary chemoradiation on QOL needs to be addressed in the setting of a multi-institutional randomized trial.

In this study, LRC and PFS are expected to be improved in patients undergoing eHNS compared to primary RT by surgical intensification treatment. How swallowing function after eHNS affects QOL from the patient’s perspective will be studied as a secondary endpoint. It is hypothesized that eHNS and risk-adapted IMRT compared to a primary chemoradiation approach will improve swallowing function and QOL by selective use of concurrent chemotheraphy (based on pathological risk factors) (Bernier 2005) and a reduction in the total RT dose of 60 Gy. Furthermore, using modified barium swallowing (MBS), we hypothesize that clinically significant aspiration can be detected as an objective measure of swallowing function.

There is compelling support for the examination of objective swallowing impairment as the health-related endpoints ascertained from MBS studies. According to the American Speech-Language-Hearing Association, the MBS is a validated standard of care procedure to determine dysphagia in a variety of patient populations. Imaging results from the MBS studies will be readily available to the treating physician as part of the medical record. However, MBS as a means to describe dysphagia has not been widely used in cooperative group studies. MBS is the only comprehensive examination of oropharyngeal dysphagia that can detect silent aspiration, a significant and potentially life-threatening toxicity. (Eisbruch, 2002; Rosenthal, 2006) To date, however, longitudinal MBS data have not been reported after an eHNS approach to oropharyngeal cancer. Hence, current data do not provide validated prospective point estimates for the prevalence of swallowing impairments (per gold-standard MBS) after eHNS. Thus, this proposed phase II study is a critical next step for head and neck oncology trials to obtain valid objective estimates of swallowing dysfunction among patients treated with upfront surgery versus those treated with upfront chemoradiation. This is a critical gap in knowledge as swallowing outcomes are acknowledged to be the primary factor that may triage patients to eHNS or chemoradiation if survival is equivalent (Weinstein 2009). Longitudinal MBS studies included in this trial will obtain these data for the first time.

Results of the baseline MBS study will be used as an adjustment variable for assessment of post-treatment swallowing outcomes. Baseline dysphagia has been shown to portend poor swallowing outcomes. (Rosenthal 2006; Hutcheson 2008; Hutcheson 2012) Thus, prevalence of the primary dysphagia endpoints (laryngeal penetration/aspiration; pharyngeal residue) will be normalized to baseline as the proportion of patients with greater laryngeal penetration/aspiration after treatment relative to baseline.

We propose to evaluate swallowing function using MBS studies as the primary objective functional measure of this trial. These data will power future comparative phase III trials, since currently no randomized prospective comparisons have been made.

As both arms will be receiving IMRT, although to different total doses, we also will be able to prospectively evaluate optimization of normal tissue dosimetry of dysphagia-associated OARs in a cooperative group setting, compare dosimetric differences in normal tissue sparing between the control arm and the eHNS + risk-adapted postoperative IMRT arm and prospectively study the relative contribution of IMRT technique on long-term swallowing outcome.
To assess swallowing function, the MDADI, MBS, and PSS-HN will be administered in both arms. To enhance the PRO data, objective correlates include a MBS performed at baseline, 6 and 24 months after treatment and clinician grading (CTCAE, v.4) to compare with patient-reported MDADI scores.

In patients undergoing eHNS and neck dissection, it is anticipated that neck dissection may impair shoulder movement. Sinclair, et al (2011) reported that nodal status predicted poorer MDADI physical scores in patients undergoing TORs with neck dissection. The use of neck dissections (particularly with dissection of level IIb) in patients undergoing eHNS is associated with additional morbidity due to mobilization / trauma to the spinal accessory nerve. This has been demonstrated on electromyography and also correlated with patient-reported QOL tools, including the University of Washington Quality of Life Questionnaire (UWQoL, v. 4, Laraway 2012) and the Neck Dissection Impairment Index (NDII). In a double blinded, randomized study of oral cancer patients undergoing elective supraomohyoid neck dissections with level IIa versus level IIb dissections, range of movement, electromyography (EMG) and nerve conduction studies (NCS) of the trapezius muscle, and PRO questionnaires using the UWQoLv.4 and the NDII at baseline, 6 weeks and 6 months after surgery showed that NCS and EMG findings were supported by both PRO questionnaires. Change in trapezius motor amplitude fell in both groups although more so in patients undergoing IIb dissections. Correlations were stronger with the UWQoLv.4 and the NDII questionnaires compared to the range of movement physical therapy assessments measuring range of motion. Change in function at 6 weeks (from baseline) reflected similar outcome at 6 months, such that the 6-week PRO evaluation would be sufficient. However, this study did not evaluate the effect of postoperative RT after neck dissection on long-term shoulder function (Parikh 2011). Taylor et al (2002), originally validated the NDII in a cohort of 54 patients in a cross sectional study, (a total of 32 accessory nerve spared modified radical (MRND) and 32 selective neck dissections (SND) were performed). The mean time to PRO assessment was 33.7 months after surgery, with a minimum of 11 months after surgery. The NDII test and retest correlation was 0.91 (p<0.001) with an internal consistency Cronbach α coefficient of 0.95. Convergent validity was assessed using the Constant’s Shoulder Scale (r=0.85, p<0.001), a validated clinical assessment of shoulder function (Chepeha 2002) and the SF-36 domains (role-physical and physical functioning domains). Patients receiving MRND demonstrated significantly worse shoulder function compared to SND. Furthermore, adjuvant RT negatively contributed to outcome.

Therefore, in this study we will assess the impact of eHNS with neck dissection on QOL and changes in shoulder function with respect to nodal disease status and type of neck dissection performed in conjunction with eHNS in a cooperative group setting. The NDII will be administered at baseline, 2-4 weeks after surgery (for short-term evaluation after neck dissection (Parikh 2011) and long term at 1 year (Taylor 2002) in the eHNS arm only. The surgeon will record the type of neck dissection performed, with or without sparing of the accessory nerve. QOL data regarding shoulder function may help inform a phase III trial by examining the degree of standardization of neck dissection practice in a cooperative group setting and may allow further comparison of QOL outcomes between surgical-based therapy to a primary chemoradiation approach.

For this trial, all protocol-eligible patients will be asked to participate in the QOL component of this study. We have limited our selection of PRO instruments to focus on the evaluation QOL measures relating to swallowing and shoulder function after eHNS and neck dissection and will compare swallowing outcomes in the eHNS group to the primary chemoradiation group. In order to participate in the PRO assessments, patient must be able to comprehend verbal English. Patients who are blind or illiterate may have questions and responses read verbatim by the investigator/RA; translation of instruments is not allowed.

If we can identify the patient population at risk for developing long-term toxicity after eHNS and define a cut point or threshold effect upon which swallowing and shoulder function after eHNS and neck dissection with risk-adapted postoperative IMRT impairs QOL outcomes, then future studies can evaluate methods for optimal postsurgery rehabilitation. Finally, improvements and
standardization of surgical techniques and RT technique in terms of dosimetric optimization of normal tissue (pharyngeal constrictor)-sparing IMRT in a multi-institutional setting can be further examined to minimize the risk and severity of permanent long-term toxicity with potential improvement in QOL.

1.7 Exploratory Correlation of Physician Derived CTVs with Locoregional Control or Failure

Physician derived clinical target volumes (CTV) are variable among radiation oncologists in head and neck and other sites. In the cooperative group setting, even among plans that meet protocol constraints, significant variability exists in target volume delineation, raising concern for poor outcome in some patients. Single institution patterns of failure (POF) analysis have correlated target volume contours with specific types of failure defined as in-field, marginal, or out-of-field. Some institutions have reported that modification of treatment planning guidelines lead to improved outcomes for subsequent patients. However, given the rapid transition from 2D to 3D IMRT, along with significant variability in head and neck "expert" target volume recommendations, head and neck target delineation is far from standardized. Physicians tend to develop individual contouring styles, leading to target volume heterogeneity. To date, no cooperative group has attempted a sophisticated 3D image based POF correlative study; however the necessary infrastructure exists within RTQA at NRG Oncology to perform such a study. A cooperative group POF analysis may elucidate relationship(s) between contouring details and local control. Such a finding would be very educational and may provide convincing evidence for increased standardization in head and neck target volume delineation in the IMRT era.

A pattern of failure analysis will be conducted on all patients enrolled on the trial. As it is required to electronically send the CT simulation scan to NRG Oncology, these images will be available for further analysis. For the patients who develop biopsy proven local-regional failure after completing the treatment protocol, a 3D radiographic image showing recurrent disease (CT, PET/CT) will be electronically transferred and stored for future analysis. The images will be fused (MIM software or similar) with the original CT simulation scan and then anonymized. The failures will be contoured or superimposed on the original CT based treatment plan and the dose encompassing the recurrent disease (GTV-r) will be assessed. Failures will be classified as in-field, marginal, or out of field based on the dose received by the GTV-r. Importantly, the group of patients who remain free of locoregional recurrence will be included in this analysis as they will have original CT simulation data already stored. We will define finer detail in the variation of CTVs; however, that will need to be derived from the plans which will be sent to NRG Oncology electronically. Quantitative rather than qualitative metrics will be derived, for example: local control as a function of GTV-CTV distance of less than or greater than 1.0 cm, local control as a function of percent of prescription dose covering the CTV, neck control as a function of contouring to the inside edge, middle, or outside edge of the sternocleidomastoid muscle, and neck control related to covering the level(s) suggested in the CTV guidelines. To date, the definition of "satisfactory" vs. "unsatisfactory" CTV has revolved around meeting the CTV objectives of the protocol. However, this has been variably related to outcome. In RTOG 0225 (Phase II trial of IMRT for nasopharyngeal carcinoma) 16% of the plans had major deviations in the treatment plan, yet the overall 2 year locoregional progression free rate was 93%, suggesting that some of the "unsatisfactory" CTV's were in fact "satisfactory" for achieving locoregional control. In this trial (0225) a few failures appear to have been related to not including level V as a target. Therefore, for nasopharyngeal carcinoma, a critical CTV guideline is to include level V as a target. The benefit of doing a study of the correlation between CTVs and local control when no standardization of the derivation of CTVs currently exists is that connecting the (variable) CTVs to outcomes (good and bad) would be a powerful way to drive consensus and standardize CTV derivation. To date, arguing the merits of CTV derivation differences with no relation to outcome has not changed opinions. The recent emergence of computer hardware and software to accomplish image fusion between the original CT simulation scan and the image showing a locoregional failure makes this study possible. As attractive as it would be to perform this analysis on a recently completed RTOG trial, electronically transferring scans showing a locoregional failure has not been required on any protocol to date.
1.8 Exploratory Analysis of the Sensitivity and Specificity of Pre-treatment CT Scans Detecting the Presence of Lymph Node Extracapsular Extension in Surgically Dissected Lymph Nodes

The study of CT imaging and extracapsular extension (ECE) is an exploratory secondary objective analyzing routine imaging required for pre-treatment staging and correlating imaging findings suggestive of ECE with histologically confirmed ECE. This will only be done for patients in the surgical (experimental) arm: an estimated 72 patients. The required time range for this imaging assessment will be within 6 weeks of surgical resection. Thus, the CT scan performed for the patient’s initial staging will be used and later correlated with histologic findings from neck dissection. Table 3 below presents the number of patients needed to precisely estimate the sensitivity and specificity of CT scans. For example, if the true prevalence is 20%, we will need 77 and 34 patients to be 95% confident that sensitivity (90%) and specificity (80%) will be within the precision (15%).

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Sensitivity: 90%, Specificity: 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>307</td>
</tr>
<tr>
<td>10%</td>
<td>154</td>
</tr>
<tr>
<td>20%</td>
<td>77</td>
</tr>
<tr>
<td>30%</td>
<td>51</td>
</tr>
<tr>
<td>40%</td>
<td>38</td>
</tr>
</tbody>
</table>

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To determine if primary treatment with transoral endoscopic head and neck surgery will improve PFS for patients with HPV-OPC.

2.2 Secondary Objectives (10/2/13)

2.2.1 To compare patterns of failure (local-regional relapse versus distant) and survival (overall and progression-free)

2.2.2 To determine the safety and efficacy (rate of positive surgical margins) of using transoral robotic surgery for patients with HPV-negative tumors of the tonsil, tongue-base, or glossopharyngeal sulcus

2.2.3 To compare head and neck cancer-specific quality of life (QOL) short-term (< 6 months) and long-term (2 years) relating to swallowing function

2.2.4 To compare subjective (patient reported) and objective (physiologic) measures of swallowing function short-term and long-term

2.2.5 To assess effect of neck dissection on shoulder function using a validated QOL instrument for patients undergoing neck dissection

2.2.6 To assess the correlation of physician derived CTV’s with locoregional control or failure

2.2.7 To determine whether specific molecular profiles are associated with overall or progression-free survival or other clinical endpoints

2.2.8 To determine the sensitivity and specificity of pre-treatment CT scans detecting the presence of lymph node extracapsular extension by examining the surgically dissected lymph nodes

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED.

3.1 Conditions for Patient Eligibility (8/19/14)

For questions concerning eligibility, please contact the study data manager.

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma of the oropharynx, localized to the tonsil, glossopharyngeal sulcus, and tongue-base within 6 weeks (42 days) of registration

3.1.2 The primary tumor must be resectable through a transoral endoscopic head and neck surgery with anticipation of resection free margins (resection does not require total or subtotal glossectomy or total laryngectomy) Specifically, patients must (1) not have trismus, (2) not have interincisor opening less than 2.5 cm, and (3) not have poor transoral exposure of the tumor itself nor surrounding soft-tissue margins, regardless of etiology.
3.1.3 Clinical stage III-IV; T1-2, N1-2b; with tumors not approaching within 1 cm of midline, and amenable to transoral eHNS

3.1.4 p16 negative by immunohistochemistry (documented by the institution’s pre-enrollment biomarker screening at a CLIA-certified lab), defined as absent, weak, and/or only focal nuclear and cytoplasmic staining in less than 70% of the tumor cells (Begum 2003)

3.1.5 Appropriate stage for protocol entry, including no distant metastases or adenopathy below the clavicles, based upon the following minimum diagnostic workup:

- History/physical examination by the treating physician (Radiation Oncologist, Medical Oncologist, or Head and Neck Surgeon) within 30 days prior to registration
- Imaging of the head and neck (CT with contrast, PET/CT, and/or MRI) within 30 days prior to registration. A CT scan with contrast is mandatory (unless contraindicated, e.g. contrast allergy, etc.). Note that a PET/CT scan alone (unless performed with contrast) is not sufficient.
- Chest CT scan (with or without contrast) or PET/CT of chest (with or without contrast) within 30 days prior to registration
- Modified barium swallow (MBS) to assess swallowing function within 30 days prior to registration
- Preoperative Mallampatti assessment as documented by attending surgeon within 30 days prior to registration (Appendix VII)

3.1.6 Zubrod Performance Status 0-1 within 30 days prior to registration

3.1.7 Age ≥ 18

3.1.8 Adequate bone marrow function within 30 days prior to registration on study, defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,800 cells/mm³ based upon CBC/differential;
- Platelets ≥ 100,000 cells/mm³ based upon CBC/differential;
- Hemoglobin ≥ 8.0 g/dl based upon CBC/differential (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.9 Adequate hepatic function within 30 days prior to registration on study, defined as follows:

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

3.1.10 Adequate renal function within 30 days prior to registration, defined as follows:

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

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

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

3.1.11 Serum pregnancy test within 14 days prior to registration for women of childbearing potential

3.1.12 Women of childbearing potential and male participants who are sexually active must practice medically effective contraception during treatment and for 42 days following completion of treatment.

3.1.13 Patient must be able to provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 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 or cervix are all permissible)

3.2.2 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable; see Section 3.2.1.

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

3.2.4 Severe, active co-morbidity, defined as follows:

- >2 based on the American Society of Anesthesiologists (ASA) physical status classification system (see Appendix IV);
• 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 before registration;
• Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
• Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; 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.

3.2.5 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.6 Prior allergic reaction to cisplatin
3.2.7 Radiographic evidence of retropharyngeal metastasis

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Required Evaluations/Management
4.1.1 Baseline audiogram within 60 days prior to treatment.
4.1.2 Dental evaluation and (if applicable) prophylaxis prior to treatment. For patients receiving surgery, dental extractions may be done at the time of transoral endoscopic resection.
4.1.3 Completed by clinician prior to treatment: Performance Status Scale for Head and Neck Cancer (PSS-HN)
4.1.4 If the patient consents to participate in the quality of life (QOL) component of the study, sites are required to administer the baseline QOL assessments prior to the start of protocol treatment: Charlson Comorbidity Index (CCI), the MD Anderson Dysphagia Inventory (MDADI), and the Neck Dissection Impairment Index (NDII). Note: Patients randomized to Arm 1 will be asked to complete the MDADI prior to eHNS+neck dissection.

4.2 Highly Recommended Evaluations/Management
4.2.1 Baseline electrocardiogram (EKG)
4.2.2 Whole body PET scan
4.2.3 Formal consultation by nutritionist, prophylactic gastrostomy tube placement (if the patient is ≥ 10% below ideal body weight – document: yes/no; if yes, for what length of time), documentation of tracheotomy (yes/no; if yes, for what length of time)

5.0 REGISTRATION PROCEDURES (8/19/14)

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. This is the same account (user id and password) used for the CTSU members’ web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.
### 5.1 Pre-Registration Requirements for Intensity Modulated Radiation Therapy (IMRT) Treatment Approach (8/19/14)

#### 5.1.1
In order to utilize IMRT and IGRT (if using reduced margins) on this study, the institution must have met specific technology requirements and have provided baseline physics information, as indicated in the table below. Instructions for completing these requirements or determining if they already have been met are available on the Imaging and Radiation Oncology Core (IROC) Houston web site at [http://irochouston.mdanderson.org](http://irochouston.mdanderson.org) by selecting “Credentialing”.

