NRG ONCOLOGY
RTOG 1008

A RANDOMIZED PHASE II/PHASE III STUDY OF ADJUVANT CONCURRENT RADIATION AND CHEMOTHERAPY VERSUS RADIATION ALONE IN RESECTED HIGH-RISK MALIGNANT SALIVARY GLAND TUMORS

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 (11/5/15)

Co-Principal Investigator/Medical Oncology
Cristina Rodriguez, MD
Seattle Cancer Care Alliance
825 Eastlake Avenue E., G4-949
Seattle, WA 98109
206-288-6748/FAX 206-288-2226
rodrigcr@uw.edu

Co-Principal Investigator/Medical Oncology
David J. Adelstein, MD
Cleveland Clinic
9500 Euclid Avenue, R35
Cleveland, OH 44195
216-444-9310/FAX 216-444-9464
adelstd@ccf.org

Radiation Oncology Co-Chair
John Kim, MD
Princess Margaret Hospital/Univ. Health Network
610 University Avenue
Toronto, Ontario, Canada M5G 2M9
416-946-2126/FAX 415-946-6561
John.Kim@rmp.uhn.on.ca

Surgical Oncology Co-Chair
Ehab Hanna, MD
MD Anderson Cancer Center
1515 Holcombe Blvd., Unit 1445
Houston, TX 77030
713-745-1815/FAX 713-794-4662
EYHanna@mdanderson.org

Correlative Studies Co-Chair
Quynh-Thu Le, MD
Stanford University
875 Blake Wilbur Drive, MC 5847
Stanford, CA 94305
650-498-5032/FAX 650-725-8231
qle@stanford.edu

Pathology Co-Chair
Adel El-Naggar, M.D., Ph.D.
MD Anderson Cancer Center
1515 Holcombe Blvd., Unit 085
Houston, TX 77030
713-792-3109/ FAX 713-792-5532
anaggar@mdanderson.org

Medical Physics Co-Chair
Peter G. Maxim, PhD
Stanford University
850 Blake Wilbur Dr.
650-724-3018/FAX 650-725-8231
pmaxim@stanford.edu

Quality of Life Co-Chair
Clement K. Gwede, PhD, RN
H. Lee Moffitt Cancer Center
12902 Magnolia Drive
Tampa, FL 33612
813-745-3052/FAX 813-745-6525
Clement.Gwede@moffitt.org

Senior Statistician
James Dignam, PhD
NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19103
215-574-3174/FAX 215-928-0153
dignamj@nrgoncology.org

Continued on next page
NRG ONCOLOGY
RTOG 1008

A RANDOMIZED PHASE II/PHASE III STUDY OF ADJUVANT CONCURRENT RADIATION AND CHEMOTHERAPY VERSUS RADIATION ALONE IN RESECTED HIGH-RISK MALIGNANT SALIVARY GLAND TUMORS

Title Page (Continued)

Document History

<table>
<thead>
<tr>
<th>Version/Update Date</th>
<th>Broadcast Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-Opened to accrual</td>
<td>January 25, 2015</td>
</tr>
<tr>
<td>Amendment 9</td>
<td>November 5, 2015</td>
</tr>
<tr>
<td>Amendment 8</td>
<td>October 13, 2015</td>
</tr>
<tr>
<td>Closure</td>
<td>November 24, 2014</td>
</tr>
<tr>
<td>Amendment 7</td>
<td>November 24, 2014</td>
</tr>
<tr>
<td>Amendment 6</td>
<td>April 22, 2014</td>
</tr>
<tr>
<td>Update</td>
<td>March 25, 2014</td>
</tr>
<tr>
<td>Amendment 5</td>
<td>October 3, 2013</td>
</tr>
<tr>
<td>Amendment 4</td>
<td>September 19, 2012</td>
</tr>
<tr>
<td>Update</td>
<td>March 6, 2012</td>
</tr>
<tr>
<td>Amendment 3</td>
<td>February 27, 2012</td>
</tr>
<tr>
<td>Amendment 2</td>
<td>October 26, 2011</td>
</tr>
<tr>
<td>Update</td>
<td>August 5, 2011</td>
</tr>
<tr>
<td>Amendment 1</td>
<td>May 4, 2011</td>
</tr>
<tr>
<td>Update</td>
<td>November 3, 2010</td>
</tr>
<tr>
<td>Activation</td>
<td>November 3, 2010</td>
</tr>
</tbody>
</table>

Protocol Agents (10/3/13)

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

Participating Sites (10/3/13)

☐ US Only
☐ Canada Only
☑ US and Canada
☒ Approved International Member Sites

NRG Oncology
1-800-227-5463, ext. 4189

This protocol was designed and developed by NRG Oncology. It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by NRG Oncology nor does NRG Oncology assume any responsibility for unauthorized use of this protocol.
# A RANDOMIZED PHASE II/PHASE III STUDY OF ADJUVANT CONCURRENT RADIATION AND CHEMOTHERAPY VERSUS RADIATION ALONE IN RESECTED HIGH-RISK MALIGNANT SALIVARY GLAND TUMORS

## CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (11/5/15)

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 E-mail: <a href="mailto:CTSURegulatory@ctsu.coccg.org">CTSURegulatory@ctsu.coccg.org</a> (for submitting regulatory documents only)</td>
<td>Please refer to Section 5.0 of the protocol for instructions on using the OPEN system. Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</td>
</tr>
</tbody>
</table>

| Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol: |

**Do not** submit study data or forms to CTSU Data Operations. **Do not** copy the CTSU on data submissions.

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 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 web site is located at** [https://www.ctsu.org](https://www.ctsu.org)
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.5</td>
<td>Storage of Blood Specimens</td>
<td>42</td>
</tr>
<tr>
<td>10.6</td>
<td>Specimen Collection Summary</td>
<td>42</td>
</tr>
<tr>
<td>10.7</td>
<td>Shipment of Biospecimens</td>
<td>43</td>
</tr>
<tr>
<td>10.8</td>
<td>Reimbursement</td>
<td>43</td>
</tr>
<tr>
<td>10.9</td>
<td>Confidentiality/Storage</td>
<td>43</td>
</tr>
<tr>
<td>11.0</td>
<td>PATIENT ASSESSMENTS</td>
<td>43</td>
</tr>
<tr>
<td>11.1</td>
<td>Study Parameters</td>
<td>43</td>
</tr>
<tr>
<td>11.2</td>
<td>Outcome Definitions</td>
<td>44</td>
</tr>
<tr>
<td>11.3</td>
<td>Criteria for Discontinuation of Protocol Treatment</td>
<td>44</td>
</tr>
<tr>
<td>11.4</td>
<td>Quality of Life (QOL) and Patient-Reported Outcomes (PRO)</td>
<td>44</td>
</tr>
<tr>
<td>12.0</td>
<td>DATA COLLECTION</td>
<td>45</td>
</tr>
<tr>
<td>12.1</td>
<td>Summary of Data Submission</td>
<td>45</td>
</tr>
<tr>
<td>12.2</td>
<td>Summary of Dosimetry Digital Data Submission</td>
<td>46</td>
</tr>
<tr>
<td>13.0</td>
<td>STATISTICAL CONSIDERATIONS</td>
<td>47</td>
</tr>
<tr>
<td>13.1</td>
<td>Primary Endpoint</td>
<td>47</td>
</tr>
<tr>
<td>13.2</td>
<td>Secondary Endpoints</td>
<td>47</td>
</tr>
<tr>
<td>13.3</td>
<td>Randomization and Stratification</td>
<td>47</td>
</tr>
<tr>
<td>13.4</td>
<td>Sample Size</td>
<td>47</td>
</tr>
<tr>
<td>13.5</td>
<td>Patient Accrual</td>
<td>49</td>
</tr>
<tr>
<td>13.6</td>
<td>Analysis Plans</td>
<td>49</td>
</tr>
<tr>
<td>13.7</td>
<td>Gender and Minorities</td>
<td>53</td>
</tr>
<tr>
<td>REFERENCES</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>APPENDIX I</td>
<td>STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT</td>
<td>60</td>
</tr>
<tr>
<td>APPENDIX I</td>
<td>STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP</td>
<td>61</td>
</tr>
<tr>
<td>APPENDIX II</td>
<td>ZUBROD PERFORMANCE SCALE</td>
<td>62</td>
</tr>
<tr>
<td>APPENDIX III</td>
<td>AJCC STAGING SYSTEM</td>
<td>63</td>
</tr>
<tr>
<td>APPENDIX IV</td>
<td>FFPE SPECIMEN PLUG KIT/INSTRUCTIONS</td>
<td>64</td>
</tr>
<tr>
<td>APPENDIX V</td>
<td>BLOOD COLLECTION KIT/INSTRUCTIONS</td>
<td>65</td>
</tr>
</tbody>
</table>
NRG ONCOLOGY

RTOG 1008

A Randomized Phase II/Phase III Study of Adjuvant Concurrent Radiation and Chemotherapy Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors

SCHEMA (2/27/12)

<table>
<thead>
<tr>
<th>Histology</th>
<th>Arm 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>S 1. Intermediate-grade adenocarcinoma</td>
<td>Arm 1</td>
</tr>
<tr>
<td>T or intermediate-grade mucoepidermoid</td>
<td>Arm 1</td>
</tr>
<tr>
<td>R carcinoma</td>
<td>Arm 1</td>
</tr>
<tr>
<td>A 2. High-grade adenocarcinoma or high-grade</td>
<td>Arm 1</td>
</tr>
<tr>
<td>T mucoepidermoid carcinoma or</td>
<td>Arm 1</td>
</tr>
<tr>
<td>I salivary duct carcinoma</td>
<td>Arm 1</td>
</tr>
<tr>
<td>F 3. High-grade acinic cell carcinoma or</td>
<td>Arm 1</td>
</tr>
<tr>
<td>Y high-grade (&gt;30% solid component)</td>
<td>Arm 1</td>
</tr>
<tr>
<td>adenoic cystic carcinoma</td>
<td>Arm 1</td>
</tr>
<tr>
<td>M</td>
<td>Arm 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal Status</th>
<th>Arm 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. N0</td>
<td>Arm 1</td>
</tr>
<tr>
<td>2. N1-3</td>
<td>Arm 1</td>
</tr>
</tbody>
</table>

Note: IMRT and IGRT are optional for this study; see Section 5.0 for required credentialing. See Section 6.0 for radiation treatment details and Section 7.0 for details of chemotherapy for Arm 1.

(9/19/12) Note: For patients who have a neck dissection, the stratification variable, "Nodal Status", is based on pathologic assessment. For patients who do not have a neck dissection (patients who are N0), this stratification variable is based on clinical assessment.

Pathologic interpretation of salivary gland malignancies can be very difficult. Patients with diagnoses such as "undifferentiated or poorly differentiated carcinoma", "carcinoma-ex pleomorphic adenoma", "carcinoma NOS" and others should be considered for this trial. A rapid, anonymous photomicrograph review can be obtained from Dr. El-Naggar to assist in identifying appropriate patients for this trial. Institutions are urged to contact either Dr. Adelstein (adelstd@ccf.org) or Dr. El-Naggar (anaggar@mdanderson.org) to expedite such a review.