#### 5.1.2
For detailed information on the specific technology requirement required for this trial, 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. IROC Houston will notify the institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

<table>
<thead>
<tr>
<th>RT Credentialing Requirements</th>
<th>Web Link for Procedures and Instructions: <a href="http://irochouston.mdanderson.org">http://irochouston.mdanderson.org</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Modality</td>
<td>Key Information</td>
</tr>
<tr>
<td>IMRT</td>
<td>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 <a href="mailto:irochouston@mdanderson.org">irochouston@mdanderson.org</a> to receive your FQ link.</td>
</tr>
<tr>
<td>Facility Questionnaire</td>
<td>X</td>
</tr>
<tr>
<td>Credentialing Status Inquiry Form</td>
<td>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 website (<a href="http://irochouston.mdanderson.org">http://irochouston.mdanderson.org</a>)</td>
</tr>
<tr>
<td>Phantom Irradiation</td>
<td>X An IMRT H&amp;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 (<a href="http://irochouston.mdanderson.org">http://irochouston.mdanderson.org</a>). Tomotherapy and Cyberknife treatment delivery modalities must be credentialled individually.</td>
</tr>
<tr>
<td>IGRT Verification Study</td>
<td>X Only institutions interested in using reduced margins will be required to to complete this credentialing step. The institution must submit a series of daily treatment images along with a spreadsheet of IGRT data from an anonymized head and neck cancer patient. This series must include a minimum of 5 daily pre-treatment images. Pre-treatment images may include three-dimensional (3D) volumetric images (either fan- or cone-beam CT with Megavoltage (MV) or kilovoltage (KV) x-ray or Orthogonal (MV or KV) 2D images. These images and the spreadsheet will be reviewed by the Medical Physics Co-Chair, Sandra Fontenla, MS, prior to certification. The IGRT credentialing details along with the spreadsheet are available on the IROC Houston web site: <a href="http://irochouston.mdanderson.org">http://irochouston.mdanderson.org</a></td>
</tr>
</tbody>
</table>

**Credentialing Notification Issued to:**

| Institution | IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met. |
5.2 Digital RT Data Submission to TRIAD (9/5/13)
TRIAD is the American College of Radiology’s (ACR) image exchange application and it is used by NRG Oncology. TRIAD provides sites participating in NRG Oncology 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 Section 5.0 of the protocol 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. 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 RTOG/NRG Oncology 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.

5.3 Regulatory Pre-Registration Requirements (8/19/14)
5.3.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Participation in this study is limited to institutions with experienced surgeons on the Institution’s NRG Oncology staff roster who are capable and trained to perform eHNS (TLM, TORS). Participating institutions must have the surgical technology as well as all related accessories and instruments in place.

Prior to the recruitment of a patient for this study, investigators must be registered members of a lead protocol organization. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU web site: http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by e-mail at pmbregpend@ctep.nci.nih.gov.

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account. Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)
CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) web sites and applications, including the CTSU members’ web site. Additional information can be found on the CTEP web site at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the CTEP Associate Registration Help Desk by email at ctepreghelp@ctep.nci.nih.gov.

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 enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Site registration forms may be downloaded from the RTOG 1221 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
- Click on the (state organization type e.g. P2C, CITN, NCTN Groupname) link to expand, then select trial protocol, RTOG 1221
- Click on the Site Registration Documents link

Requirements for RTOG 1221 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form (if applicable)

**NOTE:** Per NCI policy, all institutions that participate on protocols with a radiation therapy component must participate in the IROC Houston 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.

- IRB/REB approval letter
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification of consent translation to NRG Oncology.
- IRB/REB assurance number renewal information, as appropriate
- See the additional pre-registration requirements in Sections 5.1, 5.2, 5.5, and 5.6.

**Non-English Speaking Canadian and Non-North American Participating Sites**

*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 Oncology 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.

CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

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. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- 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 at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.3.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
Prior to clinical trial commencement, Canadian institutions must also complete and fax (215-569-0206) or e-mail (CTSURegulatory@ctsucoccg.org) to the CTSU Regulatory Office:

- Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.3.3 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 Oncology to receive approval to participate in this trial. For more details see link below:
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.

5.4 Pre-Registration Requirement: Surgeon Credentialing/Quality Control (10/2/13)

Surgeons must be credentialed by their local institution to perform transoral eHNS (TLM or TORS) prior to enrolling patients on the trial. Adequate experience in at least one of these categories of transoral eHNS must be demonstrated to ensure quality control. Surgeon credentialing for this study will be done exclusively in Medidata Rave®. Access to the Rave “Surgical Credentialing Database” for this study will be granted when IRB approval is obtained.

To register a surgeon and to complete the Head & Neck Surgeon’s Questionnaire (Appendix V):

5.4.1 The responsible research associate must send an e-mail to: HNsurgicalcredentialing@jimmy.harvard.edu with the following information:
- Surgeon's First and Last Name
- Surgeon’s CTEP ID Number
- Institution Site Name
- CTEP Site ID Number
- Surgeon's Fax Number
- Surgeon's Telephone Number

5.4.2 Participating surgeons must complete and sign the Head & Neck Surgeon’s Questionnaire, Appendix V, prior to the institution entering any patients onto this study. The questionnaire will be completed directly in Rave; institutions should keep the signed form in their Regulatory binder.

For each category of transoral surgery this experience will be confirmed, as:
- Each participating surgeon must document that he/she has performed a minimum number of 20 cases of transoral excision for OPSCC as the primary surgeon;
- Each participating surgeon must document that he/she has performed at least 5-10 transoral resections of OPC in the past 12 months;
- The Principal Investigator will review each surgeon’s submitted pathology report and operative notes for ten cases, including at least one tonsil and one tongue-base primary tumor.
5.4.3 Clarification on the Role of Advanced Technologies for Transoral Endoscopic Head and Neck Surgery

A central underlying hypothesis of ongoing efforts in transoral endoscopic head and neck surgery is that improved visualization of surgical anatomy permits surgeons to lower rates of positive margins, higher rates of local control—while preserving more normal surrounding tissue—resulting also in improved functional outcomes, compared to open surgery.

Transoral eHNS (using TORS or TLM) is essential for tumors of the tongue-base and glossopharyngeal sulcus, due to the need to approach these tumors with angled visualization.

For tumors arising in the tonsillar fossa, using a headlight and loupes, resection is possible using conventional methods (Holsinger 2005; Laccourreye 2012). However, surgeons would need to demonstrate the same level of experience and expertise using this technique for tonsillar carcinoma: i.e., attest that at least 20 cases using this technique have been performed by the surgeon and provide evidence of corresponding operative notes and pathology reports, using conventional transoral technique.

5.5 Pre-Registration Requirement: Modified Barium Swallow (MBS) Credentialing

Speech Pathologists must be credentialed to conduct MBS studies prior to enrolling patients on this trial. Participating speech pathologists must complete and sign the Modified Barium Swallow (MBS) Credentialing Checklist, Appendix IX, prior to the institution entering any patients onto this study. The institution will fax the completed form to CTSURegulatory@ctsu.coccg.org and to NRG Oncology at RTOG1221@acr.org. Institutions should allow adequate processing time (10-14 days) before calling to register the first patient.

5.6 Registration (8/19/14)

Institution’s Screening for p16 Prior to Randomization: Mandatory

The enrolling institution is responsible for screening (must be done at CLIA certified lab) for documentation of p16 negative. See Section 10.0 for details of retrospective central review.

5.6.1 OPEN Registration Instructions

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.

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 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 HIPPA authorization form (if applicable).

Access requirements for OPEN:

- See Section 5.0 for 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 NRG Oncology, you must have an equivalent ‘Registrar’ role on the relevant Group or CTSU 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 CTSU members' web site OPEN tab or within the OPEN URL. 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 web support for assistance with web registration: websupport@acr.org or call the 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.

6.0 RADIATION THERAPY (2/19/14)
NOTE: FOR THIS STUDY, IMRT IS MANDATORY AND IGRT IS OPTIONAL (Exception: IGRT is mandatory when using reduced margins).

This trial will utilize TRIAD for dosimetry digital treatment data submission. See Section 5.0 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

Note: Adjuvant radiation therapy is be given only in high-risk patients defined as patients with ≥ 5 metastatic nodes, extracapsular extension, or positive surgical margins on final surgical pathology. Patients without evidence of these high-risk features will not receive adjuvant radiation therapy with concurrent cisplatin.

Protocol treatment must begin within 6 weeks (42 days) post-surgery for Arm 1 and 4 weeks (28 days) post randomization for Arm 2.

6.1 Dose Specifications (2/19/14)

**eHNS + Adjuvant Arm (Arm 1):** The prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size (total of 30 fractions). Radiotherapy should begin on a Monday, Tuesday or Wednesday. The daily dose of 2 Gy will be prescribed such that 95% of the PTV60 volume receives 60 Gy. As described in Section 6.4.2 (also see the detailed description of the dose levels used in this study in Section 1.4), PTV54 should be defined for regions of subclinical disease, which exist in most patients. PTV66 is optional at the discretion of the radiation oncologist for areas felt to be at extremely high risk. PTV66 regions, if used, should be minimized as much as possible because the dose will be delivered at 2.2 Gy/fraction. The spinal cord dose may not exceed 48 Gy to any volume larger than 0.03 cc.

**Chemoradiotherapy Arm (Arm 2):** The prescribed radiotherapy dose will be 70 Gy in 2 Gy once-daily fraction size (total of 35 fractions). Radiotherapy should begin on a Monday, Tuesday or Wednesday. The daily dose of 2 Gy will be prescribed such that 95% of the PTV70 volume receives 70 Gy. The PTV56 is described in Section 6.4.1. The spinal cord dose may not exceed 48 Gy to any volume larger than 0.03 cc.

Treatment of the low neck: see details in Section 6.5.1 (also see the detailed description of the dose levels used in this study in Section 1.4). It is up to investigator/institution to treat the low neck with whole-neck IMRT vs. a matching technique. Whole-neck IMRT is preferred for gross primary or nodal disease extending below the vallecula. Whole-neck IMRT dose will be stratified...
according to risk as outlined in Section 6.4. Dose for Arm 1 will be 60 Gy at 2.0 Gy/fx or 54 Gy at 1.8 Gy/fx (54 Gy for subclinical disease). Dose for Arm 2 will be 70 Gy at 2.0 Gy/fx or 56 Gy at 1.6 Gy/fx (56 Gy for subclinical disease). Dose for matching techniques will be 50 Gy at 2.0 Gy/fx prescribed to 3 cm depth. Preferred matching technique is isocentric matching AP or AP/PA fields with a larynx block matched to the IMRT portals just above the arytenoids. An AP or AP/PA boost can be used in the low neck if necessary for gross or high risk disease at 2.0 Gy/day to dose levels of 60-66 Gy in Arm 1, or 70 Gy in Arm 2. AP/PA technique for lower anterior neck should use spinal cord block as well.

Missed treatments due to holidays or for logistic reasons can be compensated for by delivering an additional treatment (BID, two fractions in one day at least 6 hours apart) during the week, OR treating on the Saturday or Sunday of that week, OR adding to the end of treatment.

6.2 Technical Factors (8/19/14)

6.2.1 Treatment Planning/Delivery: Megavoltage energy photon beam irradiation is required. Any treatment planning and delivery system that has been credentialed for head and neck IMRT for previous NRG Oncology trials is acceptable.

6.2.2 Image Guidance for IGRT When Using Reduced Margins (see Section 5.1.1)

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac
- Linear-accelerator mounted kV and MV helical conebeam CT images
- Linear-accelerator mounted MV CT images (e.g. Tomotherapy)
- Other Mechanism, after discussion with the Radiation Oncology Co-chair

The institution's procedure to register 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 supraclavicular region is a part of the target volume the ROI should extend to the C6 level;
- 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 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 3 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 < 3 mm). If one or more corrections are 3-5 mm, adjustment is necessary prior to treatment; however, re-imaging 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. However, the use of numerous repeat IGRT studies should be avoided (see next section).

Management of Radiation Dose to the Patient from IGRT

Radiation from IGRT are small enough dose contributions that if there is only one imaging study done per treatment session, the dose does not need to be incorporated into treatment planning and is not expected to have any clinical relevance to the patient. However, 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 of more than 5 mm). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.
6.3 Localization, Simulation, and Immobilization

6.3.1 Patients must have an immobilization device (e.g., aquaplast mask) made prior to treatment planning CT scan. The immobilization device should include at a minimum the head and neck. It is preferred but not mandatory that the immobilization device include shoulder immobilization.

6.3.2 The treatment planning CT scan should be performed with IV contrast so that the major vessels of the neck are easily visualized. Contrast corrections are neither necessary nor recommended. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness must be 0.3 cm or less.

6.4 Target and Normal Tissue Volume Definitions (8/19/14)

6.4.1 Definition of Target Volumes for the Chemoradiotherapy Arm

CTV70: This volume will receive 2 Gy per day in 35 fractions over 7 weeks. CTV 70 consists of the primary tumor and grossly involved lymphadenopathy with a 1.0-2.0 cm expansion of the gross tumor volume (GTV) to cover potential local invasion. **This volume may approach the skin but should not approach < 2mm.** (see Section 6.1 for details of prescription for PTV1.)

- CTV 56 consists of sub-clinical disease sites, which include possible local subclinical infiltration at the primary site (Primary site CTV 56) and lymph nodes which are not clinically or radiographically involved (nodal CTV56), should be expanded by 3-5 mm to create PTV56. PTV56 should receive 1.6 Gy/fraction to a total dose of 56 Gy. (This dose assumes an alpha/beta ratio of 10 Gy for tumor and 0.7 Gy loss for each day of extending treatment time beyond the time required to deliver the dose at 2 Gy/fraction; 56/1.6 over 7 weeks would result in BED2 of approximately 50 Gy).
- CTV 50 (Low Neck Match Technique Only) consists of subclinical disease site in the low neck that is treated with a matching technique (described in Section 6.5.1) rather than whole-neck IMRT. Note there is no CTV 50 with whole-neck IMRT. In this trial, CTV 50 at 2.0 Gy/fx is considered roughly equivalent to the whole-neck IMRT dose levels of 54 Gy at 1.8 Gy/fx and 56 Gy at 1.6 Gy/fx.

CTV54: This will include all other regions felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. For example, this would apply to the contralateral hemineck being irradiated electively for base of tongue cancer, CTV 54 should be expanded 3-5 mm to create PTV 54. This volume should not approach the skin < 5 mm. This volume will receive approximately 1.80 Gy per day.

- CTV 50 (Low Neck Match Technique Only) consists of subclinical disease site in the low neck that is treated with a matching technique (described in Section 6.5.1) rather than whole-neck IMRT. Note there is no CTV 50 with whole-neck IMRT. In this trial, CTV 50 at 2.0 Gy/fx is considered roughly equivalent to the whole-neck IMRT dose levels of 54 Gy at 1.8 Gy/fx and 56 Gy at 1.6 Gy/fx.

CTV66 Optional: This may be defined at the discretion of the treating radiation oncologist. This would include a region or regions felt to be at especially high risk for recurrence (e.g., an area of very close margin of resection). **Note:** This area will be receiving a daily fraction size of 2.2 Gy and thus, the volume of CTV66 should be kept as small as possible.

Neck node coverage for both arms: This trial is limited to oropharyngeal carcinoma, and draining lymphatics for this site require coverage of bilateral nodal levels 2a, 3, and 4 (discussed below). Level Ib should be covered with a subclinical dose for any side of the neck containing gross level...
II disease. Radiographic evidence of retropharyngeal lymphadenopathy is an exclusion criterion. For N+ neck(s) the lateral retropharyngeal lymphatic region should be covered. If the primary extends (in either study arm) into the posterior oropharyngeal wall, medial and lateral retropharyngeal lymph nodes should be contoured. For a contralateral neck that is cN0, coverage of contralateral retrostyloid region and contralateral retropharyngeal LN’s is not required, but left to the discretion of the radiation oncologist. Irradiation of the contralateral neck is controversial for lateralized tonsil cancer. For T1-T2, N1-N2b lateralized tonsil cancers that do not extend to within one centimeter of midline and have no or minimal (< 1 cm) soft palate or base of tongue involvement, it will be left to the discretion of the radiation oncologist whether to use ipsilateral or bilateral neck treatment. For questions, contact the Principal Investigator, Dr. Holsinger, or the Radiation Oncology Co-Chair, Dr. Thorstad.

Planning Target Volumes (PTVs): In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered but is generally not recommended. Two PTV’s must be defined for CTVs approaching the skin surface: 1) PTV for planning, which extends beyond the skin surface and is used for adjusting treatment segments; and 2) a PTV evaluation, (called PTV_Eval) which does not reach the skin surface within 5 mm and is used for determining the dose volume histogram used to demonstrate that treatment goals have been met. In some cases the PTV will be the same as the PTV_Eval. The PTV_Eval is constructed by redrawing the PTV with its border near the skin surface maintained at a distance that is 5 mm inside the surface.

- **PTV Expansion Without Daily IGRT**
  For those institutions that are not using daily IGRT, the minimum CTV-to-PTV expansion should be 5 mm (a larger expansion may be necessary for a target volume subject to significant inter-fraction variability such as the tongue). In general, the CTV-to-PTV expansion (without IGRT) should not exceed 10 mm.

- **PTV Expansion With Daily IGRT**
  For those institutions that are using daily IGRT, the minimum CTV-to-PTV expansion is 3 mm (a larger expansion may be necessary for a target volume subject to significant intra-fraction variability, such as the non-immobilized oral tongue). In general, the CTV-to-PTV expansion (with IGRT) should not exceed 5 mm.

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

**Spinal Cord:** The cord begins at the cranial-cervical junction (i.e., the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRV_{cord} = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

**Brainstem:** The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRV_{brainstem} = brainstem + 3 mm in each dimension.

**Lips and Oral Cavity:** These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self-explanatory. The oral cavity will be defined as a composite structure consisting of the anterior \( \frac{2}{3} \) of the oral tongue/floor of mouth, buccal mucosa, and palate.

**Parotid Glands:** Parotid glands will be defined based on the treatment planning CT scan.

**OARpharynx:** This will be defined as the “uninvolved” posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level).
**Cervical Esophagus**: This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.

**Glottic/Supraglottic Larynx (GSL)**: This will be defined as a “triangular prism shaped” volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

**Mandible**: This includes the entire boney structure of the mandible from TMJ through the symphysis.

**Cochleas**: Contour both cochleas using the planning CT.

**Brachial Plexus**: The brachial plexus shall be defined based on the planning CT.

**Unspecified Tissue Outside the Targets**: This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

In cases of weight loss > 10%, significant shrinkage of lymphadenopathy during therapy, resolution of postoperative edema, etc., it is recommended that the immobilization mask will be adjusted or re-made in order to preserve adequate immobilization (should minimize patient motion inside the mask to within 0.5 cm), 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 on the new CT scan, the target doses should be the same as those used for the initial plan. The new CT dataset should be used for IGRT image registration when the patient’s shape changes significantly (resulting in 0.8 cm shift or more).