Patient Population: (See Section 3.0 for Eligibility) (2/27/12)
Patients with salivary gland carcinomas involving the major (parotid, submandibular, or sublingual glands) and minor salivary glands of the head and neck with the following histologies: intermediate-grade adenocarcinoma or intermediate-grade mucoepidermoid carcinoma; high-grade adenocarcinoma or high-grade mucoepidermoid carcinoma or salivary duct carcinoma; high-grade acinic cell carcinoma or high-grade (>30% solid component) adenoid cystic carcinoma; patients with no evidence of hematogenous metastasis, who have undergone curative intent surgical resection and are found to have the following risk factors for recurrence: T3-4, or N1-3 disease, or T1-2 N0 patients with positive or close (<1mm) microscopic margins of resection.

Required Sample Size: Phase II: 120; Phase III: 252 (includes 120 patients from phase II)
ELIGIBILITY CHECKLIST (10/3/13)
(page 1 of 4)

NRG Oncology Institution #
RTOG 1008
Case #

(Y) 1. Does the patient have a pathologically proven diagnosis of a malignant major or minor salivary gland tumor of the following histologic subtypes?
- Intermediate-grade adenocarcinoma or intermediate-grade mucoepidermoid carcinoma;
- High-grade adenocarcinoma or high-grade mucoepidermoid carcinoma or salivary duct carcinoma;
- High-grade acinic cell carcinoma or high-grade (>30% solid component) adenoid cystic carcinoma.

(Y) 2. Did the patient have a surgical resection with curative intent within 8 weeks prior to registration?

(Y) 3. Does the patient have one of the following high risk factors?
- Pathologic Stage T3-4
- Pathologic N1-3
- T1-2, N0 with a close (≤ 1mm) or microscopically positive surgical margin

(Y) 4. Was a history and physical examination performed within 8 weeks prior to registration?

(Y) 5. Is the patient free of distant metastatic disease based on the minimum diagnostic work in Section 3.1?

(Y) 6. Is there radiologic confirmation of the absence of hematogenous metastasis within 12 weeks prior to registration? (at a minimum, contrast CT imaging of the chest is required; PET/CT is acceptable)

(Y) 7. Is the patient’s Zubrod Performance Status 0-1?

(Y) 8. Is the patient ≥ 18 years of age?

(Y) 9. Does the patient have adequate bone marrow, hepatic, and renal function as specified in Section 3.1?

(Y) 10. For women of childbearing potential, was a serum pregnancy test completed within 2 weeks of registration?

(Y) If yes, was the serum pregnancy test negative?

(Y) 11. If the patient is a woman of child bearing potential or a sexually active male, is the patient willing to use effective contraception while on treatment and for 6 weeks following treatment?

(Y) 12. Was the patient evaluated by a Medical Oncologist within 4 weeks of registration?

(Y) 13. Has the patient been deemed able to comply with the treatment plan and follow-up schedule?

(Continued on next page)
NRG Oncology Institution #
RTOG 1008
Case #

___(Y) 14. Did the patient provide study specific informed consent prior to study entry, including consent for mandatory tissue submission for central review?

___(N) 15. Does the patient have residual macroscopic disease after surgery?

___(N) 16. Did the patient have prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years? (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible)

___(N) 17. Did the patient have prior systemic chemotherapy or radiation therapy for salivary gland malignancy? (Note that prior chemotherapy for a different cancer is allowable)

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

___(N) 19. Does the patient have severe, active co-morbidity, as defined in Section 3.2?

___(N) 20. Does the patient have significant pre-existing hearing loss, as defined by the patient or treating physician?

The following questions will be asked at Study Registration:
If IMRT and IGRT are used, CREDENTIALING IS REQUIRED BEFORE REGISTRATION.

_________ 1. Institutional person randomizing case.

_________(Y) 2. Has the Eligibility Checklist been completed?

_________(Y) 3. In the opinion of the investigator, is the patient eligible?

_________ 4. Date informed consent signed

_________ 5. Patient’s Initials (First Middle Last)

_________ 6. Verifying Physician

_________ 7. Patient ID

_________ 8. Date of Birth

_________ 9. Race

_________ 10. Ethnicity

_________ 11. Gender

(Continued on next page)
ELIGIBILITY CHECKLIST (10/3/13)

NRG Oncology Institution #
RTOG 1008
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. (Y/N) 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. (Y/N) 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. (Y/N) 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. (Y/N) 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. (Y/N) 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 _______________
NRG Oncology Institution #
RTOG 1008
Case #

25. Histologic Type:
   - intermediate-grade adenocarcinoma or intermediate-grade mucoepidermoid carcinoma;
   - high-grade adenocarcinoma or high-grade mucoepidermoid carcinoma or salivary duct carcinoma;
   - high-grade acinic cell carcinoma or high-grade (>30% solid component) adenoid cystic carcinoma;

26. Nodal status (N0 or N1-3)

27. Use of IMRT

28. Will IGRT be used to reduce margins?

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 Salivary Gland Malignancies (2/27/12)

Malignant tumors of the salivary gland are rare cancers that represent less than 5% of all newly diagnosed head and neck malignancies. These tumors arise from malignant transformation of the cellular components of the secretory acini, their ducts and supporting myoepithelial cells in the paired major salivary glands, (parotid, sublingual and submandibular glands), and the minor salivary glands distributed in oral cavity, oropharynx, nasopharynx, larynx and upper respiratory epithelia.

The first attempt at classifying of this diverse group of malignancies was published by Foote and Frazell (1954). The more contemporary WHO classification lists 24 distinct entities under malignant epithelial tumors of the salivary glands (Barnes 2005). European registry data and large single institution series from the United States have consistently identified the parotid gland as the most common primary site, with mucoepidermoid, adenoid cystic carcinomas, salivary duct carcinoma and high grade adenocarcinoma as the most common disease histologies.

Memorial Sloan Kettering Cancer Center reported treating 1,278 patients for malignant tumors of the salivary gland from 1939 to 1973 and identified the parotid gland followed by the submandibular glands as the most common primary sites (49% and 10%, respectively) [Spiro 1986]. The histologic frequency of these tumors was as follows: mucoepidermoid carcinoma 34%, adenoid cystic carcinomas 22%, adenocarcinoma 18%, malignant mixed tumor 13%, acinic cell carcinoma in 7%, and various other histologies 6%. Swedish Cancer Registry data describes 2557 cases of major salivary gland malignancies diagnosed between 1960 and 1989. The parotid gland was the most common primary site (57.5%), and the most common histologic types were adenoid cystic carcinomas 20%, mucoepidermoid carcinomas 19%, malignant mixed tumor 14%, adenocarcinomas 13%, acinic cell carcinomas 12%, and squamous cell carcinomas 6% (Ostman 1997). The Dutch Head and Neck Oncology Cooperative group reported on a more contemporary series of 565 patients treated from 1985-1994, found that 58% of tumors originated from the parotid gland, and were adenoid cystic in 25%, adenocarcinoma in 23% mucoepidermoid in 16%, and acinic cell 11% (Terhaard 2004). High grade disease has consistently been identified as a predictor of poorer outcome (Garden 1997, Schroeder 2008).

The advent of active therapeutic agents against specific molecular targets in various epithelial malignancies has resulted in interest in defining the molecular characteristics of salivary gland malignancies. The literature on these molecular markers underscores the remarkable morphologic diversity of these tumors. Reports on the rates of overexpression of hormone receptors, EGFR, Her-2, and c-kit vary according to the published series, staining methods, degree of overexpression, and disease histology. In general, however, EGFR expression is prevalent across all histologic subtypes. Androgen receptors and Her2 appear to have the highest rates of overexpression in the salivary duct carcinomas, and c-kit is commonly found in the adenoid cystic carcinomas. Estrogen and progesterone receptors are not frequently identified. Despite these obvious molecular targets, therapeutic trials of targeted agents have had limited success in the setting of metastatic disease, with very few objective responses (Locati 2008, Agulnik 2007, Hotte 2005, Glisson 2004, Haddad 2003). Currently, their use in salivary gland malignancies is not recommended outside of experimental trials.

1.2 Management of Nonmetastatic Disease and Published Outcomes

Surgery remains the definitive treatment of choice in patients with salivary gland malignancies without evidence of distant hematogenous metastasis. Outcomes after surgery in early stage disease are excellent. A retrospective series of patients treated from 1997 to 2002 for parotid gland carcinomas demonstrated 5-year disease free survival of 86%, with inferior disease free survival with advancing disease stage according to the 2002 AJCC classification (Schroeder 2008).

Risk factors for disease recurrence were examined in a cohort of 565 patients treated for malignant salivary gland tumors in the Netherlands (Terhaard 2004). The risk of local recurrence was increased in patients with T3 and T4 tumors, incomplete resection and bone invasion.
Regional recurrence was predicted by facial nerve weakness and positive margins on neck dissection, and the risk of distant metastasis was higher among patients with a T3-4, N2-N3 disease, and/or perineural invasion. In this series, the majority (68%) of patients were treated with surgery followed by radiation, and cumulative overall and disease free survival at 5 years were 63% and 64% respectively. Interestingly, the most common pattern of failure in patients was distant metastasis.

There is little high level clinical evidence to support the use of postoperative radiation. The data are limited to retrospective series that describe improved local control rates compared to surgical resection alone (Terhaard 2004, Garden 1997, Armstrong 1990). Registry data and single institution series have consistently demonstrated improving survival among patients with this disease over time, attributed partly to improved surgical techniques but largely to the widespread adoption of postoperative radiation. Thus, despite the absence of compelling supporting prospective data, postoperative radiation therapy is considered a standard of care for patients with high risk features after resection.

1.3 Rationale for Testing Postoperative Chemoradiation (11/5/15)
The recognition of disease characteristics that predict for regional and distant failure and the suboptimal survival in patients with locally advanced disease when treated with surgery and radiation suggests a role for intensifying therapy in this group of patients. In high risk resected squamous cell carcinomas of the head and neck, 2 large, similarly designed phase III clinical trials from the RTOG and EORTC were published in 2004 that demonstrated a benefit from the concurrent administration of cisplatin chemotherapy with postoperative radiation (Cooper 2004, Bernier 2004). Patients in these 2 trials received the identical concurrent cisplatin and radiation regimen postoperatively. With slightly different eligibility criteria, both trials demonstrated superior rates of local control in the experimental arm. Both studies reported higher overall survival rates in the experimental arm, with statistical significance achieved in the EORTC study.

The improved outcomes with postoperative chemoradiation are offset by the higher rates of treatment-related toxicity observed in both the RTOG and EORTC studies. In the RTOG study, there was a highly statistically significant rate of Grade 3 or greater toxicity in the experimental arm (77% vs 34% p=<0.001) with only 61% of patients receiving all 3 doses of cisplatin. This was reproduced in the EORTC study, where only 49% of patients received the full course of chemoradiation.