### 6.4.4 Required Structures – Standard Names for Digital RT Submission

All required RT structures must be labeled and submitted using the Standard Dicom Name as shown in the table below. Resubmission of data is necessary when labeled structures do not conform to the Standard Name.
6.5 Treatment Planning and Delivery (2/19/14)

6.5.1 Management of the Low Neck/Supraclavicular Region (Match vs. No Match)

It is recognized that comprehensive head and neck irradiation incorporating IMRT can be done in 1 of 2 ways, either of which is permitted for this study:

- **Match**: The upper cervical lymphatics and primary tumor bed are treated with IMRT. The lower cervical lymphatics and supraclavicular region are treated with a single AP (or occasionally APPA for larger patients with posterior neck at high risk) non-IMRT technique. The latter non-IMRT field(s) is matched to the upper neck IMRT fields. This technique requires comprehensive mid-line spinal cord blocking in the lower neck fields. This technique also allows for a simultaneous blocking of portions of the larynx.

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<table>
<thead>
<tr>
<th>Standard Name</th>
<th>Description</th>
<th>Required/Required when applicable/ Optional</th>
</tr>
</thead>
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<td>GTV</td>
<td>Required</td>
</tr>
<tr>
<td>CTV_7000</td>
<td>CTV70</td>
<td>Required for Arm 2</td>
</tr>
<tr>
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<td>PTV70</td>
<td>Required for Arm 2</td>
</tr>
<tr>
<td>PTV_7000_Eval</td>
<td>PTV70_Eval</td>
<td>Required- for Arm 2 when applicable</td>
</tr>
<tr>
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<td>CTV66</td>
<td>Required when applicable</td>
</tr>
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<td>PTV_6600</td>
<td>PTV66</td>
<td>Required when applicable</td>
</tr>
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<td>PTV66_Eval</td>
<td>Required when applicable</td>
</tr>
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<td>CTV60</td>
<td>Required for Arm 1</td>
</tr>
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<td>PTV60</td>
<td>Required for Arm 1</td>
</tr>
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<td>PTV60_Eval</td>
<td>Required for Arm 1 when applicable</td>
</tr>
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<td>CTV56</td>
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<td>Parotid_L</td>
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<td>Cochlea_L</td>
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<td>Skin</td>
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</tr>
<tr>
<td>NonPTV</td>
<td>Unspecified Tissue Outside the Targets-Tissue between the skull base and thoracic inlet not included in target volumes or normal tissues.</td>
<td>Required</td>
</tr>
</tbody>
</table>
hypopharynx, and cervical esophagus in the lower neck fields. In general, this technique is appropriate for irradiation of cancers of the oral cavity or oropharynx. For dose specification, see Section 6.1.

- **No Match**: The entire clinical target volume (CTV) [upper and lower neck and primary tumor bed] is irradiated with IMRT. There is no match line between upper and lower portions of the regions at risk. In this technique, limiting radiotherapy dose to organs at risk (OARs), e.g., the cervical esophagus, is entirely achieved by inverse treatment planning via IMRT algorithms. This technique in general is appropriate for irradiation of cancers of the larynx and/or oral/pharyngeal cancers that involve the hypopharynx. For dose specification see Section 6.1.

### 6.5.2 IMRT Dose Prescription to PTVs

See Section 6.4 for definitions of CTVs and PTVs. As described in Section 6.1, prescribed radiotherapy dose for the chemoradiotherapy arm will be 70 Gy at 2 Gy per fraction once-daily. The goal is for 95% of the PTV70 to receive 2 Gy per fraction with a minimum dose (cold spot) of no less than 66.5 Gy. It is recognized that portions of the PTV70 close to the skin may receive significantly less than 66.5 Gy. This is acceptable as long as cold spots within PTV1 do not exist at a depth deeper than 5 mm beneath the skin (see Section 6.7, compliance criteria). The prescribed dose for the eHNS + adjuvant arm will be 60 Gy at 2 Gy per fraction once-daily.

For inverse planning IMRT, the goal is for 95% of the PTV60 to receive 2 Gy per fraction with a minimum dose (cold spot) of no less than 56 Gy. It is recognized that portions of the PTV60 close to the skin may receive significantly less than 56 Gy. This is acceptable as long as cold spots within PTV60 do not exist at a depth deeper than 5 mm beneath the skin (see Section 6.7, compliance criteria).

For prioritization in the Chemoradiotherapy arm, PTV70 will be the highest priority target structure. PTV56 if applicable, will be ranked in the IMRT planning as lower priority than PTV70 although usually at a higher priority than normal structures other than spinal cord and brain stem. In the eHNS + adjuvant arm, PTV60 will be the highest priority target structure. PTV66 and PTV56, if applicable, will be ranked in the IMRT planning as lower priority than PTV60 although higher priority than normal structures other than spinal cord and brain stem.

### 6.5.3 IMRT Dose Constraints to Normal Structures

**Spinal Cord**: The PRVcord (as defined in Section 6.4) 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 PRVbrainstem (as defined in Section 6.4) should not exceed 52 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than the other critical structures listed below.

**Lips**: Reduce the dose as much as possible. The mean dose should be < 20 Gy and the maximum dose will be < 30 Gy.

**Oral Cavity**: Reduce the dose as much as possible. The mean dose should be < 30 Gy. If level 1b requires treatment, the mean dose should be < 50 Gy. Efforts should be made to avoid hot spots (> 60 Gy) within the oral cavity. Evaluate as oral cavity not PTV.

**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. Additional planning goals may include: 1) At least 50% of one parotid will receive < 30 Gy; and/or 2) At least 20 cc of parotid tissue (from the combination of both glands) will receive < 20 Gy.

**OARpharynx**: Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the OARpharynx exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the OARpharynx exceeds 60 Gy.
**Cervical Esophagus**: Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 45 Gy; 2) Mean dose < 35 Gy; 3) No more than 15% of the esophagus exceeds 54 Gy.

**Glottic and Supraglottic larynx (GSL)**: Reduce the dose as much as possible. It is recommended that the dose to the larynx should be kept < 45 Gy whenever feasible.

**Mandible**: Reduce the dose as much as possible. It is recognized that when level 1b requires treatment, portions of the mandible will overlap the CTVs and/or PTVs; however, hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 66 Gy.

**Brachial Plexus**: Maximum dose should be kept to < 65 Gy whenever feasible.

**Cochleas**: Maximum dose should be kept < 50 Gy or D05 < 55 Gy whenever feasible.

**Unspecified Tissue Outside the Targets**: For the chemoradiotherapy arm: No more than 1cc of unspecified tissue outside the targets can receive 74 Gy or more.

For the eHNS + Adjuvant Arm: For the typical case in which there is no CTV66, no more than 5% of unspecified tissue can receive greater than 58 Gy and no more than 1% or 1cc of unspecified tissue can receive 64 Gy or more. When a boost is used to increase the dose to high risk regions to as much as 66 Gy, these numbers can be increased. In this case, no more than 5% of the unspecified dose should exceed the level of the boost dose, and no more than 1% or 1 cc should exceed the boost dose value plus 10%.

6.5.4 Prioritization for IMRT Planning
1. Spinal Cord
2. Brainstem
3. PTV60 for Arm 1 and PTV 70 for Arm 2
4. PTV54 for Arm 1 (if applicable) and PTV56 for Arm 2 (if applicable)
5. PTV66 for Arm 1 (if applicable)
6. a. OARpharynx
   b. Parotid gland contralateral to primary tumor site
7. a. GSL
   b. Esophagus
8. a. Lips
   b. Oral Cavity
9. a. Parotid gland ipsilateral to primary tumor site
   b. Mandible
10. Unspecified tissue outside the targets

6.6 Documentation Requirements for IMRT Treatment Approach
- Pre-treatment radiation therapy planning CT scan;
- If IGRT is not used, then orthogonal images that localize the isocenter placement of IMRT are required.

6.7 Compliance Criteria (8/19/14)
Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed five treatment days at a time and ten 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 two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.
For the eHNS + Adjuvant Arm (Arm 1):

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<th></th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Deviation Unacceptable</th>
</tr>
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<tbody>
<tr>
<td>Total RT dose to 95% of the PTV60 or **PTV60_Eval</td>
<td>60 Gy</td>
<td>59-61 Gy allowed</td>
<td>Values outside the Variation Acceptable limits</td>
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<tr>
<td>Minimum dose (&quot;cold spot&quot;) within PTV60 or **PTV60_Eval, not including portion of PTV near (&lt;5 mm) skin defined for a point that is 0.03 cc in size</td>
<td>56 Gy</td>
<td>55.9 Gy</td>
<td>&lt; 50 Gy</td>
</tr>
<tr>
<td>Maximum dose (&quot;hot spot&quot; ≤0.03 cc) within PTV60 or **PTV60_Eval</td>
<td>70 Gy</td>
<td>70.1-72 Gy</td>
<td>&gt; 72 Gy</td>
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<tr>
<td>Maximum dose (&quot;hot spot&quot; ≤0.03 cc) outside of PTV60 or **PTV60_Eval</td>
<td>66 Gy</td>
<td>66.1-70 Gy</td>
<td>&gt; 70 Gy</td>
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<tr>
<td>Maximum RT dose to spinal cord PRV (≤0.03 cc)</td>
<td>48 Gy</td>
<td>48.1-50 Gy</td>
<td>&gt; 50 Gy</td>
</tr>
<tr>
<td>Overall RT treatment time</td>
<td>&lt; 45 days</td>
<td>46-50 days (without a medically appropriate indication for delay).</td>
<td>&gt; 50 days (without a medically appropriate indication for delay).</td>
</tr>
</tbody>
</table>

*Not including the region of PTV60 that falls within PTV66 (if applicable).
**When it is necessary to have a PTV60_Eval, the PTV60 will not be used for analysis.

For the Chemoradiotherapy Arm (Arm 2):
All treatment plans are to be normalized to provide exactly 95% volume coverage of the PTV1 with 70 Gy.

<table>
<thead>
<tr>
<th></th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Deviation Unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total RT dose to 95% of the PTV 70 or *PTV70_Eval</td>
<td>70 Gy</td>
<td>69-71 Gy allowed</td>
<td>Values outside of Variation Acceptable limits</td>
</tr>
<tr>
<td>Minimum dose (&quot;cold spot&quot;) within PTV 70 or *PTV70_Eval, not including portion of PTV near (&lt;5 mm) skin defined for a point that is 0.03 cc in size</td>
<td>66.5 Gy</td>
<td>59-66.4 Gy</td>
<td>≤ 59 Gy</td>
</tr>
<tr>
<td>Maximum dose (&quot;hot spot&quot; ≤0.03 cc) within PTV70 or *PTV70_Eval</td>
<td>77 Gy</td>
<td>77.1-82 Gy</td>
<td>&gt; 82 Gy</td>
</tr>
<tr>
<td>Maximum dose (&quot;hot spot&quot; ≤0.03 cc) outside the PTVs</td>
<td>74 Gy</td>
<td>74.1-77 Gy</td>
<td>&gt; 77 Gy</td>
</tr>
<tr>
<td>Total dose to PTV56 or *PTV56_Eval (to 95% of the PTV)</td>
<td>54-58 Gy</td>
<td>48-53.9 Gy or 58.1-59 Gy</td>
<td>Values outside of Variation Acceptable limits</td>
</tr>
<tr>
<td>Max RT dose to spinal cord PRV (≤0.03 cc)</td>
<td>50 Gy</td>
<td>50.1-52 Gy</td>
<td>&gt; 52 Gy</td>
</tr>
</tbody>
</table>
Overall RT treatment time | < 52 days | 53-57 days (without a medically appropriate indication for delay) | > 57 days (without a medically appropriate indication for delay)

* When it is necessary to have a PTV70_Eval or PTV56_Eval, the PTV70 or PTV56 will not be used for analysis.

6.8 R.T. Quality Assurance Reviews
The Radiation Oncology Co-Chair, Wade Thorstad, MD, and designees will perform RT Quality Assurance Reviews for this trial. These reviews will be ongoing. IROC Philadelphia RT will facilitate these reviews.

6.9 Radiation Therapy Adverse Events
The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4 will be utilized for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE, v. 4. A copy of the CTCAE, v. 4 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Grade 3 therapy-induced mucositis and/or dysphagia are expected to develop in about one third to two thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded on the appropriate case report form (see Section 12.1), as should 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 VI), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

6.10 Radiation Therapy Adverse Event Reporting
See Section 7.6 for AE reporting guidelines.

7.0 DRUG THERAPY (8/19/14)
Protocol treatment must begin within 6 weeks (42 days) after surgery for Arm 1, and within 4 weeks (28 days) after randomization for Arm 2.

7.1 Treatment (2/19/14)
7.1.1 Cisplatin

Arm 1: Cisplatin 40 mg/m² will be administered intravenously by institutional protocol on days 1, 8, 15, 22, 29, and 36 plus/minus 1 day of adjuvant radiation therapy only in high-risk patients defined as patients with ≥ 5 metastatic nodes, extracapsular extension, or positive surgical margins on final surgical pathology. Patients without evidence of these high-risk features will not receive cisplatin concurrent with adjuvant radiation therapy.

Arm 2: Cisplatin 40 mg/m² will be administered intravenously by institutional protocol on days 1, 8, 15, 22, 29, 36, and 43 plus/minus 1 day of definitive radiation therapy.

For both arms: Each dose of cisplatin can be given either before or after radiation therapy scheduled for that day, but cisplatin should not be given on a different date prior to initiation of the radiation therapy course. Cisplatin administration outside of the specified time points during radiation is allowed only in the event of holidays that do not permit drug and radiation delivery on the specific date. Subsequent chemotherapy doses should follow the protocol specified days of treatment. Cisplatin is administered concurrently with radiation therapy, except for the last dose,
which can be given up to 1 week after radiation has been completed. Missed doses of cisplatin will not be made up. In the event that radiation therapy is held, no cisplatin will be administered. If cisplatin is held, radiation therapy should be continued unless deemed unsafe by the treating physician.

Adequate hydration is strongly recommended; ≥ 1 liter of normal saline prior to cisplatin administration is recommended. The exact hydration schedule will follow the standard of the treating institutions.

The use of prophylactic anti-emetics prior to cisplatin administration is strongly recommended. A minimum regimen of a 5-HT3 antagonist and corticosteroids is recommended. The exact prophylactic anti-emetic regimen will follow the standard of the treating institutions.

Carboplatin or any other cytotoxic agent cannot be substituted for cisplatin. The use of G-CSF or pegfilgrastim are not permitted.

7.2 Cisplatin

Refer to the package insert for detailed pharmacologic and safety information.

7.2.1 Formulation: Refer to package insert for comprehensive information.

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

7.2.3 Administration: Cisplatin will be given as a bolus infusion with appropriate hydration and anti-emetics.

7.2.4 Storage and Stability: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes. See package insert for comprehensive information.

7.2.5 Adverse Effects: The following events are expected with the administration of cisplatin:

- **Nephrotoxicity**: Dose-related and cumulative renal insufficiency is one of the major dose-limiting toxicities of cisplatin. Renal toxicity has been noted in 28-36% of patients treated with a single dose of 50 mg/m². It is first noted in the second week after a dose and is manifested as elevated BUN, serum creatinine, and serum uric acid, or as a decrease in creatinine clearance. Because renal toxicity becomes more prolonged and severe with repeated courses of cisplatin, renal function must return to normal before another dose can be given. Severe renal toxicity might be minimized by induction of diuresis before, during, and after treatment.

- **Ototoxicity**: Observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m². It is manifested by tinnitus and/or hearing loss in the high frequency range. Deafness has been rarely reported.

- **Hematologic Toxicity**: Myelosuppression occurs in 25-30% of patients treated with cisplatin. Nadirs in circulating platelets and leukocytes occur between Days 18 and 23 with most patients recovering by Day 39. Thrombocytopenia, anemia, neutropenia, and fever are also possible adverse events.

- **Gastrointestinal Toxicity**: Marked nausea and vomiting occur in almost all patients treated with cisplatin. Diarrhea and anorexia have also been reported.

- **Neurotoxicity**: Usually characterized by peripheral neuropathies, has been reported. Neuropathy usually occurs after prolonged therapy (4 to 7 months); however, symptoms have been reported after a single dose. Muscle cramps, loss of taste, seizures, autonomic neuropathy, dorsal column myelopathy, and Lhermitte’s sign have also been reported.

7.2.6 Drug Supply: Cisplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.
7.3 Cisplatin Dose Modifications (2/19/14)

**Neutropenia**: The absolute neutrophil count (ANC) must be $\geq 1000$/mm$^3$ on the day of planned chemotherapy in order for cisplatin to be administered. If on the day of scheduled weekly cisplatin the absolute neutrophil count (ANC) is $< 1000$/mm$^3$, then the cisplatin should be held that week. The next weekly dose of cisplatin should be given at full dose only if the ANC has recovered to $\geq 1000$/mm$^3$. If the ANC has not recovered to $\geq 1000$/mm$^3$ within 7 days, then all subsequent cisplatin doses should be reduced to 30 mg/m$^2$ and can only be administered if the ANC is $\geq 1000$/mm$^3$. If, on the day of scheduled treatment, the patient again experiences neutropenia with an ANC $< 1000$/mm$^3$ despite a dose reduction to 30 mg/m$^2$, the cisplatin should again be held for that week. If the ANC has not recovered to $\geq 1000$/mm$^3$ within 7 days, then all subsequent cisplatin doses should be reduced to 20 mg/m$^2$ and can only be administered if the ANC is $\geq 1000$/mm$^3$. Any subsequent ANC $< 1000$/mm$^3$ on the day of scheduled treatment after 2 dose reductions will mandate permanent discontinuation of any remaining doses of cisplatin. If hematologic recovery requires more than 21 days, all subsequent cisplatin doses will be discontinued.

**Neutropenic Fever**: In the event of neutropenic fever (CTCAE, v 4 description of grade 3: ANC $< 1000$/mm$^3$ with a single temperature of $> 38.3$ degrees C (101 degrees F) or a sustained temperature of $\geq 38$ degrees C (100.4 degrees F) for more than one hour), all subsequent doses of cisplatin should be reduced to 30 mg/m$^2$. If neutropenic fever develops despite the initial dose reduction, a second dose reduction to 20 mg/m$^2$ should be given for all remaining cisplatin doses. Recurrent neutropenic fever despite 2 dose reductions will mandate permanent discontinuation of all remaining cisplatin doses.

**Thrombocytopenia**: The platelet count must be $\geq 75,000$ on the day of planned chemotherapy in order for cisplatin to be administered. If on the day of scheduled weekly cisplatin the platelet count is $< 75,000$, then the cisplatin dose should be held for that week. The next weekly dose of cisplatin should be given at full dose only if the platelet count has recovered to $\geq 75,000$. If the platelet count has not recovered to $\geq 75,000$ within 7 days, then all subsequent cisplatin doses should be reduced to 30 mg/m$^2$ and can only be administered when the platelet count is $\geq 75,000$. If, on the day of scheduled treatment, the platelet count is $< 75,000$ despite the first dose reduction, that weekly dose of cisplatin should be held. If the platelet count has not recovered to $\geq 75,000$ within 7 days, a second dose reduction to 20 mg/m$^2$ should apply to all subsequent cisplatin doses. Recurrent thrombocytopenia of $< 75,000$ despite 2 dose reductions will mandate permanent discontinuation of all remaining cisplatin doses. If hematologic recovery requires more than 21 days, all subsequent cisplatin doses will be discontinued.