This observation has led to chemoradiation strategies that attempt to limit toxicity through weekly cisplatin administration at doses that achieve similar dose intensity. Contemporary phase II data is encouraging and has consistently demonstrated improved adherence to protocol specified chemoradiation regimens (Medina 2006, Maguire 2010). Although similar rates of Grade 3 mucositis have been observed, neutropenia and myelosuppression rates are much lower.

Data on the use of chemotherapy in patients with salivary gland tumors is sparse. Even in those with metastatic disease, the role of palliative chemotherapy is not well defined, although several phase II studies have been completed (Gilbert 2006, Airolidi 2001, Vermorken 1993). Information about the adjuvant use of chemotherapy in this disease is even harder to find. Single institution data published in 2009 describes 12 patients treated with varying platinum based chemoradiation regimens (Tanvetyanon 2009). When retrospectively compared to a stage matched group of patients treated with radiation alone, superior rates of locoregional control (61 vs. 44%) and overall survival (83 vs. 44%) were observed in the chemoradiation group.

High risk resected salivary gland malignancies represent a clinical scenario with potential for improving outcomes through multimodality therapy. The obvious limitations to prospective scientific inquiry in this group of malignancies are the infrequency of the disease and the dated and retrospective quality of historical data. The cooperative group is the ideal mechanism for study of these tumors. The initial randomized phase II study was an unprecedented effort that primarily focuses on 2 objectives: determining the feasibility of a multi-institutional prospective study in this group of malignancies and obtaining preliminary data on outcomes after
postoperative chemoradiation therapy compared to radiation therapy alone. This study also provided the unique opportunity to collect tissue specimens for future translational investigation, and to establish a baseline, cooperative group database to use as a reference for future clinical trials in this disease.

Initial accrual to this trial was sluggish prompting concern about its feasibility and viability, and approximately 14 months after activation of the study, patient eligibility was significantly expanded in Amendment 3 of the protocol. As originally written, only patients with major salivary gland cancer and high-risk histologic subtypes (high-grade adenocarcinoma, high-grade mucoepidermoid carcinoma and salivary duct carcinoma) were eligible for this trial. In Amendment 3, eligibility was expanded to include patients with minor salivary gland cancers and those with intermediate-risk histologies; intermediate-grade adenocarcinoma, intermediate-grade mucoepidermoid carcinoma, and the "high-grade" acinic cell carcinoma and adenoid cystic carcinoma, which have more of an intermediate risk of recurrence. The study subsequently accrued faster than initial expectations (3.0 patients/month versus. the anticipated rate of 2.5 patients/month) and closed, ahead of schedule, in March 2015.

What has emerged is a unique opportunity to evaluate a definitive endpoint (overall survival) in a rare disease by expanding accrual. The previously enrolled phase II patients coupled with a similar number of patients enrolled in a re-opened expanded trial will be sufficient to address survival in a phase III trial. This expanded accrual also should allow preliminary efficacy comparisons within both the pathologically high-risk and intermediate-risk cohorts.

1.4 Quality of Life and Patient-Reported Outcomes

Another unique opportunity this study affords is prospectively exploring quality of life (QOL) and patient-reported outcomes (PROs) in this disease. Most curative intent multimodality treatment regimens in locally advanced head and neck cancer are associated with significant acute and late toxicities. Standard validated QOL measurements used in patients treated for carcinomas of the head and neck have demonstrated that a considerable proportion of patients report debilitating functional compromise and psychosocial morbidity (Bjordal 2000, Weymuller 2000, Ringash 2005, Martino 2008, Maguire 2010). There is also a growing body of literature supporting a relationship between better QOL and superior treatment outcomes (Siddiqui 2008, Karvonen-Gutierrez 2008). Therefore, an important goal in curative treatments that seek to improve disease control and survival is to minimize the negative impact on QOL and related outcomes (Bonner 2006, Curran 2007).

A recent phase II trial of hyperfractionated intensity modulated radiation therapy plus weekly concurrent cisplatin found good local-regional control with acceptable toxicity and QOL in patients with advanced (stage III and IVA) head and neck squamous cell carcinoma (n=35) [Maguire 2010]. While head and neck QOL and swallowing were significantly impaired at the end of treatment, by 1 month post-treatment these measures had returned to near baseline and continued to improve up to 12 months post-treatment. The most common acute grade 3+ toxicities were mucositis (38%), fatigue (28%), and dysphagia (28%). In patients receiving ipsilateral irradiation for oral and pharyngeal carcinoma treated with either radical radiotherapy or primary surgery and post-operative radiation therapy, xerostomia was estimated to range from 3% to 12.5% (Vergeer 2010, Cerezo 2009). One small study (n=20) of ipsilateral irradiation for well lateralized carcinomas of the oral cavity and oropharynx showed good tumor control and preservation of QOL (swallowing and salivary function/xerostomia) (Cerezo 2009). Thus, in this post-operative trial, which will use unilateral radiation therapy, it is expected that QOL, swallowing, and salivary function will be relatively preserved. However, it is not known whether the addition of chemotherapy will adversely impact these QOL/PROs beyond the level expected for surgery + unilateral radiation therapy, and the temporal trends of recovery post-treatment (return to baseline) are not known.

To our knowledge, data of this nature is nonexistent among patients treated with surgery + RT vs. surgery + RT + cisplatin for salivary gland malignancies, and this trial would be an ideal mechanism to collect and analyze this subjective patient reported longitudinal data. In this
context, the question is whether addition of chemotherapy to ipsilateral irradiation is associated with greater long-term impairment of QOL and other PROs beyond the acute treatment period? To that end, longitudinal assessments of QOL and key functions such as eating/swallowing (dysphagia), xerostomia (dry mouth), and fatigue are included as secondary end points in the current study. Therefore, we will explore the impact of treatment assignment on QOL and 3 PROs (eating/swallowing, fatigue, and xerostomia) using 5 validated instruments: The Functional Assessment of Cancer Therapy (FACT) H&N subscale (10 items), the Performance Status Scale – Head and Neck (PSS-HN), the Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue short form (7 items), the 15-item University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS), and the EuroQol, a 5-item questionnaire and a visual analogue scale (EQ-5D) [Ringash 2004, Ringash 2007, Henson 2001, Rodgers 2009, Christodoulou 2008, Reeve 2007, List 1996, List 1996b, List 1999, List 2000].

1.4.1 QOL and PROs Instruments

The FACT-H&N is a multidimensional, patient self-report QOL instrument specifically designed and validated for use with head and neck cancer patients. The FACT-HN consists of a 27-item core scale (FACT-G) and is supplemented with a 10-item head and neck subscale targeting head and neck related symptoms and side effects (Cella 1993; Cella 2000).

The PSS-HN was designed to evaluate performance in areas of functioning most likely affected by head and neck cancer and its treatment. It is a clinician/interviewer administered assessment that focuses on 3 functional areas: Normalcy of Diet, Eating in Public, and Understandability of Speech. The score on each of the 3 subscales ranges from 0-100, with higher scores indicating better performance (List 1996, List 1996b, List 1999, List 2000). The PSS-HN has been validated, been shown to discriminate levels of functioning across the broad spectrum of head and neck cancers, and has demonstrated good inter-rater reliability, as well as sensitivity to differences in performance and change over time.

The PROMIS-fatigue short form, developed as part of the NIH Roadmap Initiative, focused on developing a publicly available resource of standardized, accurate, and efficient PRO measures of symptoms, distress, and functioning. Two content domains of fatigue, experience and impact, were identified by a panel of experts. An item pool of 58 fatigue experience and 54 fatigue impact items were developed. The psychometric properties of these items were evaluated in a sample of 450 individuals from the general U.S. population using classical test theory indices, monotonicity, and scalability. The expert panel selected the 10 best items in each domain. These 20 items were presented to a panel of clinical experts. Only 1 item was dropped because of redundancy. The 7-item short-form fatigue measure used in this study was created using items selected for consistency in the response scale, broad coverage across the fatigue continuum (i.e., high to low), and good precision of measurement (discrimination function).

The XeQOLS instrument is patient self-report measure that consists of 15 items on a 5-point Likert-type scale covering mouth/throat dryness and its impact on 4 major domains of oral health-related quality of life: physical functioning, personal/psychological functioning, social functioning, and pain/discomfort issues (Logemann 2008; Cella 1993; List 1996). The XeQOLS takes the patient approximately 5 minutes to complete.

The EQ-5D has been more frequently employed in cooperative group studies as a general QOL measure and for cost-utility analysis (Badia 1998, Schulz 2002, Wu 2002). The EQ-5D is a two-part questionnaire that the patient can complete in approximately 5 minutes. The first part of the EQ-5D consists of five items covering five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these areas is graded on three levels: 1=no problems; 2=moderate problems; and 3=extreme problems. Health states are then derived from combinations of the
leveled responses to the five dimensions. The second part of the EQ-5D is a visual analogue scale (VAS) valuing current health state, with 0 at bottom of the scale (worst imaginable health state) and 100 at the top (best imaginable health state) (Badia 1998, Schulz 2002, Wu 2002). The 5-item index score is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score can be used in a quality adjusted survival analysis depending on the health state(s) of interest (Wu 2002). For this study we plan to report the multidimensional utilities for comparative purposes.

1.4.2 Timeframe of QOL/PRO Assessments

These patient-reported QOL and function measures will be administered at baseline (pretreatment), at the end of RT, at 3 months after completing RT, and at 12, and 24 months from start of RT. The 3, 12 and 24 months QOL assessment intervals were chosen to coincide with usual schedules of seeing a patient after completion of radiation therapy. These assessments will provide the opportunity to assess the long-term impact of radiation therapy +/- chemotherapy on QOL/PROs in this population. The investigators are interested in assessing whether there are treatment group differences in patients’ QOL, dysphagia, xerostomia, and fatigue levels and whether these measures return to near baseline (Maguire 2010).

2.0 OBJECTIVES (11/5/15)

2.1 Primary Objectives

2.1.1 Phase II:
- Determine the feasibility of conducting a cooperative group prospective clinical trial in patients with resected malignant salivary gland tumors;
- Acquire preliminary efficacy data comparing postoperative radiotherapy alone to concurrent chemotherapy and radiation using weekly cisplatin.

2.1.2 Phase III: Compare overall survival rates among patients receiving cisplatin and radiation to those receiving radiation alone.

2.2 Phase II/III Secondary Objectives

2.2.1 Compare the acute toxicities of these 2 adjuvant treatments;
2.2.2 Compare late treatment-related adverse events in patients receiving postoperative radiation to those receiving concurrent chemoradiation;
2.2.3 Compare progression-free survival rates among patients receiving cisplatin and radiation to those receiving radiation alone in both the cohort of patients with pathologically high-risk disease (high-grade adenocarcinoma, high-grade mucoepidermoid carcinoma, salivary duct carcinoma), and the patient cohort with pathologically intermediate-risk disease (all other eligible diagnoses).
2.2.4 Investigate quality of life and patient-reported outcomes in patients enrolled in the study;
2.2.5 Identify the histopathology and tumor marker expression from patients enrolled on this trial and assemble a tissue bank for future correlative studies;
2.2.6 Establish an NRG Oncology baseline database for salivary gland malignancies to serve as a resource for future exploration of innovative and/or targeted approaches for this disease.