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

**Nephrotoxicity**: Cisplatin dose should be held if creatinine $\geq 2$ mg/dl. If a patient has a creatinine measurement of $\geq 2$ mg/dl on the day of treatment, treatment should be held that week and should be resumed at a dose of 30 mg/m$^2$ only when the creatinine has recovered to $< 2$ mg/dl. If the serum creatinine again rises to $\geq 2$ mg/dl on the day of treatment, treatment should again be held for that week and should be resumed at a dose of 20 mg/m$^2$ only when the creatinine has recovered to $< 2$ mg/dl. If the creatinine is again $\geq 2$ mg/dl on the day of treatment despite 2 dose reductions, all remaining cisplatin doses will be discontinued.

**Nausea and Vomiting**: Cisplatin will be continued at full dose for $\leq$ grade 2 nausea and vomiting. For patients with grade 3 or higher nausea and vomiting refractory to maximum supportive therapy, cisplatin will be held until recovery to $\leq$ grade 2. No dose reductions for cisplatin will be made.
**Mucositis:** Maximal supportive care will be pursued. As significant mucositis (grade 3-4) is anticipated from the combination of radiation therapy and cisplatin, mucositis will not be a specific indication for cisplatin dose modification, but will be left to the discretion of the investigator.

**Ototoxicity:** If a patient experiences subjective clinical hearing loss not requiring a hearing aid (≤ grade 2) or tinnitus that interferes with activities of daily living (grade 3) that resolves prior to the next dose of cisplatin, reduce the cisplatin to 30 mg/m². If grade 3 tinnitus persists on the day of treatment, or recurs despite a dose reduction, or if there is new hearing loss requiring a hearing aid, discontinue cisplatin.

**Weight Loss:** Any weight loss >10% of patient’s baseline weight should result in chemotherapy dose recalculation.

All other grade 3-4 adverse events: With the exception of grade 4 lymphopenia, discontinue cisplatin until toxicities have recovered to grade 1.

<table>
<thead>
<tr>
<th>ANC (x 1000)</th>
<th>Platelet Count</th>
<th>≥ 75,000</th>
<th>&lt; 75,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1000</td>
<td>100%</td>
<td></td>
<td>HOLD</td>
</tr>
<tr>
<td>&lt; 1000</td>
<td>HOLD</td>
<td></td>
<td>HOLD</td>
</tr>
</tbody>
</table>

7.4 **Modality Review (8/19/14)**

The Medical Oncology Co-Chair, Katharine Price, M.D., 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 12.1. 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.

The Medical Oncology Co-Chair, Katharine Price, M.D., will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology. Dr. Price will perform the next review after complete data for the next 20 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.

7.5 **Drug/Surgical Adverse Events (including surgical device) (8/19/14)**

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 website 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 either the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613). NRG Oncology is responsible for reporting adverse events to the FDA.

### 7.5.1 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

### 7.5.2 Serious Adverse Events (SAEs)

Serious adverse events that meet expedited reporting criteria defined in the table in Section 7.6 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.6. 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.

### 7.5.3 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.

Secondary malignancies that occur following treatment with an agent should 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.

### 7.6 CTEP-AERS Expedited Reporting Requirements

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 12.1).

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=1390853624021
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 to 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 System 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 System allows submission of all reports regardless of the results of the assessment.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies Utilizing a Commercially Available Agent within 30 Days of the Last Administration of the Agent/Intervention

**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 $\geq 24$ 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>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Resulting in Hospitalization ≥ 24 hrs

10 Calendar Days

24-Hour 5 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs

Not required

10 Calendar Days

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:

o “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.

o “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1Serious 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 Commercially Available Agent:

None

8.0 SURGERY (10/2/13)
See Section 5.4 for Surgeon Credentialing/Quality Control.

8.1 Evaluation for Surgery (2/19/14)

8.1.1 Access for Transoral Endoscopic Head and Neck Surgery.
The attending surgeon will perform such preoperative assessments as necessary to determine the likelihood of transoral exposure for tumor resection, including ASA classification (Appendix IV), Mallampatti classification (Appendix VII), dentition, difficulty with c-spine extension, etc. In the judgment of the operating surgeon, the oropharynx should be sufficiently exposed intraoperatively to proceed with enrollment on this trial.

8.1.2 Surgical Staging will be performed by the attending surgeon, based on clinical and radiographic criteria as well as endoscopic examination and measurements (see AJCC T-stage criteria in Appendix III).
8.2 Transoral Endoscopic Head and Surgery (eHNS): Standardizing Technique (10/2/13)

Surgery will generally be performed within 2 weeks after randomization and not more than 4 weeks after randomization.

Any transoral approach intended to obtain negative margins of p16-negative Stage III/IV (T1-T2;N1-N2b) oropharynx SCC. Neck dissection (Levels II-IV) to be performed during resection of the primary tumor or within 4 weeks after randomization.

Surgical technique (for both TLM and TORS) will be standardized. Transoral resection of the oropharyngeal tumor will be performed at the discretion of the attending head and neck surgeon. The type of resection chosen should provide complete removal of the primary lesion with negative gross margins; this is not subject to quality assurance review.

The surgeon will first achieve transoral endoscopic exposure utilizing standardized instrumentation for direct laryngopharyngoscopy and a laryngoscope. The goal of this first portion of the procedure is two-fold: for tumor mapping and to ensure that the tumor is resectable via transoral eHNS.

Once exposure is achieved, the surgeon will proceed with TLM using a CO2 surgical laser or proceed with TORS using the da Vinci Surgical System.

For patients undergoing TLM, the use of the surgical carbon dioxide laser utilizing a wavelength of 10,600 nm is required. Laser safety precautions must be used both by the surgeon and the anesthesia team in the operating room. A “laser” safe endotracheal tube, and/or other safety precautions, where appropriate will be utilized. Additional laser safety precautions may also include covering the eyes with moistened ocular gauze pads as well as wet towels covering every aspect of the skin of the face, head and neck, to minimize the risk of airway fire. Dental guards and lip protection must be utilized to minimize the risk of trauma.

For patients undergoing TORS, surgeons will utilize the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA). Grasping instruments should be used to provide optimal traction and counter-traction. Monopolar electrocautery is utilized for both hemostasis and surgical cutting. Both 5-mm and 8-mm may be utilized based on the surgeon’s preference. Additional non-robotic instrumentation should be utilized by the bedside assistant, including an endoscopic suction catheter(s), bipolar or monopolar cautery, and standard transoral surgical instrumentation such as the Cushing or Debakey forceps, the tonsillar tenaculum. For vascular control, clip appliers such LaryngoForce (Karl Storz 8665L and 8665R) and the LT200 LIGACLIP, (Ethicon, J&J, Cincinnati, OH) should be available.

Eventual documentation of margins is required and is discussed in greater detail below. Assessment by “frozen section” at the time of surgery is preferred. Standard terminology will rely on mucosal margins along four quadrants (anterior, posterior, medial, lateral) and a deep margin.

8.2.1 For tonsillar carcinoma, simple “tonsillectomy” should not be performed. The surgeon should aim to achieve resection of tumor and surrounding structures, with an attempt made to achieve a 1 cm gross visual mucosal margin, with a minimum of 3 mm microscopic margins. The technique for transoral lateral oropharyngectomy is recommended (Holsinger 2005). For tonsillar fossa cancers, the exception to this will be the superior constrictor, which represents the deep margin, which will necessarily obviate a stipulated microscopic margin but must be histologically negative. Therefore, given the three-dimensional complexity of the superior constrictor, margin status will be assessed as a binary endpoint: as negative or positive. These stipulations are subject to quality assurance review.

8.2.2 For tongue-base carcinoma, a standard en bloc resection is preferred to include, wide mucosal margins, resection of the underlying muscle, as well as 4-quadrant mucosal margins, depending on the location of the tumor). The surgeon should aim to achieve an en-bloc resection of tumor and surrounding structures, with an attempt made to achieve a minimum of 1 cm gross visual
margins with $\geq 3$ microscopic margins. These are recommendations subject to quality assurance review.

8.2.3 For lesions arising within the glossopharyngeal/tonsillar sulcus involvement, the same principles of four-quadrant margin assessment will apply, with appropriate deep margin constituting the base of tongue (BOT) and/or constrictor muscle and/or parapharyngeal fat as the deep margin. Of note, cancers which involve the styloglossus muscle or extrinsic muscles of the tongue (e.g. hyoglossus muscle), as evident by preoperative imaging, are excluded since they are T4a cancers.

8.3 Neck Dissection (8/19/14)
8.3.1 A formal selective or modified radical neck dissection, level II-IV, will be performed in all cases. The neck dissection can be performed before Transoral eHNS, concurrently, or after transoral eHNS.

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

8.3.2 Extent of Neck Dissection: Patients will undergo ipsilateral selective or modified radical neck dissection of levels II-IV for lateralized lesions of the tongue-base, tonsillar region and/or glossopharyngeal sulcus. For patients with SCC of the base of tongue that approaches within 1 cm of the midline, a contralateral neck dissection must be performed, also of levels II-IV. For ipsilateral and contralateral lymphadenectomy, level I-b and V may be electively dissected at the discretion of the attending surgeon, but is not required. Level II-b may be spared based on the surgeon’s judgment, for N1 patients. But for patients with N2b neck classification, strong consideration should be given to dissecting level II-b.

8.3.3 For patients with SCC of the base of tongue where occult tumor is found to track during surgery to within 1 cm of the midline, a contralateral neck dissection must be performed, also of levels II-IV. For ipsilateral and contralateral lymphadenectomy, level I and/or V may be electively dissected at the discretion of the attending surgeon, but is not required. For lateralized base of tongue cancers not within 1 cm of midline, the contralateral neck treatment is at the discretion of the treating surgeon. The neck dissection should be oriented or separately partitioned in order to identify levels of lymph nodes encompassed in the neck dissection specimen.

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

8.4 Margin Assessment During Transoral Endoscopic Head and Neck Surgery (10/2/13)
8.4.1 A positive margin is defined as carcinoma in situ or invasive carcinoma at the margin of resection, not superceded by additional tissue found to be histopathologically free of disease.

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

Recommendation for standard practice (permanent section histopathology). It is recommended to perform photodocumentation of the specimen by the pathologist after these procedures, using high resolution digital photography with annotation. If the surgeon obtains additional margins from the patient, the “new margins” should refer back to the geometric orientation of the resected tumor specimen. A statement by the pathologist in the final surgical pathology report should point out that this “new” margin represents the final margin of resection in addition to its histologic status.
8.4.3 An adequate resection is defined as clear resection margins with at least enough clearance from gross tumor to obtain clear frozen section and permanent margins (defined as at least 3 mm grossly).

8.4.4 The details of resection margins should be included in the operative dictation. The margins may be assessed on the resected specimen or alternatively from the surgical bed with proper orientation. The source of these margins will be recorded and correlated with patterns of local and/or regional disease recurrence.

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

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

8.5 Reconstruction Following Transoral eHNS
Reconstruction of surgical defects should be performed using conventional techniques at the discretion of the surgeon. Primary closure is recommended when appropriate but should not be pursued at the expense of obtaining wide, tumor-free margins. Reconstructive closure with local/regional flaps, free tissue transfer, or split thickness skin or other grafts is at the discretion of the attending surgeon.

8.6 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 suggested by imaging/clinical evaluation, then selective neck dissection will be performed unless a cytologic sampling of the node is negative. Post-treatment “planned” neck dissection will be defined as being performed for residual disease and within 15 weeks (105 days) of completion of radiotherapy. Positive neck specimens removed within 105 days will be considered part of the initial treatment plan and not considered as failures of initial management; positive specimens upon neck dissection beyond 15 weeks will be considered regional failures.

Such post-treatment consolidation neck dissections will encompass only the 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 will be determined by the treating surgeon. In the case of negative PET in patients who did not achieve clinical or CT/MRI-based radiological nodal CR, follow-up PET scans are recommended every 3-4 months for 24 months, then every 6 months for years 3-5, as well as careful recording of the clinical dimensions of the residual abnormality.

8.7 Surgical Quality Assurance Reviews (2/19/14)
The Principal Investigator, Floyd Christopher Holsinger, MD, will perform a Quality Assurance Review after complete data for the first 10 cases enrolled has been received at NRG Oncology. Dr. Holsinger will perform the next review after complete data for the next 10 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.

8.7.1 Goals of Surgical Quality Assurance
- To assure eligibility and correct surgical staging of patients
- To assure safety of patients undergoing resection
- To assure adequate resection of the primary tumor and neck dissection

8.7.2 Surgical Protocol Compliance Criteria
**Variations:**
- "Close" margin, (< 3mm)
- Suboptimal neck dissection (<20 nodes removed)
Deviations Unacceptable:
Those deviations that affect patient safety/outcome, which will result in an institution being suspended from further participation in the study, such as:
- Positive Margin rate exceeding 20% (assessed every 5 cases accrued)
- Inadequate nodal dissection (<15 nodes removed)
- Bleeding requiring operative control exceeding 20% (assessed every 5 patients accrued)

8.8 Surgical Adverse Events (including surgical device) (10/2/13)
Surgical Adverse Events include:
- Spinal accessory nerve dysfunction and shoulder immobility
- Long-term dysphagia, requiring permanent gastrostomy
- Aspiration pneumonia
- Need for long-term tracheostomy
- Need for long-term gastrostomy
- Oropharyngeal hemorrhage
- Injury to major nerves, major blood vessels (carotid artery, or any smaller branches) in the oropharynx and neck
- Leakage of “chyle” from the thoracic duct with resulting fluid collection in the neck
- In association with tracheotomy, pneumomediastinum pneumothorax
- Death

NOTE regarding device-related adverse event reporting: CTEP-AERS accepts adverse events attributed to the devices related to transoral robotic surgery (TORS) and transoral laser CO2 microsurgery (TLM). See details in Sections 7.5.2 and 7.6 for other surgical related SAEs and reporting.

9.0 OTHER THERAPY
9.1 Permitted Supportive Therapy
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.

9.1.1 Antiemetics: Prophylactic anti-emetics and supportive therapy for nausea and vomiting are permitted and highly recommended given that cisplatin is highly emetogenic. Anti-emetics should be administered according to institutional guidelines.

9.1.2 Analgesics: The use of narcotic analgesics is often required for treatment of mucositis pain in patients undergoing concurrent chemoradiation to the head and neck. Administration of analgesics will be at the discretion of the treating investigator and in compliance with institutional standards.

9.1.3 Nutritional supplementation: The use of nutritional supplementation with oral formulations or via gastrostomy tube feeding should be considered in patients unable to maintain oral intake and hydration and specifically in patients who experience more than a 10% loss of body weight due to mucositis.

9.2 Non-permitted Supportive Therapy
The use of G-CSF or pegfilgrastim will not be permitted. Erythropoiesis stimulating agents are not permitted.

10.0 TISSUE/SPECIMEN SUBMISSION
NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or quality of life assessment

If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient’s specimens as specified in Section 10.0 of the protocol. Note:
Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 **Tissue/Specimen Submission**

The NRG Oncology Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, it is required that each enrolling institution screen the patient’s tissue for p16 (must be p16 negative) using a CLIA-certified lab. Confirmation of the institution’s local p16 review by the NRG Oncology Biospecimen Resource will be mandatory, and each enrolling institution must submit the tissue to the NRG Oncology Biospecimen Resource (See Section 10.6). Participation in the trial's translational research component is recommended.

10.2 **Surgical Margin Assessment**

See Section 8.3.

10.3 **Local p16 Testing Requirements**

p16 testing by immunohistochemistry as a surrogate marker for oncogenic HPV infection must be performed using a CLIA-certified laboratory at each site. Cases must be p16 negative. Individual institutional validation of p16 will use the standard proposed by El-Naggar and Westra, (H&N 2012) i.e. strong and diffuse nuclear and cytoplasmic staining in >70% of tumor cells.

10.4 **Specimen Collection for Central p16 Confirmation (Mandatory)**

The following material must be provided to the NRG Oncology Biospecimen Resource for central p16 confirmation:

- One H&E slide
- One p16 IHC slide

At the conclusion of the trial, H&E and p16 IHC slides will be reviewed by NRG Oncology for confirmation.

10.5 **Specimen Collection for Tissue Banking and Translational Research (Highly Recommended)**

For patients who have consented to participate in the tissue/blood component of the study (See sample informed consent).

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.5.1 One H&E stained slide (slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide.)

10.5.2 A corresponding paraffin-embedded tissue block of the tumor (the block must match the H&E being submitted) or 15 unstained sections (cut at 5 micron) labeled with the surgical pathology number. Block or unstained slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.5.3 A Pathology Report documenting that the submitted block or unstained slides contains tumor. The report must include the NRG Oncology protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and block information must NOT be removed from the report.
10.5.4 A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for central review to the NRG Oncology Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient’s case number and consent information.

10.5.5 For plasma, serum, and whole blood: For collection, processing, and kit instructions, see Appendix VIII. The following materials must be submitted to the NRG Oncology Biospecimen Resource: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the NRG Oncology protocol number, the patient’s case number, time point of study, and method of storage (for example, stored at -80°C), must be included.

10.5.6 Storage Conditions
Store frozen specimens at -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the ST Form the storage conditions used and time stored.

10.6 Specimen Collection Summary

<table>
<thead>
<tr>
<th>Specimens for Central p16 Confirmation (Mandatory)</th>
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<tbody>
<tr>
<td>Specimens taken from patient:</td>
</tr>
<tr>
<td>Collected when:</td>
</tr>
<tr>
<td>Submitted as:</td>
</tr>
<tr>
<td>Shipped:</td>
</tr>
</tbody>
</table>

Mandatory p16 testing by IHC (must be negative)

Pre-treatment

Screened at enrolling institution, using a CLIA-certified laboratory

Mandatory H&E stained slide (1 slide) and p16 IHC slide (1 slide)

Slides shipped ambient

Specimens for Banking/Translational Research (Highly Recommended)

Representative H&E stained slides of the primary tumor

Pre-treatment

H&E stained slide

Slide shipped ambient

A paraffin-embedded tissue block or 15 unstained tumor slides (cut at 5 micron) of the primary tumor taken before initiation of treatment

Pre-treatment

Paraffin-embedded tissue block or unstained slides

Block or unstained slides shipped ambient

SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge

(1) Pre-treatment

(2) At 6 months from the end of radiation treatment

(3) At 2 years (24 months) from the end of radiation treatment

Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)

Serum sent frozen on dry ice via overnight carrier

PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge

(1) Pre-treatment

(2) At 6 months from the end of radiation treatment

(3) At 2 years (24 months)

Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)

Plasma sent frozen on dry ice via overnight carrier
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix</td>
<td>Pre-treatment&lt;br&gt;Note: If site missed this collection time point they may collect whole blood for DNA at a later time point instead but must note this on the ST Form.</td>
</tr>
<tr>
<td>Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (three to five)</td>
<td>Whole blood sent frozen on dry ice via overnight carrier</td>
</tr>
</tbody>
</table>

10.7 Submit materials for Central p16 Confirmation, Banking, Translational Research as follows:

**U. S. Postal Service Mailing Address: For Non-urgent or Non-frozen Specimens Only**
NRG Oncology Biospecimen Resource
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

**Courier Address (FedEx, UPS, etc.): For Central Pathology Material and Frozen Specimens**
NRG Oncology Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu

10.8 Reimbursement (8/19/14)
NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

10.9 Confidentiality/Storage

10.9.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient’s case number only. The NRG Oncology Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.9.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

10.10 Translational Research (Recommended but not required) (10/2/13)
**Note:** The following correlative studies are proposed as outlined below; however, these proposed studies require the results of the parent study. Specifically, the number of events for the 2 clinical endpoints, PFS and OS, which are necessary to carry out a realistic statistical power justification, cannot be ascertained until the parent study is completed. Therefore, no marker assays will be
conducted on the collected specimens other than those required for patient enrollment (i.e., p16).
When sufficient information is available from the parent study, a full correlative study document for the marker studies will be submitted to and reviewed by CTEP.

10.10.1 The Role of PI3K/PTEN/mTOR Pathway in Local-Regional Recurrence of HPV-Negative Oropharyngeal Carcinoma

**Rationale**
The phosphotidylinositol-3-kinase (PI3K) pathway is a well-known oncogenic pathway in numerous cancers and activated by several receptor tyrosine kinases including epidermal growth factor receptor (EGFR), a key pathway in HNSCC. PI3K activation 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. Activating mutation of the PI3K catalytic subunit, PIK3CA, is seen in approximately 5% of HNSCC (Agrawal 2011; Stransky 2011). In addition, PTEN loss of function, the negative regulator of PI3K, is seen in approximately 40% of HNSCC resulting in uncontrolled activation of PI3K (Okami 1998). Thus, the PI3K/mTOR pathway may serve as a critical biomarker in the management of HPV-negative OPC while its role in this disease is poorly understood. Improved understanding of this pathway potentially serves as an important therapeutic target to improve clinical outcomes in HPV-negative HNC patients. We hypothesize that PI3K/mTOR pathway deregulation is a poor prognostic marker in HPV-negative HNSCC, and the deregulation is defined as: (a) loss of PTEN and activation of p70S6K determined by immunohistochemistry; and (b) PIK3CA activating mutations determined by tumor DNA sequencing.

**Specimen Collection and Submission**
A paraffin-embedded tissue block or 15 unstained sections cut on adherent slides at 5 microns will be collected for immunohistochemistry and PIK3CA mutation testing. See Sections 10.6 and 10.7 for specimen collection requirements and for the address information for sending specimens.

10.10.2 Genomic Profile of Distant Metastasis

**Rationale**
Recent whole exome sequencing data showed that the HPV-negative tumors are genetically complex with several mutations compared to HPV-positive tumors (Agrawal 2011; Stransky 2011). While the mutations are profiled, their biological and clinical contributions to distant metastasis and prognosis are unknown. One hundred ninety-six cancer genes with known mutations, translocations, amplifications, and deletions will be assessed, and these genetic abnormalities will be correlated with the clinical outcomes. We hypothesize that a set of genetic abnormalities will be delineated as a genomic profile of distant metastasis or poor prognosis.

The genetic abnormalities of 196 cancer genes will be determined in one experiment of exon capture-based next generation sequencing by Illumina platform. The DNA will be obtained from tumors and whole blood, and the sequences will be compared between the tumor DNA and normal DNA from whole blood.

**Specimen Collection and Submission**
A paraffin-embedded tissue block or 15 unstained slides (5 micron cut) of tumor will be collected for 196 cancer gene genetic aberration testing. In addition, germline DNA from whole blood will be tested in comparison to the tumor DNA in order to ensure that the detected genetic aberration is specific to tumors. See Sections 10.6 and 10.7 for specimen collection requirements and for the address information for sending specimens.

10.10.3 TGF-beta Polymorphism, Inflammatory Cytokine Profile and Toxicity

**Rationale**
TGF-beta polymorphism and high levels of inflammatory cytokines such as plasma TGF-β1 have been associated with increased risk of radiation-induced lung toxicity suggesting that inflammatory/immunomodulatory cytokines may play an important role in developing acute and
chronic toxicities (Zhao, 2009). Therefore, examining the correlation among the TGF-beta polymorphism, inflammatory cytokine levels in plasma and/or serum and radiation-induced toxicities which may result from acute and chronic inflammation and fibrosis can potentially provide a biomarker to identify patients at risk of chronic radiation-induced toxicities. Changes in the inflammatory cytokine profiles before the treatment, 6 months and 2 years from the completion of the radiation therapy will be determined. The cytokine profile results will be correlated with functional measures determined in PROs and QOL studies described in Sections 1.6 and 11.3. Early identification of the patients at risk of toxicities may benefit from early supportive intervention.

**Specimen Collection and Submission**

Serum and plasma will be collected before initiating any treatment and at 6 months and 2 years from the completion of the radiation therapy. The inflammatory cytokines including TGF-β1, TGF-β2, TGF-β3, IL-10, IL-6, IFN-α, IFN-γ, IL-2, IL-12 p70 or p40/p70, IL-15, TNF-α VEGF, IL-8 and HGF will be measured with multiplex bead assays. See Sections 10.6 and 10.7 for specimen collection requirements and for the address information for sending specimens.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

See Appendix I for a summary of assessments and time frames. See the section below for details of evaluations.

11.2 Details of Evaluations (2/19/14)

11.2.1 Evaluation in Follow Up

An imaging study (CT, MRI and/or PET/CT) within 6 months after completion of therapy to assess for presence or absence of persistent disease.

11.2.2 Scan Submission (Post RT) Patients with Local-Regional Failure

CT scan of patients with local-regional failure (post RT) is to be sent via TRIAD (see Section 12.2.3). The Scan report will be uploaded into RAVE. NOTE: Use of IV contrast is preferred for CT images (unless contraindicated, e.g., contrast allergy, etc.). When a PET/CT is available the CT part of the study (usually done without contrast) can be submitted.

11.3 Patient-Reported Outcome (PRO) and Quality of Life (QOL) Assessments

**NOTE:** Patients must be offered the opportunity to participate in the correlative components of the study, such as quality of life assessment. If the patient consents to participate in the quality of life (QOL) component of the study, sites are required to administer the baseline QOL and functional assessments prior to the start of protocol treatment. See below and Appendix I for the timing of the PRO and QOL assessments.

11.3.1 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 negative population, pre-existing comorbidities are expected to be higher compared to the HPV positive 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 2 treatment arms.

11.3.2 The Performance Status Scale for Head and Neck Cancer (PSS-HN)

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. It is not a PRO; hence, it can be completed quickly by investigators without adding to patient burden.

11.3.3 The MD Anderson Dysphagia Inventory (MDADI)

The MDADI is a 20-item PRO instrument, scored on a scale from 1 to 5, 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. 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. MDADI includes global, emotional, physical, and functional subscales. Scores range from 0 (extremely low functioning) to 100 (high functioning). The MDADI has been validated in head and neck cancer patients in single institutional series (Chen 2001). Reliability (internal consistency reliability) was established with the overall Cronbach $\alpha$ 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 ranged from 0.69-0.88 (global, 0.69; emotional, 0.88; functional, 0.88 and physical, 0.86). Spearman correlation coefficients between MDADI and 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). Furthermore, the MDADI has been used to evaluate patient-reported swallowing outcomes after transoral robotic surgery (Sinclair 2011).

11.3.4 The Neck Dissection Impairment Index (NDII)
The NDII is a 10-item (completed within 5 minutes) validated PRO instrument used to specifically measure QOL-related shoulder dysfunction in patients who have undergone neck dissection. It is available only in English. Scores range from 0-100, with higher scores indicating better shoulder function. Individual items from the NDII are scored from 1-5 with 5 representing higher QOL responses. The total NDII score is then scaled to a 100-point cumulative score. Factors that affect QOL after neck dissection include the patient's age, weight, radiation treatment, and type of neck dissection. The NDII has been validated against the Constant Shoulder scale, which is a general shoulder function assessment of pain, function, and objective measurements of range of movement in patients with shoulder disorders. The NDII includes an evaluation of pain, stiffness, self-care, ability to lift objects, and the effect on social, recreational, and work activities after treatment of the neck (Taylor 2002).

11.4 Outcomes Criteria
11.4.1 All patients in Arm 1 (transoral eHNS arm/experimental arm) must have no measurable tumor following surgery. Gross residual disease immediately following surgery should be documented in the clinical record and will be considered local failure. However, patients intended to have post-operative adjuvant therapy due to adverse features and/or equivocal imaging findings prior to adjuvant therapy would not be considered local failure.

11.4.2 For patients in Arm 2 (chemoradiation/ control arm), clinical or radiographic evidence of progressive local-regional disease beyond 15 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 CXR or 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, CXR or CT of chest will be needed to rule out distant disease or second primaries at the designated evaluation intervals as outlined above.

11.4.3 Local-Regional Relapse/Progression
Arm 1: Recurrent cancer in the tumor bed and/or neck not clearly attributable to a second primary neoplasm; both imaging and biopsy confirmation are strongly recommended. 
Arm 2: 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.

Local-regional relapse/progression will be further subdivided into three subcategories:

- **In-Field Local-Regional Relapse**
  Review of the imaging of the local-regional relapse and the patient’s previous surgery and/or IMRT treatment data reveals that the “epicenter” of the local-regional relapse is within CTV60 and received an estimated dose of at least 50 Gy.
• **Marginal Local-Regional Relapse**
  Review of the imaging of the local-regional relapse and the patient’s previous surgery and/or IMRT treatment data reveals that the “epicenter” of the local-regional relapse was “near” CTV60. This is defined as an estimated dose to this region that is between 20 and 50 Gy.

• **Out-of-Field Local-Regional Relapse**
  Review of the imaging of the local-regional relapse and the patient’s surgery and/or previous IMRT treatment data reveals that the “epicenter” of the local-regional relapse was not near CTV60 or CTV56 and received an estimated dose < 20 Gy. An example would be recurrence in the retropharyngeal nodal space for a patient with oral cavity cancer.

11.4.4 **Distant Relapse**: Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. Multiple foci of disease will be assumed to be distant metastases; a solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise. If there is any question whether or not a malignancy is a recurrence of the original primary cancer versus a new primary, contact the Principal Investigator, Dr. Holsinger.

11.4.5 **Second Primary Neoplasm**: All second primary neoplasms will be biopsy proven with documentation of specific histology. Modified rigorous criteria for a second primary (below) have been adapted from the definition by Warren and Gates (1932). Localized non-melanoma skin cancers are not considered new primary tumors.

  • A distinct lesion separated from the primary tumor site by > 2 cm of normal epithelium;
  • A new cancer with different histology;
  • Any cancer, regardless of head and neck mucosal subsite, occurring 5 or more years after initial treatment;
  • In the lung, new primary tumors, if squamous cell cancer, must have histologic findings of dysplasia or CIS.

11.5 **Toxicity Assessment**
Toxicity Assessment will include clinician-reporting and grading of CTCAE, v.4 symptoms, clinical examination findings, the Performance Status Scale for Head and Neck Cancer (PSS-HN), laboratory examinations, and objective functional assessments, including a modified barium swallow (MBS) examination.

Patient-Reported Outcome (PRO) assessments will include 2 PRO tools: the MD Anderson Dysphagia Inventory (MDADI) and the Neck Dissection Impairment Index (NDII), which will assess effect of eHNS and neck dissection with risk-adapted RT on QOL related to swallowing and shoulder function, respectively, from the patient’s perspective.

For dysphagia assessments, 6 (in the control arm) and 7 (in the eHNS arm) time points for protocol-specific toxicity and PRO assessments using the MDADI to capture short and long-term effects of eHNS and risk adapted radiotherapy on swallowing function at the following time points: Baseline prior to treatment; 2-4 weeks after eHNS and prior to RT (in the eHNS arm only); at completion of RT; at 3, 6, 12, and 24 months after completion of RT.

Objective measurements of swallowing function will include MBS at baseline, postoperatively (on the surgical arm 2-4 weeks after eHNS), and at 6 and 24 months after completion of RT. Evaluation of gastrostomy tube retention rates will be recorded at each follow-up visit corresponding to the PRO measurements.

11.5.1 **Modified Barium Swallow (MBS)** (8/19/14)
Radiographic assessment using the MBS exam is the gold standard to define physiology and aberrations in bolus transit. MBS events including aspiration and pharyngeal residue predict adverse health effects (ie, pneumonia) after cancer therapy.
Patients with oropharyngeal primary tumors demonstrate a high burden of dysphagia. In a population-based analysis of over 8,000 HNSCC, patients with cancers of the oropharynx had the second-highest prevalence of dysphagia (Francis 2010). In addition, 31% of patients demonstrated elevated occurrences of aspiration relative to baseline > 1 year after treatment, and 22% developed pneumonia in an oropharyngeal cancer trial of chemotherapy and IMRT that was designed to protect dysphagia-organs-at-risk using specific dose-constraints (Eisbruch 2011). Furthermore, aspiration based on MBS findings was significantly predictive of pneumonia in the trial of chemotherapy and IMRT for oropharyngeal cancer (p=0.017, Se 80%, Sp 60%), and silent aspiration was evident on MBS studies in 63% of patients who developed pneumonia. In addition, pharyngeal residue on MBS studies was significantly associated with the development of pneumonia after chemotherapy and IMRT (p<0.01) (Hunter 2012). These results offer compelling support for the examination of objective swallowing impairment (ie, “airway protection” and “pharyngeal transit”) as these health-related endpoints cannot be obtained by complementary patient-reported outcomes (PROs). Therefore, we hypothesize that clinically significant aspiration can be detected with greater precision and permit an objective comparison between our control (IMRT) and experimental (eHNS) arms.

To date, however, longitudinal MBS data have not been reported after an eHNS approach to oropharyngeal cancer. Hence, currently available data do not provide validated prospective point estimates for swallowing impairment (per gold-standard MBS) after an eHNS approach. Thus, this proposed phase II study is a critical next step for the head and neck oncology community to obtain valid estimates of swallowing dysfunction among patients treated with upfront surgery versus those treated with upfront radiation. These data will power future comparative phase III trials, since up to now no randomized prospective comparisons have been made. This is a critical gap in knowledge as swallowing outcomes are acknowledged to be the primary factor that may triage patients to eHNS or chemoradiation if survival is equivalent (Weinstein 2009). Longitudinal MBS studies included in this trial will obtain these data for the first time.

Modified Barium Swallow studies will be performed according to the assessment schedule below to objectively evaluate the patients’ swallowing function. MBS studies will be performed at participating institutions by a certified speech pathologist and radiologist according to a standard protocol outlined by the Functional Outcomes Co-Chair for RTOG 1221 (Jan S. Lewin, PhD). Participating institutions will be vetted against a checklist of requirements prior to study activation to ensure adherence to a standard MBS protocol. Institutions must be assessed and declare their participation in this aspect of the study prior to site opening to accrual.

<table>
<thead>
<tr>
<th>Table 1. Schedule of Dysphagia Assessment (MBS)</th>
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<tbody>
<tr>
<td>Time point in Trial</td>
</tr>
<tr>
<td>Short term:</td>
</tr>
<tr>
<td>Baseline, prior to treatment</td>
</tr>
<tr>
<td>Within 2-4 weeks after eHNS, but prior to RT</td>
</tr>
<tr>
<td>6 months post RT</td>
</tr>
<tr>
<td>Long term:</td>
</tr>
<tr>
<td>2 years after completion of RT</td>
</tr>
<tr>
<td><strong>Total Number of MBS Studies</strong></td>
</tr>
</tbody>
</table>

A standardized contrast medium (Varibar® thin liquid and pudding contrast, Bracco Diagnostics, Inc. Princeton, NJ) will be used, and images will be digitally recorded for MBS studies at a rate of 30 frames/second. **Note:** MBS image capture rates below 15 frames/second are not accepted. Sites using an MBS capture rate outside the standard 30 frames/second but above 15
frames/second may participate, provided the site documents the exact capture rate (frames/second) on the MBS form.

The patient is seated upright in the fluoroscopy suite and administered barium contrast in liquid and solid food preparations according to an evidence-based standardized protocol (Martin-Harris 2008). Training guidelines will be provided to all participating institutions to standardize MBS conduct. Participating institutions will be evaluated prior to conducting MBS studies to ensure quality control. The quality assurance checklist will include documentation of national credentials (American Speech Language Hearing Association) by speech pathologists, commitment to use of Varibar barium contrast agents, and documentation of videorecording capabilities.

Using the MBS study, the risk of dysphagia will be determined by the SLP using three discrete swallowing outcomes:

1) Laryngeal penetration (yes, no);
2) Aspiration (none, sensate, silent),
3) Pharyngeal residue (no, < 50%, > 50%)

and recorded on a standardized study specific case report form by speech pathologists conducting MBS studies at participating sites. These have been selected as universal items generally reported by swallowing clinicians that have been shown to significantly predict pneumonia in patients with oropharyngeal cancers. Prevalence of these dysphagia endpoints will be estimated at each time point and compared between arms. Summary ratings will be obtained as a representation of global impairment on the MBS study, rather than ratings of discrete bolus trials.

Clinicians conducting MBS studies at participating sites will be asked to submit summary ratings on a standard data collection form. The form includes rules for standardization of the MBS procedure, rating guidelines and definitions. Digital MBS video files will be submitted to NRG Oncology and submitted for central review by an expert speech pathologist blinded to study arm, MBS timing, participant, and site. The study team will review the initial 2 blinded digital MBS videos submitted to NRG Oncology for quality assurance. A process evaluation checklist will be completed as outlined in Table 2.