3.0 PATIENT SELECTION (4/22/14)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, contact the study data manager.

3.1 Conditions for Patient Eligibility (4/22/14)

3.1.1 Pathologically proven diagnosis of a malignant major salivary gland tumor or malignant minor salivary gland tumor of the head and neck of the following histologic subtypes:
- intermediate-grade adenocarcinoma or intermediate-grade mucoepidermoid carcinoma;
• high-grade adenocarcinoma or high-grade mucoepidermoid carcinoma or salivary duct carcinoma;
• high-grade acinic cell carcinoma or high-grade (>30% solid component) adenoid cystic carcinoma.

Pathologic interpretation of salivary gland malignancies can be very difficult. Patients with diagnoses such as "undifferentiated or poorly differentiated carcinoma", "carcinoma-ex pleomorphic adenoma", "carcinoma NOS" and others should be considered for this trial. A rapid, anonymous photomicrograph review can be obtained from Dr. El-Naggar to assist in identifying appropriate patients for this trial. Institutions are urged to contact either Dr. Adelstein (adelstd@ccf.org) or Dr. El-Naggar (anaggar@mdanderson.org) to expedite such a review.

3.1.2 Surgical resection with curative intent within 8 weeks prior to registration;
3.1.3 Pathologic stage T3-4 or N1-3 or T1-2, N0 with a close (≤1mm) or microscopically positive surgical margin (AJCC, 7th ed.; see Appendix IV); patients must be free of distant metastases based upon the following minimum diagnostic workup:
   • History/physical examination within 8 weeks prior to registration;
   • Radiologic confirmation of the absence of hematogenous metastasis within 12 weeks prior to registration; at a minimum, contrast CT imaging of the chest is required; PET/CT is acceptable.
3.1.4 Zubrod Performance Status 0-1;
3.1.5 Age ≥ 18;
3.1.6 CBC/differential obtained within 8 weeks prior to registration, with adequate bone marrow function defined as follows:
   • Absolute neutrophil count (ANC) ≥ 1,800 cells/mm³;
   • Platelets ≥ 100,000 cells/mm³;
   • Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)
3.1.7 Adequate renal and hepatic function within 8 weeks prior to registration; defined as follows:
   • Serum creatinine < 2.0 mg/dl;
   • Total bilirubin < 2 x the institutional ULN;
   • AST or ALT < 3 x the institutional ULN.
3.1.8 Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential;
3.1.9 Women of childbearing potential and male participants who are sexually active must practice adequate contraception during treatment and for 6 weeks following treatment.
3.1.10 All patients must have a Medical Oncology evaluation within 4 weeks prior to registration;
3.1.11 Patients must be deemed able to comply with the treatment plan and follow-up schedule.
3.1.12 Patients must provide study specific informed consent prior to study entry, including consent for mandatory tissue submission for central review.

3.2 Conditions for Patient Ineligibility (2/27/12)
3.2.1 Patients with residual macroscopic disease after surgery;
3.2.2 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
3.2.3 Prior systemic chemotherapy or radiation therapy for salivary gland malignancy; note that prior chemotherapy for a different cancer is allowable;
3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
3.2.5 Severe, active co-morbidity, defined as follows:
   • Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
• Transmural myocardial infarction within the last 6 months;
• Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
• Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
• Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; Note, however, coagulation parameters are not required for entry into this protocol.
• 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.
• Pre-existing ≥ grade 2 neuropathy;
• Prior organ transplant.

3.2.6 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;

3.2.7 Significant pre-existing hearing loss, as defined by the patient or treating physician.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT
NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (4/22/14)
4.1.1 Tissue submission for central pathology review is required within 2 weeks of study entry (see Section 10.2 for details of collection and submission);
4.1.2 Surgical evaluation within 6 weeks prior to treatment clearing the patient to begin postoperative treatment;
4.1.3 For Arm 1 patients (randomized to radiation therapy and cisplatin): CBC/differential, serum creatinine, total bilirubin, and AST or ALT are required within 2 weeks prior to treatment.
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 treatment: the Functional Assessment of Cancer Therapy (FACT) H & N subscale, the Performance Status Scale-Head and Neck (PSS-HN), the Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue short form, the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) and the EuroQoL (EQ-5D);
4.1.5 Dental evaluation within 8 weeks prior to treatment;
4.1.6 For Arm 1 patients (randomized to radiation therapy and cisplatin): Baseline audiogram within 8 weeks prior to treatment.

4.2 Highly Recommended Evaluations/Management
4.2.1 Nutritional evaluation within 8 weeks prior to treatment

5.0 REGISTRATION PROCEDURES (10/3/13)
Access requirements for OPEN 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.
Note: This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See below for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

**IMRT and IGRT are optional for this study.** For reduced margins, IGRT is mandatory, and the institution must be credentialed for head and neck image guided radiotherapy (IGRT) in order to enroll patients on this trial.

### 5.1 Pre-Registration Requirements for Image-Guided Radiotherapy (IGRT) Treatment Approach (for sites that utilize this approach) (10/3/13)

#### 5.1.1
In order to utilize head and neck IGRT for reduced margins, the center must be credentialed for its use. This means the institution must have met technology requirements and have provided the baseline physics information. This information is available on the NRG Oncology/RTOG web site, [http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1008](http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1008).

In order to become credentialed for head and neck IGRT, the institution must have already become credentialed for either 3DCRT and/or IMRT. Institutions that have not been credentialed by NRG Oncology to perform 3DCRT and/or IMRT MUST apply for 3DCRT and/or IMRT credentialing as described below in Sections 5.2 and 5.3.

#### 5.1.2 IGRT Credentialing Process (4/22/14)

Note: If an institution has been approved for head and neck IGRT credentialing, the site will NOT have to re-credential for this study.

Each institution will be required to undergo credentialing for head and neck IGRT (review of at least one case from each institution) if using reduced margins. The first step is for the institution or investigator to update an existing or complete a new Facility Questionnaire and a Credentialing Status Inquiry Form, available on the Imaging and Radiation Oncology Core (IROC) Houston (former Radiological Physics Center [RPC]), [http://irochouston.mdanderson.org](http://irochouston.mdanderson.org).

Next, 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 with targets similar to the patients that will be treated on this protocol. See the NRG Oncology/RTOG web site, [http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1008](http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1008), for IGRT Data Submission and the spreadsheet. 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 Radiation Oncology Co-Chair, John Kim, MD and/or the Medical Physics Co-chair, Peter Maxim, PhD, prior to certification. IGRT data and the completed spreadsheet are submitted to TRIAD. Upon approval of these images, NRG Oncology will notify the institution that they have completed IGRT credentialing.

### 5.2 Pre-Registration Requirements for IMRT Treatment Approach (4/22/14)

#### 5.2.1
In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the IROC Houston web site. Visit [http://irochouston.mdanderson.org](http://irochouston.mdanderson.org) and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the IROC Houston web site, [http://irochouston.mdanderson.org](http://irochouston.mdanderson.org); select “Credentialing” and “NRG Oncology”. Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and NRG Oncology that the institution has completed
this requirement. Subsequently, NRG Oncology will notify the institution that the IMRT credentialing requirement has been met.

5.2.2 The institution or investigator must update an existing or complete a new IMRT Facility Questionnaire and a Credentialing Status Inquiry Form (available on the IROC Houston web site, http://irochouston.mdanderson.org) and send it to NRG Oncology for review prior to entering any cases. NRG Oncology will notify the institution when all requirements have been met and the institution is RT credentialed to enter patients onto this study.

5.3 Pre-Registration Requirements for 3DCRT Treatment Approach (4/22/14)

5.3.1 Institutions having IMRT credentialing are not required to complete another questionnaire for 3D-CRT or perform an additional Dry Run.

5.3.2 The new or updated Facility Questionnaire (one per institution, available on the IROC Houston web site, http://irochouston.mdanderson.org) is to be sent to NRG Oncology for review prior to entering any cases. NRG Oncology will notify the institution when all requirements have been met and the institution is RT credentialed to enter patients onto this study.

5.4 Digital RT Data Submission to NRG Oncology Using TRIAD (10/3/13)

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 NRG Oncology/RTOG web site 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.

5.5 Regulatory Pre-Registration Requirements (4/22/14)

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

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, CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site.
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.) An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites 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 1008 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 1008.
- Click on the Site Registration Documents link

Requirements for RTOG 1008 site registration:
- CTSU IRB Certification (for sites not participating via the NCI CIRB);
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB);
- CTSU RT Facilities Inventory Form (if applicable);
- 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.

Non-English Speaking Canadian and Non-North American Institutions:
*Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG 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.

Submit completed forms along with a copy of your IRB Approval and Informed Consent to the 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

5.5.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
In addition to the requirements above, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.5.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS (5/4/11)
For institutions that do not have an approved LOI for this protocol:
International sites must receive written approval of submitted LOI forms from NRG Oncology prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.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.

5.6 OPEN Registration (11/5/15)
5.6.1 Patient registration can occur only after pre-treatment 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. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and a ‘Registrar’ role on either the LPO or participating organization roster. See Section 5.0 for obtaining a CTEP-IAM account. 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).

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

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

5.6.2 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 (10/3/13)

**Note:** This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See Section 5.4 for information on installing TRIAD for submission of digital RT data prior to enrolling patients

Protocol treatment must begin within 2 weeks after registration.

If there are wound complications after surgery (e.g. a major active fistula or wound dehiscence), which causes a delay in starting radiation treatment, sites will document this on the appropriate case report form (see Section 12.1).

6.1 **Dose Specifications (11/24/14)**

A total dose of 60-66 Gy at 2.0 Gy/fraction in 30-33 fractions over 6 or 6.5 weeks will be delivered with either 3-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT).

Radiation treatment (RT) must start on Monday, Tuesday or Wednesday in order for the patient to receive at least 3 consecutive RT fractions before 2 non-work day interruption.

6.1.1 **Dose Specifications for 3D Conformal Radiotherapy (3D-CRT)**

If 3D-CRT is used, there will be at least 2 sequential plans generated: one for PTV50 and one for PTV60. In cases with close or involved surgical margin or with extracapsular nodal extension (ECE), a 3rd boost plan will need to be generated.

PTV50 (see definition below), which is the initial target volume, encompassing the tumor bed and the ipsilateral neck will receive 2 Gy/fraction/day to 50 Gy. The uninvolved lower neck nodes can be treated with a matching conventional AP ipsilateral supraclavicular field to a total dose of 50 Gy at 2 Gy/fraction for 25 fractions. The dose is prescribed to a depth of 3 cm from the anterior surface for the AP field.