<table>
<thead>
<tr>
<th>TABLE 2. QUALITY ASSURANCE CHECKLIST FOR MBS DIGITAL VIDEO FILES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MBS Standard</strong></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>1 FRAME RATE CORRECT?</td>
</tr>
<tr>
<td>2 TIME CODE IMPRINTED?</td>
</tr>
<tr>
<td>3 BOLUS PROTOCOL FOLLOWED?</td>
</tr>
<tr>
<td>4 FIELD CORRECT</td>
</tr>
</tbody>
</table>

Description of the scoring procedures and type of data to be acquired:
Three MBS outcomes will be rated: 1) Laryngeal penetration, 2) Aspiration, and 3) Pharyngeal residue. These have been selected as universal items generally reported by swallowing clinicians that have been shown to significantly predict pneumonia in patients with oropharyngeal cancers. Laryngeal penetration and aspiration represent impairments in airway protection, whereas pharyngeal residue represents impairment in bolus clearance. Factor analyses have established these as valid constructs of pharyngeal dysphagia in patients with head and neck cancer. (Frowen, 2008) Prevalence of these dysphagia endpoints will be estimated at each time point and compared between arms. Summary ratings will be obtained as a representation of global impairment on the MBS study, rather than ratings of discrete bolus trials.

Outcomes will be summarized and scored on ordered categorical scales for two domains of pharyngeal swallowing function: **airway protection** and **pharyngeal residue**. Examples of ordered ratings of **airway protection** and **pharyngeal residue** are summarized in still images in Figures 1 and 2, respectively.

**Figure 1. Airway Protection Ratings per MBS**

A) No laryngeal entry of bolus. B) Laryngeal airway entry above true vocal folds (TVF). C) Laryngeal airway entry below TVF with subsequent clearance. D) Laryngeal airway entry below TVF without response or clearance.

**Figure 2. Pharyngeal Residue Ratings per MBS**

A) No residue. B) <50% pharyngeal residue. C) >50% pharyngeal residue.

Scoring guidelines for MBS studies will follow widely-accepted, psychometrically validated measures. Penetration-Aspiration ratings will be rated according to guidelines from the Penetration-Aspiration Scale (Rosenbek 1996), and Pharyngeal Residue ratings according to guidelines from the MBSImp (Martin-Harris 2008) as outlined in Tables 3 and 4, respectively. See also MBSImp Manual (http://bit.ly/UxOAdo).
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 intrarater reliability on the Penetration-Aspiration Scale were 0.96 and 0.95-0.97, respectively. (Rosenbek, 1996) Scoring guidelines for ordinal ratings of laryngeal penetration and aspiration for RTOG 1221 are defined in Table 3.

### TABLE 3. SCORING GUIDELINES FOR LARYNGEAL PENETRATION AND ASPIRATION

<table>
<thead>
<tr>
<th>PENETRATION-ASPIRATION SCALE (Rosenbek, 1998)</th>
<th>RTOG 1221 ITEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Laryngeal Penetration</td>
</tr>
<tr>
<td>1= Material does not enter the airway</td>
<td>0 = No</td>
</tr>
<tr>
<td>2= Material enters the airway, remains above TVF, ejected from airway</td>
<td>0 = No</td>
</tr>
<tr>
<td>3= Material enters airway, remains above TVF, not ejected</td>
<td>1 = Yes</td>
</tr>
<tr>
<td>4= Material enters airway, contacts TVF, ejected from airway</td>
<td>1 = Yes</td>
</tr>
<tr>
<td>5= Material enters airway, contacts TVF, not ejected</td>
<td>1 = Yes, sensate</td>
</tr>
<tr>
<td>6= Material enters airway, below TVF, ejected</td>
<td>1 = Yes, silent</td>
</tr>
<tr>
<td>7= Material enters airway, below TVF, not ejected despite effort</td>
<td>2</td>
</tr>
<tr>
<td>8= Material enters airway, below TVF, not effort to eject</td>
<td>2</td>
</tr>
</tbody>
</table>

Pharyngeal residue is also 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; 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). Scoring guidelines for ordinal ratings of pharyngeal residue in RTOG 1221 are defined in Table 4.

### TABLE 4. SCORING GUIDELINES FOR PHARYNGEAL RESIDUE

<table>
<thead>
<tr>
<th>MBSIMP PHARYNGEAL RESIDUE Component 16 (Martin-Harris, 2008)</th>
<th>RTOG 1221 ITEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharyngeal Residue</td>
<td></td>
</tr>
<tr>
<td>0 = No pharyngeal residue</td>
<td>0 = None or coating of pharyngeal structures</td>
</tr>
<tr>
<td>1 = Trace residue (&quot;coating&quot;) pharyngeal structure</td>
<td>1 = Yes, &lt; 50% residue</td>
</tr>
<tr>
<td>2 = Collection residue on or within pharyngeal structures</td>
<td>2 = Yes, ≥ 50% residue</td>
</tr>
<tr>
<td>3 = Majority residue on or within pharyngeal structures (half or more)</td>
<td>3</td>
</tr>
<tr>
<td>4 = Minimal/no pharyngeal clearance</td>
<td>4</td>
</tr>
</tbody>
</table>
Post-treatment MBS scores will be normalized to baseline function. Risk for the development of dysphagia after treatment will be estimated using prevalence rates of dysphagia in the control and experimental arm. If there is a 20% difference in objective dysphagia, as defined in MBS studies between groups in this randomized Phase II-b trial, this "cut-point" would be used to power a Phase III clinical trial comparing surgery versus radiation therapy for patients with HPV-negative oropharyngeal cancer—provided that there is no difference in oncologic outcomes between the two groups.

Using MBS, we hypothesize that clinically significant aspiration can be detected between arms. Aspiration is a sensitive marker of differences in normal tissue toxicity, and predictor of aspiration pneumonia. (Eisbruch, 2011; Hunter, 2012) Probabilities of baseline-adjusted aspiration have been evaluated as a function of laryngeal and pharyngeal constrictor normal tissue dose after chemoradiation for oropharyngeal cancer. The sigmoidal shape of the normal tissue complication probability curve (NTCP) for aspiration suggests that risk-based postoperative IMRT (60 Gy) rather than a definitive dose (70 Gy) will reduce the rate of aspiration after treatment. At a mean pharyngeal constrictor dose of 70 Gy, NTCP curves estimate roughly 70% baseline-adjusted risk of aspiration ≥12-months compared with less than 40% risk when the mean pharyngeal constrictor dose is lowered to 60 Gy. (Eisbruch, 2011) Thus, we hypothesize that baseline-adjusted risk of aspiration 6- and 24-months after treatment may significantly differ between arms in RTOG 1221 as a function of difference in normal tissue toxicity by pharyngeal dose sparing.

The SLP conducting the MBS study at participating institutions will provide summary rating for 3 discrete MBS outcomes as outlined above. Operational definitions and grading guidelines will be provided by the Functional Outcomes Co-Chair to minimize variability of ratings. Ratings from participating sites will be captured on a study specific case report form and submitted to the coordinating center. Thereafter, digital media files will be submitted for central review (NRG Oncology, then transmitted to the Functional Outcomes Co-Chair, Jan S. Lewin, PhD) to assess reliability of clinician ratings submitted from participating sites and to permit secondary analyses. A certified speech pathologist supervised by Dr. Lewin will conduct frame-by-frame analysis of MBS studies for the 3 summary ratings, blinded to treatment arm and time point of assessment. The speech pathologist(s) conducting central review will demonstrate adequate experience with MBS studies to ensure quality control and reliability. Didactic training (4-8 hours) will be held with Dr. Lewin and SLPs conducting central review. The speech pathologists conducting central review will meet reliability standards in the MDACC laboratory prior to analyzing MBS studies for RTOG 1221. Kappa statistics will be used to summarize the inter-rater reliability.

MBS endpoints used to compare arms in RTOG 1221 will be extracted exclusively from central review of MBS studies to ensure quality control. As a supplementary outcome, however, ‘real-time’ reporting of MBS outcomes by clinicians conducting MBS at participating sites will also allow NRG Oncology to establish reliability of ratings from SLPs at participating sites and conduct process evaluation to determine deviations from the study specific MBS protocol. These feasibility data regarding the reliability of “real-time” MBS reporting will be imperative to inform decisions about data collection from MBS studies in future cooperative group trials.

As an exploratory objective, the MDADI and MBS results obtained will be correlated with the changes in plasma TGF-β1 levels comparing pre- and post-treatment at 6 months and at 2 years and with TGF-β1 single nucleotide polymorphism, T869C variants (TC+CC). We hypothesize that persistent elevation of plasma TGF-β1 post-treatment will be associated with increased fibrosis-related, long-term toxicities such as dysphagia, and patients with TGF-β1 T869C variants (TC+CC) are predisposed to dysphagia due to a higher level of TGF-β1 compared to wild type (TT). TGF-β1 and 35 additional immunomodulatory and inflammatory cytokines including TGF-β2, IFN-α, TNF-α, IFN-γ, VEGF, IL-6, IL-8, etc. levels in plasma will be measured by the multiplex bead assay using the Luminex system and TGF-β1 T869C variants will be determined by PCR-based Taqman Assay using DNA from whole blood.
For the shoulder function assessment, the NDII will be administered only in patients undergoing neck dissection at the following time points: Baseline prior to eHNS + neck dissection; 2-4 weeks and 12 months after neck dissection.

11.6 Criteria for Discontinuation of Protocol Treatment
- Progression of disease;
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0.
- Patient refusal

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION (8/19/14)
This study will utilize Medidata Rave® for remote data capture (RDC) of all data. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS. To access iMedidata/Rave see Section 5.0 of the protocol.

Each person responsible for data entry must be on the NRG Oncology roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS (Regulatory Support System), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (imediadata-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 will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1 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. The following section provides information about expedited reporting. For this trial the Protocol Specific Adverse Events and Other Adverse Events forms are used for routine AE reporting in Rave.
<table>
<thead>
<tr>
<th>Folder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration via the OPEN System</td>
</tr>
</tbody>
</table>
| Enrollment When pushed into RAVE there will be 5 forms representing registration | **Demography Form**  
**Step Information Form**  
**Treatment Assignment Form**  
**Eligibility Checklist Form** |
| Baseline | **Patient History Form** (formerly known as the A5)  
**Work Up**  
**Lab Results Baseline**  
**Diagnostic Staging**  
**Prior Treatment**  
**Exclusion Criteria**  
**Protocol Specific AE Form**  
**Scan Submission** (Refer to Section 12.3)  
**PSS-HN**  
**MBS**  
**CCI** |
| Baseline RT | **Digital Data** (Refer to Section 12.2) |
| 2-4 Weeks Post Surgery (Arm 1 Only) | **Surgery**  
**PSS-HN**  
**Protocol Specific AE Form**  
**Other Adverse Event Forms** – if new or continuing adverse events = ‘yes’  
**MBS** |
| End of RT (Arm 1 Only) | **RT Administration**  
**RT Treatment**– if was radiation therapy given = ‘yes’  
**RT Treatment Record**- if was radiation therapy given = ‘yes’ (Upload of report required)  
**Cisplatin**  
**Protocol Specific AE Form** |
<table>
<thead>
<tr>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other Adverse Event Forms</strong></td>
<td>if new or continuing adverse events = ‘yes’</td>
</tr>
<tr>
<td><strong>Supportive Care</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Follow Up Head and Neck</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PSS-HN</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IF CONSENTED FOR QOL:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MDADI Cover page</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MDADI</strong></td>
<td>if questionnaire completed = ‘yes’</td>
</tr>
<tr>
<td><strong>End of RT (Arm 2 Only)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>RT Administration</strong></td>
<td></td>
</tr>
<tr>
<td><strong>RT Treatment</strong></td>
<td>if was radiation therapy given = ‘yes’</td>
</tr>
<tr>
<td><strong>RT Treatment Record</strong></td>
<td>if was radiation therapy given = ‘yes’ (Upload of report required)</td>
</tr>
<tr>
<td><strong>Cisplatin</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Protocol Specific AE Form</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Other Adverse Event Forms</strong></td>
<td>if new or continuing adverse events = ‘yes’</td>
</tr>
<tr>
<td><strong>Supportive Care</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Follow Up Head and Neck</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PSS-HN</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IF CONSENTED FOR QOL:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MDADI Cover Page</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MDADI</strong></td>
<td>if questionnaire completed = ‘yes’</td>
</tr>
<tr>
<td><strong>Weeks 1-8 Labs</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Lab Results Follow Up Weeks 1-8</strong></td>
<td>(During Treatment Labs)</td>
</tr>
<tr>
<td><strong>MONTH 1 (Post RT)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Patient Contacted</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>if Patient able to be Contacted = ‘yes’</td>
</tr>
<tr>
<td><strong>Follow-up Head and Neck</strong></td>
<td>if Patient able to be Contacted = ‘yes’</td>
</tr>
<tr>
<td><strong>Disease Assessment</strong></td>
<td>if Documented clinical assessment = ‘yes’</td>
</tr>
<tr>
<td><strong>Scan Submission</strong></td>
<td>if local or regional recurrence or progression = ‘yes’</td>
</tr>
<tr>
<td><strong>New Primary Cancer</strong></td>
<td>If New Primary Cancer = ‘yes’</td>
</tr>
<tr>
<td><strong>Non-Protocol Treatment</strong></td>
<td>if non-protocol cancer therapy = ‘yes’</td>
</tr>
<tr>
<td><strong>Protocol Specified AE Form</strong></td>
<td>if Patient able to be Contacted = ‘yes’</td>
</tr>
<tr>
<td><strong>Other Adverse Events</strong></td>
<td>if new or continuing adverse events = ‘yes’</td>
</tr>
<tr>
<td><strong>Primary Cause of Death</strong></td>
<td>if Patient’s Vital Status = ‘dead’</td>
</tr>
</tbody>
</table>
| MONTH 3 (Post RT) | • **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'  
• **Scan Submission** - if local or regional recurrence or progression = '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'  
• **PSS-HN**  
**IF CONSENTED FOR QOL:**  
• **MDADI Cover page**  
• **MDADI** – if questionnaire completed = ‘yes’ |
| MONTH 6 (Post RT) | • **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'  
• **Scan Submission** - if local or regional recurrence or progression = '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’  
• **PSS-HN**  
• **MBS**  
**IF CONSENTED FOR QOL:**  
• **MDADI Cover page**  
• **MDADI** – if questionnaire completed = ‘yes’ |
| MONTH 9 (Post RT) | • **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'  
• **Scan Submission** - if local or regional recurrence or progression = '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’  
• **PSS-HN**  
• **MBS**  
**IF CONSENTED FOR QOL:**  
• **MDADI Cover page**  
• **MDADI** – if questionnaire completed = ‘yes’  
• |
| Follow-up Head and Neck - if Patient able to be Contacted = 'yes' |
| Disease Assessment - if Documented clinical assessment = 'yes' |
| Scan Submission - if local or regional recurrence or progression = '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' |

MONTH 12 (Post RT)  

| 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'  
| Scan Submission - if local or regional recurrence or progression = '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'  
| PSS-HN  
| IF CONSENTED FOR QOL:  
| MDADI Cover page  
| MDADI - if questionnaire completed = 'yes'  
| NDII Cover Page (Arm 1 only)  
| NDII (Arm 1 only) – if questionnaire completed = 'yes'  

MONTH 15 (Post RT)  
MONTH 18 (Post RT)  
MONTH 21 (Post RT)  

| 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'  
| Scan Submission - if local or regional recurrence or progression = 'yes'  

RTOG 1221, Version Date 8/19/14
### MONTH 24 (Post RT)
- **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’

### MONTH 30 (Post RT) and MONTH 36 (Post RT) and MONTH 42 (Post RT) and MONTH 48 (Post RT) and MONTH 54 (Post RT) and MONTH 60 (Post RT)
- **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’
- **Scan Submission**: if local or regional recurrence or progression = ‘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’
- **PSS-HN**
- **MBS**

**IF CONSENTED FOR QOL:**
- **MDADI Cover page**
- **MDADI**: if questionnaire completed = ‘yes’
12.2 Summary of Dosimetry Digital Data Submission (8/19/14) Submit to TRIAD; see Section 5.0.

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>Digital Data Submission – Treatment Plan submitted in DICOM format to TRIAD exported from treatment planning machine by Physicist</td>
<td></td>
</tr>
<tr>
<td>Digital data submission includes the following:</td>
<td></td>
</tr>
<tr>
<td>• CT data, critical normal structures, all GTV, CTV, and PTV contours</td>
<td></td>
</tr>
<tr>
<td>• Digital beam geometry for beam sets</td>
<td></td>
</tr>
<tr>
<td>• Doses for concurrently treated beams</td>
<td></td>
</tr>
<tr>
<td>• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan</td>
<td></td>
</tr>
<tr>
<td>• All Required Structures MUST be labeled per the specifications of Section 6.4.4</td>
<td></td>
</tr>
<tr>
<td>• All Digital RT Data must be in DICOM format</td>
<td></td>
</tr>
<tr>
<td>• RTOG 1221 Datasheet, located on the RTOG/NRG Oncology web site at <a href="http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1221">http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1221</a></td>
<td></td>
</tr>
<tr>
<td>to be submitted via TRIAD with RT Digital Data listed above</td>
<td></td>
</tr>
</tbody>
</table>

Upon submission of the digital data via TRIAD: Complete a DDSI Form located at: [http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx](http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx)

<table>
<thead>
<tr>
<th>Final Dosimetry Information</th>
<th>Within 1 week of RT end</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy Form Protocol Specific Form Daily Treatment Chart Upload</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.
12.3 **Scan Submission via TRIAD (2/19/14)**

Post RT: CT scan (with scan report) of patients with Local-Regional failure is to be submitted via TRIAD. When a PET/CT is available, the CT part of the study is to be submitted. (see Sect. 11.2.2)

The scan report is to be uploaded into RAVE.

*Due*: Within 1 week of scan date

12.4 **Digital MBS Video files submission via TRIAD (8/19/14)**

Digital MBS video files will be submitted (DICOM format preferred) to TRIAD. (Refer to Section 11.5.1 for time points and details of the study.) Sites must de-identify MBS files prior to uploading to TRIAD.

*Due*: Within 1 week of MBS study date

13.0 **STATISTICAL CONSIDERATIONS**

13.1 **Primary Endpoint**

13.1.1 Progression-free survival (PFS)

13.2 **Secondary Endpoints (10/2/13)**

13.2.1 Patterns of failure (local, regional, distant)

13.2.2 Overall survival (OS)

13.2.3 Rate of grade 4-5 oropharyngeal hemorrhage and involved surgical margin

13.2.4 Objective swallowing function

13.2.5 Shoulder function

13.2.6 Exploratory correlation of physician derived CTVs with locoregional control or failure

13.2.7 Correlative study endpoints

13.2.8 To determine the sensitivity and specificity of pre-treatment CT scans detecting the presence of lymph node extracapsular extension by examining the surgically dissected lymph nodes

13.2.9 Quality of life: head and neck-specific (swallowing domain and shoulder function) at <6 months and at 2 years

13.3 **Randomization and Stratification (10/2/13)**

Patients will be randomized to 1 of 2 treatment arms. Additionally, patients will be stratified according to T stage (T1 vs. T2); N stage (N1 vs. N2); and Zubrod performance status (0 vs. 1).