PTV60, which is the boost volume encompassing the tumor bed and regions of involved cervical nodes (see definition below), will receive a 10 Gy boost at 2 Gy/fraction to a total dose of 60 Gy. If all surgical margins are negative and are > 1 mm from the tumor edge and there is no extracapsular nodal extension (ECE), the total radiation dose will be 60 Gy, and no additional boost is required.
PTV66 will be defined only for tumors with tumor cells extending within 1 mm from the final surgical margin or microscopically involved surgical margins or with ECE. A boost dose of 6 Gy at 2 Gy/fraction will be delivered for tumors with close or microscopically involved surgical margins or ECE.

6.1.2 Dose Specifications for Intensity Modulated Radiotherapy (IMRT)

If IMRT is used, PTV54 and PTV60 are incorporated into a single plan with dose painting. In cases with close or involved surgical margin or with ECE, a 2nd sequential boost plan will need to be generated.

Radiation therapy will be administered based on the following prescription:

- PTV54 will receive 54 Gy at 1.8 Gy/fraction for 30 fractions;
- PTV60 will receive 60 Gy at 2 Gy/fraction for 30 fractions;
- PTV66: will receive a sequential boost dose of 6 Gy at 2 Gy/fraction for tumors with \( \leq 1 \) mm or microscopically involved surgical margins or ECE.

Alternatively, the uninvolved ipsilateral low neck can be treated with a conventional AP ipsilateral supraclavicular field to a total dose of 50 Gy at 2Gy fraction for 25 fractions. The dose is prescribed to a depth of 3 cm from the anterior surface for the AP field. The junction between the IMRT or 3DCRT fields and the low-neck fields will be dependent on the institutional IMRT techniques; however, each institution is required to record the dosimetric details at the match-line to ensure dose homogeneity and to prevent overdosing of the spinal cord.

6.2 Technical Factors (11/5/15)

6.2.1 Megavoltage equipment capable of delivering 3DCRT or IMRT (either static or dynamic) is required. For institutions using IMRT, any treatment planning and delivery system that has been credentialed for head and neck IMRT by IROC Houston is acceptable.

6.2.2 Image Guidance for IGRT (see Section 5.1)

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

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac;
- Linear-accelerator mounted kV and MV conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy);
- Other mechanism, after discussion with the Radiation Oncology Co-Chair and/or Medical Physics Co-chair.

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

- Region-of-interest (ROI) or “clip box” for fusion should be set to encompass the high dose PTV and adjacent spinal cord; if the 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 surgical clips and soft tissue structures (e.g. optic nerves and/or optic chiasm).
- Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are less than 2.5 mm (this typically corresponds to one half of the usual PRV margin), the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 2.5
mm). If one or more corrections are 2.5-5 mm, adjustment is necessary prior to treatment; however, 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.

6.3 Localization, Simulation, and Immobilization

6.3.1 Immobilization

The immobilization device should include at least the head and neck. It is strongly encouraged that the participation centers also utilize shoulder immobilization especially when comprehensive nodal IMRT, including the ipsilateral low neck, is utilized.

6.3.2 Treatment Planning CT Scan (5/4/11)

A treatment planning CT scan will be required to delineate the CTV and PTV. Other imaging studies such as pre-surgical MRI and PET-CT scans can aid in volume delineation. The treatment planning CT scan should be acquired with the patient immobilized in the same treatment position. All tissue irradiated should be included in the treatment planning CT scan, which should be less than or equal to 3 mm slice thickness.

6.4 Treatment Planning/Target Volumes (4/22/14)

The definition of the target volumes should conform to the 1993 ICRU report #50.

6.4.1 Clinical Target Volume (CTV)

CTV delineation is based on preoperative imaging, preoperative physical exam, operative findings and pathologic findings. It is strongly recommended to map preoperative GTV(s) onto the postoperative radiation therapy planning CT scan using image registration with pre-surgical CT, MRI or PET-CT scans.

Parotid Gland Cancer

CTV50 (3DCRT) or CTV54 (IMRT) should include the entire preoperative volume of the involved parotid gland and postoperative surgical bed. Typically, this volume will be at least the preoperative GTV + 1.5 – 2 cm respective tissues not deemed to be at risk for microscopic spread. For superficial lobe tumors when a superficial parotidectomy has been performed, CTV50 or CTV54 should encompass the deep lobe (to depth of styloid process) in all cases. For deep lobe tumors or when a complete parotidectomy has been performed, CTV50 or CTV54 should include the parapharyngeal space to ensure coverage of the deep lobe and regions at risk for microscopic spread. CTV50 or CTV54 should be delineated to the skull base up to the stylomastoid foramen if the VII nerve (facial nerve) is not grossly involved or to include the facial nerve canal through the petrous temporal bone if it is grossly involved.

For nodal coverage, ipsilateral level II, III and IV should be included. If there is nodal involvement in level II, then the ipsilateral retrostyloid space and level IB should also be included. Ipsilateral level V is included if there is nodal involvement in level IIIB, IIIB or IVB. The surgical scar should be outlined and also included in CTV50 or CTV54. Prophylactic nodal irradiation for the N0 neck is not mandatory for adenoid cystic carcinomas but should be considered for advanced primary T-category (T3,T4).

Submandibular and Sublingual Gland Cancer

CTV50 (3DCRT) or CTV54 (IMRT) should cover the entire preoperative volume and postoperative surgical bed. Typically, this volume will be at least the preoperative GTV + 1.5 – 2 cm respective tissues not deemed to be at risk for microscopic spread and should include the entire submandibular space. If the mandible is eroded, the involved part of the mandible + 1.5-2 cm margin should also be included. If the tumor grossly involves one of the named large nerves in that area, such as the lingual nerve (branch of V3), the inferior alveolar nerve (branch of V3) or the hypoglossal nerve ( Cranial nerve XII), then the skull base will need to be included in this volume, up to the hypoglossal canal for hypoglossal nerve
involvement or foramen ovale for V3 branches involvement. Moreover, if the inferior alveolar nerve (branch of V3) is involved, CTV50 or CTV54 also should encompass the mandible proximally to the mandibular foramen. In situations where V3 is involved near the skull base, CTV50 or CTV54 should include Meckel’s cave.

For nodal coverage, ipsilateral level 1B, II, III and IV should be included for all cases. If there is nodal involvement in level II, then the ipsilateral retrostyloid space should be included. If ipsilateral level I is involved, consideration should be made to include the contralateral level I and II nodes. Ipsilateral level V is included if there is nodal involvement in level IIB, IIIB or IV. The surgical scar should be outlined and also covered in CTV50 or CTV54. Prophylactic nodal irradiation for the N0 neck is not mandatory for adenoid cystic carcinomas but should be considered for advanced primary T-category (T3,T4).

Minor Salivary Gland Cancer
CTV50 (3DCRT) or CTV54 (IMRT) should cover the entire preoperative volume and postoperative surgical bed. Typically, this volume will be at least the preoperative GTV + 1.5 – 2 cm respective tissues not deemed to be at risk for microscopic spread. If a named large nerve is involved, CTV50 or CTV54 should include the anatomic route of the nerve proximally to the skull base.

For nodal coverage, ipsilateral level 1B, II, III, and IV should be included for all cases. Bilateral necks should be treated for all midline primary lesions and the contralateral neck should be treated for primary lesions with 1 cm of the midline. For lateralized lesions, if there is nodal involvement in ipsilateral level II, then the ipsilateral retrostyloid space should be included. If ipsilateral level I is involved, consideration should be made to include the contralateral level I and II nodes. Ipsilateral level V is included if there is nodal involvement in level IIB, IIIB, or IV. Prophylactic nodal irradiation for the N0 neck is not mandatory for adenoid cystic carcinomas but should be considered for advanced primary T-category (T3,T4).

CTV60 should include all regions deemed to be at high risk for microscopic disease, all potential routes of spread, and the high-risk nodal regions. Specifically, it should encompass the resected tumor bed with a 1 cm margin (respecting anatomic landmarks) and site of involved named nerves +1 cm margin. CTV60 should include all known involved nodal regions. The entire involved nodal region should be included (e.g. entire level II if there is a positive level II node). If there is pathologic extracapsular extension (ECE), then a further boost is required (CTV66).

CTV66 (defined only for patients with close (≤ 1 mm) or involved surgical margins or ECE) should include the tumor bed based on pretreatment imaging studies with a 5 mm margin (respecting anatomic landmarks) and only the involved nodal bed(s) with pathologic extracapsular extension.

6.4.2 Planning Target Volume (PTV)

**PTV Expansion Without IGRT**
For those institutions that are not using daily IGRT (see Section 5.1 above), 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 (see Sections 5.1 and 6.2.2), the minimum CTV-to-PTV expansion is 2.5 mm for parotid and 3 mm for submandibular/sublingual tumors (a larger expansion may be necessary for a target
volume subject to significant intra-fraction variability). In general, the CTV-to-PRV expansion (with IGRT) should not exceed 5 mm.

6.5 Critical Structures (11/5/15)

Note: All structures marked “required” in the table below must be contoured and submitted for review. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

The following table outlines the naming of the various normal and critical structures for submission to TRIAD:

<table>
<thead>
<tr>
<th>New Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>Required</td>
</tr>
<tr>
<td>CTV_6000</td>
<td>Primary Tumor Bed plus involved nodes</td>
</tr>
<tr>
<td></td>
<td><strong>Required for 3DCRT and IMRT</strong></td>
</tr>
<tr>
<td>CTV_5400</td>
<td>At risk regions</td>
</tr>
<tr>
<td></td>
<td><strong>Required for IMRT only</strong></td>
</tr>
<tr>
<td>CTV_6600</td>
<td>only for patients with close (≤ 1 mm) or involved surgical margins</td>
</tr>
<tr>
<td></td>
<td><strong>Required when applicable</strong></td>
</tr>
<tr>
<td>CTV_5000</td>
<td><strong>Required for 3DCRT only</strong></td>
</tr>
<tr>
<td>PTV_6000</td>
<td>CTV-PTV 5 mm margin without IGRT; 2.5 mm with Daily IGRT</td>
</tr>
<tr>
<td></td>
<td><strong>Required for 3DCRT and IMRT</strong></td>
</tr>
<tr>
<td>PTV_6000m08</td>
<td>PTV_6000 excluding 8mm from skin</td>
</tr>
<tr>
<td></td>
<td><strong>Required for 3DCRT and IMRT</strong></td>
</tr>
<tr>
<td>PTV_5400</td>
<td>CTV-PTV 5 mm margin without IGRT; 2.5 mm with Daily IGRT</td>
</tr>
<tr>
<td></td>
<td><strong>Required for IMRT only</strong></td>
</tr>
<tr>
<td>PTV_6600</td>
<td>CTV-PTV 5 mm margin without IGRT; 2.5 mm with Daily IGRT</td>
</tr>
<tr>
<td></td>
<td><strong>Required when applicable</strong></td>
</tr>
<tr>
<td>PTV_6600m08</td>
<td>PTV_6600 excluding 8mm from skin</td>
</tr>
<tr>
<td></td>
<td><strong>Required when applicable for 3DCRT and IMRT</strong></td>
</tr>
<tr>
<td>PTV_5000</td>
<td><strong>Required for 3DCRT only</strong></td>
</tr>
<tr>
<td>SpinalCord</td>
<td>Spinal Cord</td>
</tr>
<tr>
<td></td>
<td><strong>Required</strong></td>
</tr>
<tr>
<td>SpinalCord_05</td>
<td>Planning risk Volume of 5 mm</td>
</tr>
<tr>
<td></td>
<td><strong>Required</strong></td>
</tr>
<tr>
<td>BrainStem</td>
<td>Brain Stem</td>
</tr>
<tr>
<td></td>
<td><strong>Required</strong></td>
</tr>
<tr>
<td>BrainStem_03</td>
<td>Planning Risk Volume of 3 mm</td>
</tr>
<tr>
<td></td>
<td><strong>Required</strong></td>
</tr>
<tr>
<td>Parotid_L</td>
<td>Left Parotid</td>
</tr>
<tr>
<td></td>
<td><strong>Required</strong></td>
</tr>
<tr>
<td>Parotid_R</td>
<td>Right Parotid</td>
</tr>
<tr>
<td></td>
<td><strong>Required</strong></td>
</tr>
<tr>
<td>OralCavity</td>
<td>Oral Cavity</td>
</tr>
<tr>
<td></td>
<td><strong>Required when applicable</strong></td>
</tr>
<tr>
<td>Lips</td>
<td>Lips</td>
</tr>
<tr>
<td></td>
<td><strong>Required when applicable</strong></td>
</tr>
<tr>
<td>Mandible</td>
<td>Mandible</td>
</tr>
<tr>
<td></td>
<td><strong>Required</strong></td>
</tr>
<tr>
<td>Pharynx</td>
<td>Uninvolved posterior pharyngeal wall plus adjacent constrictor muscles;</td>
</tr>
<tr>
<td></td>
<td>should not include PTVs</td>
</tr>
<tr>
<td>Structure</td>
<td>Notes</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Required when applicable</td>
</tr>
<tr>
<td>Cervical Esophagus</td>
<td></td>
</tr>
<tr>
<td><strong>Required when applicable</strong></td>
<td>(for node+ in lower neck)</td>
</tr>
<tr>
<td>Larynx</td>
<td>Glottic/Supraglottic Larynx</td>
</tr>
<tr>
<td><strong>Required</strong></td>
<td></td>
</tr>
<tr>
<td>External</td>
<td>External border of patient used to define Unspecified Tissue</td>
</tr>
<tr>
<td><strong>Required</strong></td>
<td></td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>Brachial Plexus</td>
</tr>
<tr>
<td><strong>Required when applicable</strong></td>
<td></td>
</tr>
<tr>
<td>Cochlea_L</td>
<td>Left Cochlea</td>
</tr>
<tr>
<td><strong>Required when applicable</strong></td>
<td></td>
</tr>
<tr>
<td>Cochlea_R</td>
<td>Right Cochlea</td>
</tr>
<tr>
<td><strong>Required when applicable</strong></td>
<td></td>
</tr>
<tr>
<td>Eye_L</td>
<td>Left Eye</td>
</tr>
<tr>
<td><strong>Required when applicable</strong></td>
<td></td>
</tr>
<tr>
<td>Eye_R</td>
<td>Right Eye</td>
</tr>
<tr>
<td><strong>Required when applicable</strong></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>Brain</td>
</tr>
<tr>
<td><strong>Required when applicable</strong></td>
<td></td>
</tr>
<tr>
<td>OpticNerve_L</td>
<td>Left Optic Nerve</td>
</tr>
<tr>
<td><strong>Required when applicable</strong></td>
<td></td>
</tr>
<tr>
<td>OpticNerve_R</td>
<td>Right Optic Nerve</td>
</tr>
<tr>
<td><strong>Required when applicable</strong></td>
<td></td>
</tr>
<tr>
<td>Chiasm</td>
<td>Required when applicable</td>
</tr>
<tr>
<td>Lens_L</td>
<td>Required when applicable</td>
</tr>
<tr>
<td>Lens_R</td>
<td>Required when applicable</td>
</tr>
</tbody>
</table>

The following critical structure contours are **mandatory**. The remainder can be used as guidelines.

- For all tumors: Mandible, brainstem, spinal cord, larynx, and parotid glands
- For parotid tumors: Brain and cochlea
- For submandibular/sublingual tumors: Lip/oral cavity and OAR pharynx
- As necessary: Brachial plexus and esophagus (for node+ in lower neck), eyes/optic nerves/chiasm

### 6.5.1 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 should be below the lowest slice level that has PTV on it. The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

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

**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. For parotid cancers, the oral cavity will be defined as a composite structure consisting of the anterior ½ to 2/3 of the oral tongue/floor of...
mouth, buccal mucosa, and palate. For submandibular/sublingual cancers, the oral cavity will be defined as the subset of this composite structure that does not overlap with PTV.

**Parotid Glands:** Parotid glands will be defined based on the treatment planning CT scan. For parotid cancer, the contralateral parotid will be delineated. For submandibular/sublingual cancer, both parotid glands are outlined. The ipsilateral parotid gland volume will not include any portion of any of the CTVs, although they can overlap the PTVs.

**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). This should not overlap the PTVs.

**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 suprahypoid epiglottis.

**Mandible:** This includes the entire bony structure of the mandible from TMJ through the symphysis. It is recognized that for submandibular/sublingual cancers, this may overlap with CTVs and PTVs.

**Brachial plexus:** Brachial plexus contouring can be delineated as outlined by Hall 2008. It comprises of linear structures of 5 mm thickness that extend from the neural foramina of C5 through T1 to the small space between the anterior and middle scalene muscles. For CT slices where no neural foramen is present, one can contour only the space between the anterior and middle scalene muscles. If one follows the space between these muscles inferiorly; one will find the cords of the brachial plexus posterior to subclavian neurovascular bundle. They are the non-enhanced structures posterior to the enhanced subclavian vein. These cords extent laterally along the axillary vein into the axilla.

**Cochlea:** Contour for all cases.

**Brain:** Contour the brain for all cases, especially the parotid tumor.

**Eyes:** Contour the globes and lens for all cases.

**Optic Nerves:** Contour for all cases. Care should be given to contour optic nerves through the optic canal in continuity with the chiasm.

**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.

### 6.5.2 Dose Prescription to the PTVs (4/22/14)

See Sections 6.1.1 (3D-CRT) and 6.1.2 (IMRT) for detailed dose specifications. See Section 6.4 for definitions of CTVs and PTVs. As described above, prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size for most patients and a sequential boost of 6 Gy (total dose 66 Gy) will be required for patients with ≤ 1 mm or involved surgical margins or ECE. The goal is for 95% of the PTV60 to receive ≥ 2 Gy 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 8 mm beneath the skin and does not fall on the outlined surgical scar.

For IMRT planning and prioritization, PTV60 will be the highest priority target structure. PTV66 and PTV54, 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 Dose Constraints to Normal Structures (11/24/14)

Note: See Section 6.5 for mandatory normal tissue constraints. Dose constraints should be evaluated using a composite plan of all phases for 3D-CRT and IMRT plans.

**Spinal Cord:** The PRVcord (as defined in Section 6.5) should not exceed 45 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 48 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.

**Brainstem:** The PRVbrainstem (as defined in Section 6.5) should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm) unless the skull base is included in CTV50 (3DCRT) or CTV54 (IMRT). When the skull base is treated, the PRVbrainstem (as defined in Section 6.5) 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 the same priority as the PRVcord.

**Lips:** Reduce the dose as much as possible. The mean dose should be < 20 Gy. For parotid cancers, the maximum dose will be < 30 Gy. For submandibular/sublingual gland cancers, the maximum dose will be < 45 Gy.

**Oral Cavity:** Reduce the dose as much as possible. For parotid cancers, the mean dose should be < 30 Gy. For submandibular/sublingual gland cancers, the mean dose should be < 50 Gy. Efforts should be made to avoid hot spots (> 60 Gy) within the oral cavity, particularly for parotid cancers.

**Parotid Glands:** For parotid gland cancer, the goal is keep the mean dose to the contralateral parotid gland to < 26 Gy. For submandibular/sublingual gland cancers, the goal is to keep the mean dose to the contralateral gland to < 26 Gy and the ipsilateral gland to < 30 Gy if not involved directly. 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 < 40 Gy; 3) No more than 10% 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 30% of the esophagus exceeds 45 Gy; 2) Mean dose < 35 Gy; 3) No more than 10% 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 < 35 Gy Dmean whenever feasible.

**Mandible:** Reduce the dose as much as possible. It is recognized that particularly for these cancer, 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 $< 64$ Gy for a prescribed total dose of $60$ Gy is prescribed, and $< 70$ Gy for a prescribed total dose of $66$ Gy.

**Brachial plexus:** The maximum dose to the ipsilateral brachial plexus should be kept $< 60$ Gy if there are no involved low neck nodes. If the low neck is involved, the maximum brachial plexus dose should be kept $< 66$ Gy.

**Cochlea:** It is recommended to keep the ipsilateral cochlea maximum dose $< 50$ Gy. It is recognized that this will not be possible when it is required to include the temporal bone in the clinical target volume.

**Brain:** It is recommended that the brain maximum dose should not exceed $60$ Gy to any volume in excess of $0.03$ cc (approximately $3$ mm x $3$ mm x $3$ mm) when the skull base is not included in CTV60. It is recommended that the brain maximal dose should not exceed $66$ Gy for all cases.

**Eyes:** The maximum dose should not exceed $30$ Gy. Particular attention should be given to keep the lens maximum dose $< 2.5$ Gy.

**Optic Nerves:** The maximum dose should not exceed $30$ Gy.

**Chiasm:** The maximum dose should not exceed $30$ Gy.

**Unspecified Tissue Outside the Targets:** 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 $1$ cc of unspecified tissue can receive $64$ Gy or more. When a boost is used to treat CTV66 to $66$ Gy, these numbers can be increased. In this case, no more than $5\%$ of the unspecified volume 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** (if IMRT is used) *(4/22/14)*
1. Spinal Cord and brainstem
2. PTV60
3. PTV50 (3DCRT) or PTV54 (IMRT)-if applicable
4. PTV66 (if applicable)
5. Chiasm
6. Optic Nerve
7. Brain
8. Eyes
9. Lens
10. Parotid gland contralateral to primary tumor site
11. OARpharynx
12. GSL
13. Esophagus
14. Lips
15. Oral Cavity
16. Parotid gland ipsilateral to primary tumor site
17. Mandible
18. Unspecified tissue outside the targets

6.6 **Documentation Requirements** *(10/3/13)*
- Pre-treatment radiation therapy planning CT scan;
- If IGRT is not used, then orthogonal images that localize the isocenter placement of IMRT are required. This information should be archived by the submitting institution, so it can be made available for possible future review;
6.7 Compliance Criteria (11/5/15)

6.7.1 Dose Compliance

The reported dose for each PTV should include the prescribed dose, maximal point dose, mean dose, the percent of PTV that receive > 110%, > 115% and < 93% of the prescribed dose.