13.4 **Sample Size Determination (10/2/13)**

From available, reliable data in RTOG 0129, the expected 2-year PFS for patients in the control arm of the proposed trial is 55%. We expect the 2-year PFS for the experimental arm to be 70%, based on published studies (Quon 2011; Cohen 2011). To test this hypothesis with one-sided 10% type I error and 80% power, we require 72 PFS events and 124 patients. Inflating the number of patients to 144 to allow for 10% ineligibility and 4% p16 IHC discordance, and assuming an annual accrual of 38 patients, this trial will require an approximate 3.8 year accrual period and 5.3 years of total study duration.

13.4.1 **Definitions of Failure**

The following table shows how each first event will be counted for progression-free survival, local-regional failure, and distant metastasis. Anything not explicitly in the table (e.g., second primary tumor) is not considered an event, and the patient will continue to be followed for failure. For overall survival, death from any cause will be considered a failure. All failure times will be measured from randomization to the date of failure, competing risk, or last follow-up. The treatment arms have different disease assessment times relative to the date of randomization. For example, the 3-month post-RT assessment for patients on the surgical arm will occur approximately 24-29 weeks after randomization, while the same assessment will occur 21-24 weeks after randomization for the chemoradiation arm. To account for this bias, PFS time will be adjusted for the surgery arm by subtracting off the time from surgery to the start of radiation therapy, unless the first event is death. Other time-to-event endpoints, other than overall survival, will also be adjusted in this way.
<table>
<thead>
<tr>
<th>First event</th>
<th>Progression-Free Survival</th>
<th>Local-Regional Failure</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Censored</td>
<td>Censored</td>
<td>Censored</td>
</tr>
<tr>
<td>Gross residual tumor following eHNS (Arm 1 only)</td>
<td>Failure</td>
<td>Failure</td>
<td>Competing risk</td>
</tr>
<tr>
<td>Local progression or recurrence</td>
<td>Failure</td>
<td>Failure</td>
<td>Competing risk</td>
</tr>
<tr>
<td>Regional progression or recurrence</td>
<td>Failure</td>
<td>Failure</td>
<td>Competing risk</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>Failure</td>
<td>Competing risk</td>
<td>Failure</td>
</tr>
<tr>
<td>Death due to study cancer or from unknown causes</td>
<td>Failure</td>
<td>Failure</td>
<td>Competing risk</td>
</tr>
<tr>
<td>Death due to any other reason</td>
<td>Failure</td>
<td>Competing risk</td>
<td>Competing risk</td>
</tr>
<tr>
<td>Salvage surgery of primary with tumor present/unknown (Arm 2 only)</td>
<td>Failure</td>
<td>Failure</td>
<td>Competing risk</td>
</tr>
<tr>
<td>Salvage neck dissection with tumor present/unknown, &gt;15 weeks from end of RT (Arm 2 only)</td>
<td>Failure</td>
<td>Failure</td>
<td>Competing risk</td>
</tr>
</tbody>
</table>

### 13.5 Monitoring of Study Accrual (10/2/13)

The study design is based on a 36-month accrual period with an average of approximately 3.2 patient entries per month. However, during the first 6 months following activation, little accrual is anticipated while the trial is being approved by institutional IRBs. It is projected that 2 patients in total will be entered during study months 1-6 (none in months 1-3; 1 patient in the 4th month; and 1 patient in months 5-6), and then the average monthly accrual rate after study month 6 will be 3.2 patients. If the total accrual during months 13 through 18 of the study is ≤ 20% of the targeted accrual (≤ 4 cases in total), then the protocol will be discontinued. If the total accrual is between 21-49%, then the protocol will continue to accrue subjects pending approval to remain open by the NRG Oncology Data Monitoring Committee (DMC) and NCI-CTEP. If continued, the study must accrue at least 50% of targeted accrual (≥ 5 cases in total) during months 22 through 24 in order to remain open beyond 2 years.

### 13.6 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. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of adverse events.

### 13.7 Analysis for Reporting the Treatment Results (10/2/13)

This analysis will include all eligible patients with follow up based on the treatment arm to which they were randomized, regardless of whether they started the assigned treatment. The experimental arm will be compared to the control arm when the 144 patients have been followed for 2 years for a total of 72 events for PFS. A one-sided log rank test will be used to compare the PFS at a significance level of 0.094. The PFS and the OS rates will be estimated using the
Kaplan-Meier method (1958) for each arm. The toxicity analysis will be done in 2 ways: 1) Analysis will be based upon only adverse events (AEs) attributed by the investigator to be definitely, probably, or possibly related (if relationship is missing) to protocol treatment; 2) Analysis will be based upon all reported adverse events regardless of attribution. Rates of grade 3+ adverse events for the CTCAE, v. 4 system organ classes, such as gastrointestinal disorders, will be generated for each analysis method.

The usual components of this analysis are:
- Tabulation of all cases entered and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Observed results with respect to the endpoints described in Section 13.1.

13.8 Interim Analysis for the Data Monitoring Committee (DMC) (10/2/13)
The NRG Oncology 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.

The interim analysis for efficacy and futility will be performed when there are 36 events for PFS, and the results will be reported to the NRG Oncology DMC. If the p-value from the log rank test is less than 0.02 according to the O'Brien-Fleming type spending function, then we stop for efficacy and if the hazard ratio is greater than 1 favoring the control arm, then we would recommend stopping for futility. Surgical morbidity also will be reviewed twice yearly, reviewing specific surgical AE endpoints of oropharyngeal hemorrhage, high rates of positive margins, and/or local recurrence. In addition, the surgical PI will review the experimental (surgical) arm for unexpected surgical morbidity and frequently incident lower grade CTCAEs.

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

13.9 Early Stopping Rules (2/19/14)
If grade 4 oropharyngeal hemorrhage turns out to be as high as 11%, then the study should be terminated as early as possible. Therefore, a decision will be made on whether to continue the study after the first 36 patients have completed the transoral surgery and their forms (CTCAE, v. 4) have been submitted. If 4 or more of these patients have grade 4 oropharyngeal hemorrhage, then the study will be terminated. The probability of stopping early is 57% if the true grade 4 oropharyngeal hemorrhage rate is 11% and 81% if the true grade 4 oropharyngeal hemorrhage rate is 15%. The probability of stopping early is 10% if the true grade 4 oropharyngeal hemorrhage rate is 5%. The study will continue accrual while we are waiting for the early-stopping decision for oropharyngeal hemorrhage.

The incidence of Grade 5 toxicity after transoral eHNS has not yet been prospectively studied. However, Salassa et al. found the rate of death from hemorrhage to be less than 1% (Salassa et al. 2008) for patients undergoing TLM, while the incidence after TORS remains unknown. However, the Grade 5 toxicity associated with chemoradiation varies from 1% (Machtay et al. 2008) to 5% (Forastiere et al. 2003). Therefore, we shall monitor deaths related to (grade 5) oropharyngeal hemorrhage on the surgical arm as follows: if there are more than 2 deaths related to oropharyngeal hemorrhage among the 62 analyzable patients on the TORS arm, then the study will be terminated.

If the positive margin rate turns out to be as high as 10%, then the study should be terminated as early as possible. Therefore, a decision will be made as to whether to continue the study after the first 36 patients have completed the transoral surgery and their forms (CTCAE, v. 4) have been
submitted. If 3 or more of these patients have positive margins, then the study will be terminated. The probability of stopping early is 71% if the true positive margin rate is 10% and 92% if the true positive margin rate is 15%. The probability of stopping early is 27% if the true positive margin rate is 5%. The study will continue accrual while we are waiting for the early-stopping decision for positive margins.

For margins of ≤ 3 mm, the table below summarizes probabilities of early stopping. For example, if the local failure rate turns out to be as high as 10%, then the study should be terminated as early as possible. Therefore, a decision will be made as to whether to continue the study after the first 36 patients have completed the transoral eHNS and their forms (CTCAE, v. 4) have been submitted. If 24 patients have margins of < 3 mm, and 3 or more of these patients fail locally, then the study will be terminated. The probability of stopping early is 44% if the true positive margin rate is 10% and 72% if the true positive margin rate is 15%. The probability of stopping early is 12% if the true positive margin rate is 5%. The study will continue accrual while we are waiting for the early-stopping decision for positive margins of ≤ 3 mm.

<table>
<thead>
<tr>
<th>N</th>
<th>15%</th>
<th>10%</th>
<th>5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>92%</td>
<td>71%</td>
<td>27%</td>
</tr>
<tr>
<td>24</td>
<td>72%</td>
<td>44%</td>
<td>12%</td>
</tr>
<tr>
<td>12</td>
<td>26%</td>
<td>11%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Six months or one year PFS rate will be assessed for the control arm with sufficient time prior to the interim efficacy analysis with about 36 patients. If it is higher than the rate for the current design such that timing of the final analysis is lengthened by more than a year, an increase of sample size may be explored; however, before any changes can be made to the sample size for this study, CTEP will need to review and approve the change through a formal amendment to the study.

### 13.10 Final Analysis (10/2/13)

PFS and OS rates will be estimated for both treatment arms using the Kaplan-Meier method (1958). Their distributions will be compared between treatment arms with a one-sided log rank test (Mantel 1966) at an alpha level of 0.094 to account for the interim analysis. The cumulative incidence method will be used to estimate local-regional 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. Multivariate analysis will be performed using the Cox proportional hazards model. The study is powered for analyses with the entire trial population; however, stratified tests (T1 vs. T2; N1 vs. N2; Zubrod performance status 0 vs. 1) can be used and estimates for each group can be provided and we will assess the corresponding statistical power for each subgroup given the observed differences.

An overall toxicity analysis will be done 2 ways: 1) The first method will be based upon only adverse events (AEs) attributed by the investigator to be definitely, probably, or possibly related (if relationship is missing, it will be considered related) to protocol treatment; 2) The second method will be based upon all reported AEs regardless of attribution. Rates of grade 3+ AEs (CTCAE, v. 4) for acute and late toxicities and the CTCAE system organ classes, such as gastrointestinal disorders, will be generated for each method. These rates 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.

Quality of life analysis focused on swallowing outcome and shoulder function will be compared using a two-sample independent t test and paired t test if the comparison is within the experimental arm between different time points. Overall score and change from baseline will be summarized using mean and standard deviation at each time point for each arm. Binary endpoints will be compared using Fisher’s exact test.
Sensitivity and specificity will be determined by results from a CT scan and examination of surgically dissected lymph nodes. Correlations between CTVs and LRC/LRF will be determined. Details of power calculations and the analysis plan can be found in Section 13.11 of the Correlative Science Section below.

In the table below, (15% PFS difference is based on the current design) we have outlined our decision making process of how to interpret the phase II data with regards to PFS and QOL in order to proceed to a future phase III. If PFS is significantly better for the surgical arm then we will proceed to a phase III trial using overall survival as the primary endpoint as a superiority study (row 1). If PFS is better but not significant and swallowing function is significantly better for the surgical arm, we will be testing swallowing function as the primary endpoint for the phase III trial. For any other outcome combinations in the phase II, we will not proceed to a phase III trial (row 3-6). In this study, we will be using the MDADI as the primary QOL instrument to measure swallowing outcome from the patient’s perspective. With an effect size of 0.5 or 0.333, an expected mean change in MDADI score from baseline between the two arms of 5, and SD estimated to be between 10-15 (Sinclair et al 2011) at 1 year from completion of chemoradiation with a two-sided, two-sample independent t-test with alpha of 0.05, effect size 0.5 and 144 patients, we will have 84% power for the 2 arms combined. If PFS is better for the experimental arm but not significant, then this difference in MDADI scores will be used to proceed to a phase III trial with QOL as the primary endpoint.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>PFS (Surg - CRT)</th>
<th>QOL related swallowing functions (Surg - CRT)</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Better, significant (&gt;15%)</td>
<td>Regardless</td>
<td>Phase III – superiority OS</td>
</tr>
<tr>
<td>2</td>
<td>Better, not significant (0% but &lt;15%)</td>
<td>Significantly better for the surgical arm</td>
<td>Phase III – superiority swallowing function related QOL</td>
</tr>
<tr>
<td>3</td>
<td>Better, not significant (0% but &lt;15%)</td>
<td>Not significantly better for the surgical arm</td>
<td>No Phase III</td>
</tr>
<tr>
<td>4</td>
<td>Worse, not significant (&gt;15%, &lt;0%)</td>
<td>Significantly better for the surgical arm</td>
<td>No Phase III</td>
</tr>
<tr>
<td>5</td>
<td>Worse, not significant (&gt;15%, &lt;0%)</td>
<td>Not significantly better for the surgical arm</td>
<td>No Phase III</td>
</tr>
<tr>
<td>6</td>
<td>Harm, significant (&lt;-15%)</td>
<td>Regardless</td>
<td>No Phase III</td>
</tr>
</tbody>
</table>

13.11 Statistical Considerations for Correlative Studies

13.11.1 The predictive and prognostic potential for the 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 conducted on the collected specimens other than those required for patient selection (i.e. p16). 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.

13.11.2 Measuring Toxicity, Patient-Reported Outcomes (PROs), and Quality of Life (QOL)

To compare change of scores (swallowing-related QOL, global, physical, PSS-HN, etc.) with an effect size of 0.5 or 0.333 (expected mean change in MDADI scores from baseline between the 2 arms: 5, and SD estimated to be between 10-15; Sinclair 2011) between the 2 arms at 1 year from completion of chemoradiation with a 2-sided, 2-sample independent t test with alpha of 0.05, effect size 0.5 and 144 patients, we will have 84% power for the 2 arms combined. Assuming various attrition rates based on previous head and neck trials, the table below summarizes results of power analysis.
In the phase II study, we will compare prevalence rates measured by MBS at different time points based on chi-squared test, for example for a binary outcome, we estimate the two-year rate for the control group to be 30% (Change from baseline, Eisbruch 2011), with two sided alpha of 5% and 144 patients, we have 69% power to detect a 20% difference between two arms. The power is 86% if the increase is 25%. Assuming various attrition rates based on previous head and neck trials, the table below summarizes results of power analysis for binary outcome. The large difference in the probability of aspiration between 70 Gy and 60 Gy pharyngeal constrictor dose estimated by the NTCP analysis cited above suggests adequate effect size even if a subset of the surgical arm receives chemotherapy and slightly reduced doses of radiotherapy.

<table>
<thead>
<tr>
<th>Percent missing</th>
<th>Available patients</th>
<th>Power, effect size=0.5</th>
<th>Power, effect size=0.333</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>116</td>
<td>76%</td>
<td>42%</td>
</tr>
<tr>
<td>30%</td>
<td>100</td>
<td>69%</td>
<td>37%</td>
</tr>
<tr>
<td>40%</td>
<td>86</td>
<td>63%</td>
<td>33%</td>
</tr>
</tbody>
</table>

To compare MDADI scores at baseline and at 6 weeks after eHNS and the NDII before and after eHNS, we also estimate power using a paired t test. With a 2-sided paired t test with an alpha of 0.05, effect sizes of 0.5 and 0.333, and 72 patients, we will have 98% power for the experimental arm. Assuming various attrition rates based on previous head and neck trials, the table below summarizes results of power analysis.

<table>
<thead>
<tr>
<th>Percent missing</th>
<th>Available patients</th>
<th>Power, 20% increase</th>
<th>Power, 25% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>116</td>
<td>59%</td>
<td>78%</td>
</tr>
<tr>
<td>30%</td>
<td>100</td>
<td>50%</td>
<td>72%</td>
</tr>
<tr>
<td>40%</td>
<td>86</td>
<td>43%</td>
<td>65%</td>
</tr>
</tbody>
</table>

A chi square test for contingency tables will be used to compare each of the two prevalence rates from baseline based on MBS. Prevalence of these dysphagia endpoints as measured by MBS will be estimated at each time point and compared between arms. Summary ratings will be obtained as a representation of global impairment on the MBS study, rather than ratings of discrete bolus trials. Outcomes will be summarized and scored on ordered categorical scales for two domains of pharyngeal swallowing function: **airway protection** and **pharyngeal residue**. Kappa statistics will be used to summarize the inter-rater reliability. QOL analysis including overall score and change from baseline will be summarized using mean and standard deviation at each time point for each arm. Overall and head and neck-specific QOL, swallowing short term and long term using the MDADI, PSS-HN will be compared using a two sample independent t test and paired t test if the comparison is within the experimental arm between different time points. 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. In addition to comparing the change scores, overall trends in these scores will be modeled using the general linear mixed effect model. Other potential covariates evaluated for the multivariate models would be assigned treatment, age, gender, race, Zubrod performance status, T-stage, N-stage, primary site, and smoking history. A logistic regression model will be used to summarize the number of missing data and to test if the dropout process is missing completely at random (MCAR). Analyses of complete cases and cases with imputations will be considered as a sensitivity analysis. A pattern mixture or selection model may be used to assess treatment effect to see if it is dropout dependent. Binary and categorical endpoints (such as MBS) will be compared using
Fisher’s exact test and/or chi-squared tests at each time point. A longitudinal model for categorical outcomes based on the general estimating equation (GEE) approach may be considered for comparing categorical outcomes across time. Effects of prevalence rate change from baseline will be estimated based on linear or generalized linear mixed models using QOL, swallowing outcomes as dependent variables and MBS as independent variables while adjusting for other covariates as listed above. Correlation between MBS, MDADI, NDII, the PSS-HN, and toxicity, PRO assessments, and biomarker levels 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.

13.11.3 Exploratory Correlation of Physician Derived CTVs with Locoregional Control or Failure
We will conduct the exploratory analysis of physician derived CTVs and locoregional control or failure as follows: univariable and multivariable analysis will be performed using the cause specific Cox proportional hazards model. Potential covariates evaluated for the multivariate models would be assigned treatment, age, gender, race, Zubrod performance status, T-stage, N-stage, primary site, and smoking history, as well as tumor markers as binary variables. In addition, exploratory analysis will be performed to determine if there is any outcome difference between the marker risk group and treatment arm. A Cox regression model will be used with the following covariates: 1) assigned treatment; 2) marker status; and 3) assigned treatment by marker status interaction. The covariate for interaction will provide an estimate as to whether the treatment effect is similar for the marker-positive + and the marker-negative patients. Correlations can be estimated 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.

13.11.4 Sensitivity and Specificity of Pre-treatment CT Scans Detecting the Presence of Lymph Node Extracapsular Extension
We will summarize each of the measures as follows:

(#=number)
Sensitivity = TP/(TP + FN) = (# of true positive assessment)/(# of all positive assessment)
Specificity = TN/(TN + FP) = (# of true negative assessment)/(# of all negative assessment)

In addition, we may also explore the accuracy of CT scan to identify ECS:

Accuracy = (TN + TP)/(TN+TP+FN+FP)
= # of correct assessments/# of all assessments

The sensitivity, specificity and accuracy are proportions. Thus the according confidence intervals can be calculated by using standard methods for proportions. These include asymptotic and exact 95% confidence interval for binomial proportions. Also, the true positive rate (TPR) against false positive rate (FPR) can be measured, where TPR= TP/(TP+FN) and FPR = FP/(FP+TN). As we can see from the above equations, TPR is equivalent to sensitivity and FPR is equivalent to (1 – specificity).
### Projected Distribution of Gender and Minorities

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td></td>
<td>26</td>
<td>118</td>
<td>144</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td></td>
<td>26</td>
<td>118</td>
<td>144</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Gender</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black or African American</td>
<td></td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>26</td>
<td>113</td>
<td>139</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td></td>
<td>26</td>
<td>118</td>
<td>144</td>
</tr>
</tbody>
</table>
REFERENCES


Bruner DW. Should patient-reported outcomes be mandatory for toxicity reporting in cancer clinical trials? J Clin Oncol. 2007;25:5345-7. PMID: 18588404


## APPENDIX I

### STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS

*(See Sections 3.0 and 4.0 for details.)*

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Time Point (may be required for eligibility)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 days</td>
</tr>
<tr>
<td><strong>Clinician Assessments</strong></td>
<td></td>
</tr>
<tr>
<td>Histologically or cytologically confirmed SCC</td>
<td>x</td>
</tr>
<tr>
<td>Specimen for central confirmation</td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td></td>
</tr>
<tr>
<td>H&amp;P performed by rad onc/med onc/H&amp;N surgeon</td>
<td>x</td>
</tr>
<tr>
<td>Weight</td>
<td>x</td>
</tr>
<tr>
<td>Performance Status</td>
<td>x</td>
</tr>
<tr>
<td>Chest CT or PET/CT of chest</td>
<td>x</td>
</tr>
<tr>
<td>CT or MR imaging of head &amp; neck (CT w/contrast, PET/CT and/or MRI)</td>
<td>x</td>
</tr>
<tr>
<td>Preoperative Mallampatti assessment</td>
<td>x</td>
</tr>
<tr>
<td>Audiogram</td>
<td>x</td>
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<tr>
<td>Dental evaluation and (if applicable) prophylaxis</td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td>x</td>
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<tr>
<td>Whole body PET scan</td>
<td>x</td>
</tr>
<tr>
<td>Tracheotomy</td>
<td></td>
</tr>
<tr>
<td>Eval for placement of feeding tube</td>
<td>Document if patient required procedure: (y/n; if yes, for what length of time)</td>
</tr>
<tr>
<td><strong>Functional Assessments</strong></td>
<td></td>
</tr>
<tr>
<td>Modified Barium Swallow</td>
<td>x</td>
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</table>

-continued on next page-
<table>
<thead>
<tr>
<th>Assessments</th>
<th>Time Point (may be required for eligibility)</th>
<th>60 days</th>
<th>42 days</th>
<th>30 days</th>
<th>14 days</th>
</tr>
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<tbody>
<tr>
<td><strong>PROs/QOL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI</td>
<td>Arm 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior to surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-HN (clinician)</td>
<td>Arm 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior to surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDADI</td>
<td>Arm 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior to surgery</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Prior to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDII</td>
<td>Arm 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior to surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/diff</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin;</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST or ALT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine and</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>creatinine clearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test (if applicable)</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Serum, plasma &amp; whole blood for banking (if patient consents)</td>
<td>Prior to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-continued on next page-
## STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Time Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-4 wks. post-eHNS &amp; neck dissection <em>(Arm 1)</em></td>
</tr>
<tr>
<td><strong>Clinician Assessments</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>x</td>
</tr>
<tr>
<td>Physical exam performed by rad onc/med onc/H&amp;N surgeon</td>
<td>x</td>
</tr>
<tr>
<td>Weight</td>
<td>x</td>
</tr>
<tr>
<td>CT scan w/contrast or CT/PET scan and/or MRI of head &amp; neck</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>Chest CT scan or chest CT/PET scan</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>Biopsy</td>
<td>As clinically indicated: to check for tumor recurrence</td>
</tr>
<tr>
<td>Performance Status</td>
<td>x</td>
</tr>
<tr>
<td>Tracheotomy</td>
<td>Document if patient required procedure during protocol tx: (y/n; if yes, for what length of time)</td>
</tr>
<tr>
<td>Placement of feeding tube</td>
<td></td>
</tr>
<tr>
<td><strong>Functional Assessments</strong></td>
<td></td>
</tr>
<tr>
<td>Modified Barium Swallow</td>
<td>x</td>
</tr>
<tr>
<td><strong>PROs/QOL</strong></td>
<td></td>
</tr>
<tr>
<td>PSS-HN (clinician)</td>
<td><em>Arm 1</em></td>
</tr>
<tr>
<td>2-4 weeks post-surgery and prior to RT</td>
<td>N/A</td>
</tr>
<tr>
<td>End of RT</td>
<td>End of RT</td>
</tr>
<tr>
<td>MDADI</td>
<td><em>Arm 1</em></td>
</tr>
<tr>
<td>2-4 weeks post-surgery and prior to RT</td>
<td>N/A</td>
</tr>
<tr>
<td>End of RT</td>
<td>End of RT</td>
</tr>
<tr>
<td>NDII</td>
<td><em>Arm 1</em></td>
</tr>
<tr>
<td>2-4 weeks post-surgery and prior to RT</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
</tr>
<tr>
<td>CBC w/diff</td>
<td>Weekly; additional lab evals at discretion of treating physician.</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td></td>
</tr>
<tr>
<td>Sodium, potassium, magnesium</td>
<td></td>
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</tbody>
</table>

-continued on next page-
### APPENDIX I (continued)

**STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW-UP**

(See Section 11.2 for details.)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Time Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinician Assessments</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>At 1 mo. post-RT q3 mos. from end of RT for 2 yrs; q6 mos. for 3 yrs; then annually</td>
</tr>
<tr>
<td>Physical exam performed by rad onc/med onc</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>x</td>
</tr>
<tr>
<td>Imaging: CT, MRI and/or PET/CT</td>
<td>x</td>
</tr>
<tr>
<td>Imaging Post RT: CT with local regional failure (Sect. 11.2)</td>
<td>At 6 months; see also Sections 8.6 and 11.2 As clinically indicated</td>
</tr>
<tr>
<td>Performance Status</td>
<td>x</td>
</tr>
<tr>
<td>Tracheotomy</td>
<td>Document if patient required procedure in follow-up: (y/n; if yes, for what length of time)</td>
</tr>
<tr>
<td>Placement of feeding tube</td>
<td>Document if patient required procedure in follow-up: (y/n; if yes, for what length of time)</td>
</tr>
<tr>
<td><strong>Functional Assessments</strong></td>
<td></td>
</tr>
<tr>
<td>Modified Barium Swallow</td>
<td>At 6 and 24 months</td>
</tr>
<tr>
<td><strong>PROs/QOL</strong></td>
<td>Arm 1</td>
</tr>
<tr>
<td>PSS-HN (clinician)</td>
<td>3,6,12 &amp; 24 mos. from end of RT</td>
</tr>
<tr>
<td>MDADI</td>
<td>3,6,12 &amp; 24 mos. from end of RT</td>
</tr>
<tr>
<td>NDII</td>
<td>12 mos. from end of RT</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
</tr>
<tr>
<td>Post-treatment follow-up labs at the discretion of the physician.</td>
<td>At 6 months and 24 months</td>
</tr>
<tr>
<td>Serum and plasma for banking (if patient consents)</td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX II
### ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
APPENDIX III

AJCC Staging System

HEAD & NECK

<table>
<thead>
<tr>
<th>STAGING-PRIMARY TUMOR (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIP and ORAL CAVITY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease*</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced disease</td>
</tr>
</tbody>
</table>

*Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

<table>
<thead>
<tr>
<th>NASAL CAVITY and PARANASAL SINUSES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary Sinus</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease</td>
</tr>
</tbody>
</table>

Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses

Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx or clivus
**Nasal Cavity and Ethmoid Sinus**

T1  Tumor restricted to any one subsite, with or without bony invasion
T2  Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3  Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribiform plate
T4a Moderately advanced local disease

Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b Very advanced local disease

Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

**PHARYNX**

**Nasopharynx**

T1  Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity with out parapharyngeal extension*
T2  Tumor with parapharyngeal extension*
T3  Tumor involves bony structures of skull base and/or paranasal sinuses
T4  Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor.

**Oropharynx**

T1  Tumor 2 cm or less in greatest dimension
T2  Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3  Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a Moderately advanced local disease

Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
T4b Very advanced local disease

Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

*Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.

**Hypopharynx**

T1  Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2  Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3  Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4a Moderately advanced local disease

Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue.*
T4b Very advanced local disease

Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal
structures
*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

**LARYNX**

**Supraglottis**

T1  Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2  Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3  Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or inner cortex of thyroid cartilage
T4a Moderately advanced local disease

Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease

Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

**Glottis**

T1  Tumor limited to the vocal cord(s) [may involve anterior or posterior commissure] with normal mobility
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2  Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3  Tumor limited to the larynx with vocal cord fixation, and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a Moderately advanced local disease

Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease

Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

**Subglottis**

T1  Tumor limited to the subglottis
T2  Tumor extends to vocal cord(s) with normal or impaired mobility
T3  Tumor limited to larynx with vocal cord fixation
T4a Moderately advanced local disease

Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease

Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.
REGIONAL LYMPH NODES (N) Excluding Nasopharynx

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

REGIONAL LYMPH NODES (N) Nasopharynx

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

DISTANT METASTASIS (M)

M0  No distant metastasis
M1  Distant metastasis

STAGE GROUPING, Excluding Nasopharynx  

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis, N0, M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td></td>
<td>T1-3, N1, M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a, N0-1, M0</td>
</tr>
<tr>
<td></td>
<td>Any T, N2, M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b, Any N, M0</td>
</tr>
<tr>
<td></td>
<td>Any T, N3, M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>

STAGE GROUPING Nasopharynx

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis, N0, M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td></td>
<td>T1-T3, N1, M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a, N0-2, M0</td>
</tr>
<tr>
<td></td>
<td>T1-3, N2, M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T, N3, M0</td>
</tr>
<tr>
<td></td>
<td>T4b, Any N, M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>
## APPENDIX IV

### American Society of Anesthesiologists (ASA) Physical Status (PS) Classification System*

<table>
<thead>
<tr>
<th>ASA PS Category</th>
<th>Preoperative Health Status</th>
<th>Comments, Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA PS 1</td>
<td>Normal healthy patient</td>
<td>No organic, physiologic, or psychiatric disturbance; excludes the very young and very old; healthy with good exercise tolerance</td>
</tr>
<tr>
<td>ASA PS 2</td>
<td>Patients with mild systemic disease</td>
<td>No functional limitations; has a well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy</td>
</tr>
<tr>
<td>ASA PS 3</td>
<td>Patients with severe systemic disease</td>
<td>Some functional limitation; has a controlled disease of more than one body system or one major system; no immediate danger of death; controlled congestive heart failure (CHF), stable angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure; bronchospastic disease with intermittent symptoms</td>
</tr>
<tr>
<td>ASA PS 4</td>
<td>Patients with severe systemic disease that is a constant threat to life</td>
<td>Has at least one severe disease that is poorly controlled or at end stage; possible risk of death; unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure</td>
</tr>
<tr>
<td>ASA PS 5</td>
<td>Moribund patients who are not expected to survive without the operation</td>
<td>Not expected to survive &gt; 24 hours without surgery; imminent risk of death; multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy</td>
</tr>
<tr>
<td>ASA PS 6</td>
<td>A declared brain-dead patient who organs are being removed for donor purposes</td>
<td></td>
</tr>
</tbody>
</table>

*ASA PS classifications from the American Society of Anesthesiologists
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APPENDIX V

RTOG 1221 (10/2/13)
Surgeon Credentialing: Head & Neck Surgeon's Questionnaire

Please complete this questionnaire following a careful review of the eligibility (Section 3.0) and surgical (Section 8.0) sections of RTOG 1221 and return this form to your Research Associate. Surgeon credentialing is a pre-registration requirement (Section 5.5).

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

YES ________           NO________

Comments:

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

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

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

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

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

YES_______ NO_______

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

YES_______ NO_______

7. Please upload to the Medidata Rave Surgeon Credentialing site ten paired pathology report and operative notes for ten transoral eHNS cases, including at least one tonsil and one tongue-base primary tumor.

(Continued on the next page)
APPENDIX V (Continued)

RTOG 1221
Surgeon Credentialing: Head & Neck Surgeon's Questionnaire

If you have any specific questions about this form or other aspects of the trial, please contact:

Floyd Christopher Holsinger, MD, FACS
Phone: 650-725-5968
E-mail: holsinger@stanford.edu

If affiliated with more than one institution, please specify below the NRG Oncology Institution Number/CTEP ID Number for each institution.

<table>
<thead>
<tr>
<th>Signature of Surgeon completing this form</th>
<th>Institution Name</th>
</tr>
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<tr>
<td>Printed Name of Surgeon</td>
<td>Telephone Number of Surgeon</td>
</tr>
<tr>
<td>Surgeon’s Fax Number Number</td>
<td>Site NRG Oncology Institution Number/CTEP ID Number</td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>Site NRG Oncology Institution Number/CTEP ID Number</td>
</tr>
</tbody>
</table>

Return this form to your Research Associate.

Research Associates: To register a surgeon and to complete the credentialing questionnaire, the responsible CRA must send an e-mail to HNsurgicalcredentialing@jimmy.harvard.edu
Dental Care for 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 VII

Mallampati Score, as Modified by Samsoon

Class 1: Full visibility of tonsils, uvula and soft palate

Class 2: Visibility of hard and soft palate, upper portion of tonsils and uvula

Class 3: Soft and hard palate and base of the uvula are visible

Class 4: Only Hard Palate visible


Shipping Instructions:

U.S. Postal Service Mailing Address: For Non-urgent FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Resource
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens for Central Review
NRG Oncology Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- Include all NRG Oncology paperwork in pocket of biohazard bag.
- Check that the Specimen Transmittal (ST) Form has the consent boxes checked off.
- Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

**FFPE Specimens:**
- Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
- FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the slides shaking it is likely that they will break during shipping.
- Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice.**

**Frozen Specimens:**
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
- Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
- Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
- Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80°C until ready to ship.

For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Resource by e-mail: RTOG@ucsf.edu or phone: 415-476-(7864) or Fax: 415-476-5271.

(continued on next page)
BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood (as specified by the protocol):

Kit contents:
- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal ST Form and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube

Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials “serum”.

Process:
1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90°C until ready to ship on dry ice. See below for storage conditions.

Please make sure that every specimen is labeled and include collection time point on the ST Form.

(B) Plasma (if requested): Purple Top EDTA tube #1

Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials “plasma”.

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

Please make sure that every specimen is labeled and include collection time point on the ST Form. (continued on next page)
BLOOD COLLECTION KIT INSTRUCTIONS (continued)

(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2
- Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials “blood”.

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “blood”.
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80°C.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

Freezing and Storage:
- Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- Store at –80°C (-70°C to -90°C) until ready to ship.
  - If a -80°C Freezer is not available,
    ▪ Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - OR:
    ▪ Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).
  - OR:
    ▪ Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:
- Ship specimens on Dry Ice overnight Monday-Wednesday (Monday-Tuesday from Canada) to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.

(continued on next page)
Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice from breaking the tubes.

Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.

For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864.

Shipping Address:
Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: RTOG@ucsf.edu
APPENDIX IX (2/19/14)

RTOG 1221
Modified Barium Swallow (MBS) Credentialing Checklist

Please complete this questionnaire and return this form to your Research Associate. **MBS credentialing is a pre-registration requirement** *(Section 5.6)*. If any of the answers to questions 1, 2, 4a, and 5 are 'No', your institution will not be allowed to enroll a patient on RTOG 1221.

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

   YES_______ NO_______

2. (Y) Are your MBS videos recorded digitally at a minimum frame rate of 30 frames/second (i.e., accurate to 0.01 time code imprints)? **Note**: MBS image capture rates below 15 frames/second are not accepted. Sites using an MBS capture rate outside the standard 30 frames/second but above 15 frames/second may participate, provided the site documents the exact capture rate (frames/second) on the MBS form.

   YES_______ NO_______

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

   YES_______ NO_______

4. (Y/N) Do you use Varibar contrast agents specified in this protocol, including Varibar Thin Liquid and Varibar Pudding?

   YES_______ NO_______
   
   a. (Y) If no, can you access Varibar contrast agents for MBS studies conducted per RTOG protocol 1221?

      YES_______ NO_______

5. (Y) Are you (speech pathologists) willing to follow the MBS protocol as written in RTOG 1221 (including the sequence of bolus administration, use of Varibar products, and volumes/viscosities specified)?

   YES_______ NO_______

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

   a. Number of speech pathologists at your institution who perform MBS studies? _______
   
   b. Average number of total MBS studies conducted at your institution each week? _______
   
   c. Average number of MBS studies conducted on patients who have head and neck cancer each week? _______

   – Continued on next page –
APPENDIX IX (Continued)
Modified Barium Swallow (MBS) Credentialing Checklist

If affiliated with more than one institution, please specify below the NRG Oncology Institution Number/CTEP ID Number for each institution.

<table>
<thead>
<tr>
<th>Signature of Speech Pathologist completing this form</th>
<th>Institution Name</th>
</tr>
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<td>Printed Name of Speech Pathologist</td>
<td>Telephone Number of Speech Pathologist</td>
</tr>
<tr>
<td>Fax Number Number</td>
<td>Site NRG Oncology Institution Number/CTEP ID</td>
</tr>
</tbody>
</table>

Site NRG Oncology Institution Number/CTEP ID Number

Site NRG Oncology Institution Number/CTEP ID Number

Site NRG Oncology Institution Number/CTEP ID Number

Research Associates: E-mail the completed form to CTSURegulatory@ctsu.c0ccq.org and to RTOG1221@acr.org.