6.7.2 Definitions of Protocol Compliance and Violations

*For 3D-CRT:* The definitions of protocol compliance and violations apply to evaluation of PTV60 on the composite plan of PTV50 and PTV60 or evaluation of PTV3 on a composite plan of all phases depending on the total dose prescribed 60 or 66 Gy.

*For IMRT:* The definitions of protocol compliance and violations apply to evaluation of PTV60 on the first phase (PTV54 and PTV60 treated with a single phase) or the evaluation of PTV66 on a composite plan of all phases depending on the total dose prescribed 60 or 66 Gy.

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Deviation Unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose to 95% of PTV_{6000}: D95%(Gy)</td>
<td>60</td>
<td>58-61</td>
</tr>
<tr>
<td>Minimum dose in Gy (&quot;cold spot&quot; within PTV_{6000}, not including portion of PTV_{6000} near (&lt;8 mm) skin)-PTV_{6000m08}</td>
<td>56</td>
<td>54-56</td>
</tr>
<tr>
<td>Maximum dose in Gy (&quot;hot spot&quot;) within PTV_{6000*}</td>
<td>&lt; 67</td>
<td>67-70</td>
</tr>
<tr>
<td>Total dose to 95% of PTV_{6600}: D95%(Gy)</td>
<td>66-70</td>
<td>64-66 or 70-72</td>
</tr>
<tr>
<td>Minimum dose in Gy (&quot;cold spot&quot; within PTV_{6600} not including portion of PTV_{6600} near (&lt; 8 mm) skin)-PTV_{6600m08}</td>
<td>60</td>
<td>59-60</td>
</tr>
<tr>
<td>Maximum dose in Gy (&quot;hot spot&quot;) within PTV_{6600*}</td>
<td>&lt; 77</td>
<td>77-79.2</td>
</tr>
<tr>
<td>Dose to 95% of PTV_{5400}: D95%(Gy)</td>
<td>&gt;54</td>
<td>48.6-54</td>
</tr>
<tr>
<td>Dose to 95% of PTV_{5000}: D95%(Gy)</td>
<td>&gt;50</td>
<td>45-50</td>
</tr>
<tr>
<td>Total RT dose to spinal cord PRV (0.03 cc) [for composite plan of PTV_{6000} if there is no boost and PTV_{6600} if there is a boost]: D0.03cc(Gy)</td>
<td>&lt; 45</td>
<td>45-48</td>
</tr>
<tr>
<td>Total RT dose to spinal cord PRV (0.01 cc) [for composite plan of PTV_{6000} if there is no boost and PTV_{6600} if there is a boost]: D0.01cc(Gy)</td>
<td>&lt; 48</td>
<td>48-50</td>
</tr>
</tbody>
</table>
### Total RT dose to brainstem PRV (0.03 cc) [for composite plan of PTV_6000 if there is no boost and PTV_6600 if there is a boost]: D0.01cc(Gy)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 48 if skull base is not included in PTV50 (3DCRT) or PTV54 (IMRT)</td>
<td>48-52 if skull base is not included in PTV50 (3DCRT) or PTV54 (IMRT)</td>
</tr>
<tr>
<td>&lt; 52 if skull base is included in PTV50 (3DCRT) or PTV54 (IMRT)</td>
<td>52-55 if skull base is included in PTV50 (3DCRT) or PTV54 (IMRT)</td>
</tr>
<tr>
<td>&gt; 52 if skull base is included in PTV50 (3DCRT) or PTV54 (IMRT)</td>
<td>&gt; 55 if skull base is included in PTV50 (3DCRT) or PTV54 (IMRT)</td>
</tr>
</tbody>
</table>

### Overall treatment time

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Gy only (PTV_6000)</td>
<td>45 days</td>
</tr>
<tr>
<td>66 Gy (PTV_6600 included)</td>
<td>50 days</td>
</tr>
</tbody>
</table>

### Non-Medically Indicated Treatment Interruptions

<table>
<thead>
<tr>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 days</td>
</tr>
<tr>
<td>2-4 days</td>
</tr>
<tr>
<td>&gt; 4 days</td>
</tr>
</tbody>
</table>

**Note:** Minimum dose is evaluated to 99% of the volume.

**6.7.3 Treatment Breaks**

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Ideally, treatment breaks, if necessary, should not exceed 5 treatment days at a time and 10 treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding 2 treatment days for reasons other than toxicity/illness will be considered a protocol deviation (see table above).

**6.8 R.T. Quality Assurance Reviews (4/22/14)**

The Radiation Oncology Co-Chair, John Kim MD, will perform RT Quality Assurance Reviews. These reviews will be ongoing and performed remotely. RT Quality Assurance Reviews will be facilitated by IROC Philadelphia RT.

**6.9 Radiation Therapy Adverse Events**

Grade 3 and 4 (CTCAE, v. 4) mucositis is anticipated in approximately 66% of patients undergoing chemoradiation. Placement of a nasogastric or gastrostomy tube to facilitate nutrition may be necessary during or upon completion of therapy. Nutritional evaluation prior to beginning chemoradiation is highly recommended (see Section 4.2). Expected acute and late adverse events with chemoradiation include: fatigue, weight loss, alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, skin erythema and desquamation within the treatment fields.

**6.10 Radiation Therapy Adverse Event Reporting (3/25/14)**

See CTEP-AERS Expedited Reporting Requirements in Section 7.6.
7.0 DRUG THERAPY (4/22/14)
Protocol treatment must begin within 2 weeks after registration. Only patients randomized to Arm 1 will receive cisplatin.

7.1 Arm 1 Treatment (9/19/12)
7.1.1 Cisplatin
Cisplatin, 40 mg/m², will be given intravenously over 60 minutes on days 1, 8, 15, 22, 29, 36 and 43 of radiation therapy; 7 doses for a total of 280 mg/m². (Radiation therapy will begin on a Monday, Tuesday or Wednesday.) Cisplatin can be given prior or after the patient’s radiation at the treating physician’s discretion. Cisplatin administration outside of these specified time points during radiation is only allowed 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 concurrent with radiation therapy, except for the last dose, which can be given up to 1 week after radiation has been completed. No cisplatin will be given before initiation of radiation therapy. Doses of cisplatin that are not given or which are held will not be made up. In the event that radiation therapy is held, no cisplatin will be administered.

Adequate hydration is strongly encouraged, at least 1 liter of normal saline is recommended prior to the administration of the cisplatin dose.

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

Note: Carboplatin cannot be substituted for cisplatin, and G-CSF or pegfilgrastim are not permitted (see Section 9.2.1).

7.2 Cisplatin (10/3/13)
Refer to the package insert for detailed pharmacologic and safety information.
7.2.1 Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.
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, infused over 1 hour along 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.
7.2.5 Adverse Events: Human toxicity includes nausea, vomiting, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected.
Supply: Cisplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.3 Dose Modifications for Cisplatin (9/19/12)

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

If ANC remains < 1000/mm³ for more than 7 days, all subsequent cisplatin doses will be reduced to 30 mg/m², and the next weekly dose only given when the ANC is > 1000/mm³. In the event of neutropenic fever, reduce all subsequent doses of cisplatin to 30 mg/m² and administer only when the ANC is ≥ 1000/mm³.

If, on the day of scheduled treatment, the patient again experiences an ANC < 1000/mm³ despite the first cisplatin dose reduction, the cisplatin dose for that week will again not be given.

If recovery has not occurred by the following week, or if neutropenic fever develops, there will be a second dose reduction to 20 mg/m² for all remaining cisplatin doses, which can be given only after recovery of the ANC to ≥1000/mm³.

Any subsequent ANC < 1000/mm³ on the day of scheduled treatment or any recurrent neutropenic fever after 2 dose reductions will mandate discontinuation of all remaining doses of cisplatin chemotherapy.

7.3.2 Thrombocytopenia: If on the day of cisplatin chemotherapy the platelet count is < 75,000, the dose will be held for the week. Cisplatin will be given full dose the following week if the platelets recover to ≥ 75,000/mm³.

If the platelets remain < 75,000/mm³ for more than 7 days, then all subsequent cisplatin doses will be reduced to 30 mg/m², and the next weekly dose only given when the platelet count ≥ 75,000/mm³.

If the platelet count is again < 75,000/mm³ on the day of scheduled treatment despite the first dose reduction, that dose of cisplatin will be held.

If recovery has not occurred by the following week, there will be a second dose reduction to 20 mg/m² for all remaining cisplatin doses, which can be given only after recovery of platelet count to ≥ 75,000/mm³.

Any subsequent platelet count < 75,000/mm³ on the day of scheduled treatment, after 2 dose reduction will mandate discontinuation of all remaining cisplatin doses.

7.3.3 Neurotoxicity: If grade 2 neurotoxicity develops, hold cisplatin until toxicity improves to ≤ grade 1, then reduce all subsequent doses of cisplatin to 30mg/m². If the patient experiences grade 3 or greater neurotoxicity or if grade 2 neurotoxicity recurs, all remaining doses of cisplatin will be discontinued.

7.3.4 Renal: Cisplatin will only be administered if serum creatinine is < than 2 mg/dl. If a patient develops a rise in serum creatinine ≥ 2gm/dL on the day of treatment, cisplatin will be discontinued for that week and held until recovery to < 2 mg/dL. All subsequent cisplatin doses will then be reduced to 30 mg/m². If, despite this first dose reduction, the serum creatinine is again ≥ 2 mg/dl on the day of treatment, that week’s cisplatin
dose will not be given, treatment will be held until renal recovery, and all subsequent cisplatin doses reduced to 20 mg/m². If the creatinine is again ≥ 2 mg/dl on the day of treatment despite 2 dose reductions, or if the serum creatinine does not improve to < 2 mg/dL in 14 days, all remaining cisplatin doses will be discontinued.

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

7.3.6 Mucositis: Significant mucositis from both the radiation and the cisplatin is expected and will not be an indication for cisplatin dose modification. Appropriate supportive care will be provided.

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

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

7.4 Modality Review (11/5/15)
The Co-Principal Investigators, Cristina Rodriguez, MD, and David Adelstein, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 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.

7.5 Adverse Events (3/25/14)
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 web site at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

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

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 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.

7.5.1 Adverse Events (AEs) (10/3/13)
Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.5.2 Serious Adverse Events (SAEs) (4/22/14) — Serious adverse events (SAEs) 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.

**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 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) (10/3/13)**

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

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

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

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

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

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

**7.6 CTEP-AERS Expedited Reporting Requirements (3/25/14)**

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

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.
CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

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

- CTEP-AERS-24 Hour Notification requires that a 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 a 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 a CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the dedicated SAE FAX, 215-717-0990.

- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

### Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies 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 agent(s)/intervention (21 CFR 312.64)

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

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

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

<table>
<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>
</table>

---

37 RTOG 1008, Version Date: 11/5/15
<table>
<thead>
<tr>
<th>Resulting in Hospitalization ≥ 24 hrs</th>
<th>10 Calendar Days</th>
<th>24-Hour 5 Calendar Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td>10 Calendar Days</td>
</tr>
</tbody>
</table>

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

**Expedited AE reporting timelines are defined as:**

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

1 Serious adverse events that occur more than 30 days after the last administration of the 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.

**NOTE:** Deaths clearly due to progressive disease should NOT be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

---

**Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND:**
Not applicable to this study.

8.0 **SURGERY**

(11/3/10) Postoperative radiation therapy should start no earlier than 4 weeks after surgery to allow for adequate wound healing; however, treatment must begin within 10 weeks of surgery. Major wound complications such as infection, dehiscence, exposure of bone, or major vessels may delay the beginning of radiation.

8.1 **Primary Tumor Resection (2/27/12)**

The goal of surgery should be complete tumor resection with tumor free surgical margins. The extent of surgery will depend on the location and size of the primary tumor. Tumors located in the superficial lobe of the parotid gland will require a superficial parotidectomy. Tumors that also extend to, or originate from the deep lobe will require a total parotidectomy. The facial nerve will be carefully dissected and preserved unless it is grossly invaded by the tumor or in the presence of preoperative facial nerve paresis or paralysis. In such cases the facial nerve will be sacrificed. Extension outside the parotid gland may require mastoidectomy, temporal bone resection, mandibulectomy, or resection of the contents of the infratemporal fossa.

Tumors located in the submandibular gland will require en bloc resection of the submandibular gland and any involved structures in the submandibular triangle including hypoglossal or lingual nerves; digastric or mylohyoid muscles, floor of mouth, or mandible. Frozen section diagnosis, whenever feasible, should be obtained to help achieve tumor free surgical margins.
Surgical resection of cancer of the minor salivary glands depends on their site of origin and the extent of disease. These cancers will require a radical excision which might include a marginal or segmental mandibulectomy, partial or total resection of the hard or soft palate, partial or total maxillectomy, infratemporal fossa dissection, and/or anterior craniofacial resection. The branches of the second (V2) and third (V3) divisions of the trigeminal nerve are at high risk for perineural spread of minor salivary gland malignancy and may provide an avenue for early skull base invasion. Resection of the cranial base may be required in some cases to eradicate the tumor and obtain negative margins.

8.2 Neck Dissection
Patients with clinical or radiographic evidence of lymph node metastasis (N+) will require a therapeutic comprehensive neck dissection. A selective neck dissection in conjunction with the primary tumor resection should be carried out in patients with no clinical evidence of lymph node metastasis (N0).

8.3 Surgical Quality Assurance Reviews (11/5/15)
The Surgical Oncology Co-Chair, Ehab Hanna, MD, will perform a modified Quality Assurance Review to specifically examine the issue related to eligibility and the presence of high risk features.

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 antiemetics and supportive therapy for nausea and vomiting are permitted and highly recommended in patients participating in this study. These interventions should be made according to institutional guidelines.

9.1.2 Nutritional Supplementation
Close monitoring of patients’ volume status and body weight is strongly recommended. Nutritional supplementation through a nasogastric or gastrostomy feeding tube should be considered in patients who are unable to maintain hydration or experience more than 10% loss of body weight due to mucositis.

9.2 Non-permitted Supportive Therapy
9.2.1 Hematopoietic Growth Factors
Hematopoietic growth factors are not permitted during radiation therapy. Growth factors are only permitted if administered after radiation therapy has been completed. Erythropoiesis stimulating agents are not permitted.

10.0 TISSUE/SPECIMEN SUBMISSION (11/5/15)
NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission.

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 10.3 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 Bank 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 Bank-San Francisco 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. The NRG Oncology Biospecimen Bank-San Francisco also collects tissue for Central Review of pathology.

In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank-San Francisco for the purpose of central review of pathology (mandatory) and for specimen banking (highly recommended). Specimen banking for future correlative studies will permit study of the biology of this cancer and will help in the design of future trials. Duplicate cores from the tissue submitted for central review will be derived and used to generate a tissue micro array (TMA) [Liu 2002]. The TMA will be used to generate tissue sections for future translational studies.

Since the clinical data will not be available for correlative analysis for many years, it is premature to propose a firm plan for biomarker studies. Assay technology, particularly for high throughput tests, is evolving rapidly. Based on currently available data, the lead candidates include the following:

- Expression of the Her members, including EGFR (expression and amplification), Her-2 (expression and amplification), Her-3 and Her-4 (expression);
- Dimerization between EGFR and one of the other Her members (by in-situ proximity ligation assay);
- Lysyl oxidase expression by AQUA staining – a marker for tumor hypoxia, which has also been shown to predict for distant metastasis;
- E-cadherin expression by AQUA staining – a marker for epithelial-to-mesenchymal transition, which is a feature associated with a higher risk of recurrence;
- ERCC1 expression by AQUA staining – a predictor of cisplatin resistance;
- Expression of different DNA repair protein (expression by AQUA staining) & SNIP (by SNIP array) – as possible predictor for locoregional failure.

10.2 Tissue Collection for Central Review – Mandatory (11/5/15)

Tissue will be taken from the surgical specimen and must be submitted for central review within 2 weeks of study entry. The following material must be provided to the NRG Oncology Biospecimen Bank-San Francisco for retrospective central review:

10.2.1 Representative H & E stained slides from the area with the highest grade within the tumor (slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide). This H&E slide must be sent with all submissions and must be the same as the block or punch being submitted in Section 10.2.2.

10.2.2 One paraffin block of tumor (preferred); Note: If sites are unable to provide the block, then two 2 mm cores of the block taken with a punch tool and embedded in paraffin is acceptable. A corresponding H&E of the punch block must also be submitted. A specimen plug kit can be requested from the NRG Oncology Biospecimen Bank-San Francisco (see Appendix V for instructions). If the site is unable to embed the punches, the site should send the punches to the Biospecimen Bank to embed and mark on the H&E (see Section 10.2.1) from the original block where the punches were taken.

10.2.3 A Pathology Report documenting that the submitted block or cores contain 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 date of procedure information must NOT be removed from the 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.

10.2.4 A copy of the gross description of the tumor must accompany the specimen.

10.2.5 A Specimen Transmittal (ST) Form stating that the tissue is being submitted for Central Review. The Form must include the NRG Oncology protocol number and the patient’s case number.

10.2.6 Central Review will be performed for every case by the Pathology Co-Chair, Adel El-Naggar, MD.
10.3 Specimen Collection for Banking – Highly Recommended (11/5/15)

For patients who have consented to participate in the tissue component of the study (See Appendix I)

See Appendices V-VII for detailed collection instructions, including information pertaining to collection kits. Note: Kits include a pre-paid shipping label for shipment of frozen biospecimens.

10.3.1 Tumor Tissue
Tissue for banking will be taken from the submitted tumor tissue block or punches submitted for central review (see Section 10.2.2).

10.3.2 Serum, Plasma, and Whole Blood Collection
Serum, plasma, and whole blood will be collected pre-treatment. Serum and plasma also will be collected at week 4 of radiation treatment (during a weekly clinic visit), and 3 months post-completion of radiation. If a site misses the pretreatment blood collection, then whole blood can be collected at any time the patient is being treated or at follow up. See Appendix VI for blood collection kit and detailed collection instructions.

Frozen Plasma Samples for Biomarker Analysis
- a. Collect one 10 ml tube of blood using one EDTA (purple top) tube.
- b. Invert six to seven times to ensure adequate mixing with anticoagulant.
- c. Centrifuge within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4°C (preferred) for 10 minutes.
- d. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
- e. Carefully pipette and transfer ~1ml aliquots of plasma into 4-5 cryovials taking care to avoid collecting any blood cells (red/white blood cells).
- f. Place tops on cryovials and make sure tops of cryovials are on securely.
- g. Tube should be clearly labeled (see Section 10.5).
- h. Wrap cryovials in paper towel, and place into a biohazard bag.
- i. Store plasma cryovials at -80°C until packed and shipped.

Frozen Whole Blood Sample for DNA
- a. Collect 1 10 ml tube of blood using one EDTA (purple top) tube.
- b. Invert tube to mix, then aliquot ~1.0 ml whole blood into 3-5 cryovials.
- c. Tubes should be clearly labeled (see Section 10.5).
- d. Wrap cryovials in paper towel, and place into a biohazard bag.
- e. Store whole blood cryovials at -80°C until packed and shipped (shipped on dry ice).

Frozen Serum Samples for Biomarker Analysis
- a. Collect one 10 ml tube of blood without coagulants (Red top).
- b. Sit at room temperature for 30 min to allow clot formation.
c. Centrifuge in a standard clinical centrifuge at ~2500 RPM at 4° Celsius (preferred) for 10 minutes.
d. Transfer ~1ml aliquots of separated serum into 4-5 cryovials.
e. Place tops on cryovials and make sure tops of cryovials are on securely.
f. Tubes should be clearly labeled (see Section 10.5).
g. Wrap cryovials in paper towel, and place in a biohazard bag.
h. Store serum cryovials at -80°C until packed and shipped.

10.4 Documentation for Submission of Serum, Plasma, and Lymphocytes (11/5/15)
The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection, time point of collection of the serum, plasma, and whole blood; the NRG Oncology protocol number; the patient’s case number; and method of storage (e.g., stored at -80° C), must be included.

10.5 Storage of Blood Specimens (5/4/11)
Store at frozen specimens -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).

10.6 Specimen Collection Summary (11/5/15)

<table>
<thead>
<tr>
<th>Specimens for Tissue Banking/Central Review/Translational Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimens taken from patient:</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Representative H&amp;E stained slides of the primary tumor and H&amp;E of punch block if punch is being submitted instead of tumor tissue block</td>
</tr>
<tr>
<td>A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment OR two 2 mm diameter core of tissue, punched from the tissue block with a punch tool and embedded in paraffin.</td>
</tr>
<tr>
<td>SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge.</td>
</tr>
<tr>
<td>PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge</td>
</tr>
<tr>
<td>DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix</td>
</tr>
</tbody>
</table>
10.7 **Shipment of Biospecimens (11/5/15)**
Submit materials for Central Review and Banking as follows:

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

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

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

10.8 **Reimbursement (11/24/14)**
NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the National Clinical Trials Network (NCTN) Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system.

10.9 **Confidentiality/Storage (11/5/15)**

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 Bank 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, using their shipment account.

11.0 **PATIENT ASSESSMENTS (11/5/15)**

11.1 **Study Parameters**
See Appendix I for a summary of assessments and timeframes. **Note:** Clarifications of or exceptions to the study parameters are indicated in Appendix I with an asterisk (*) and are discussed below:

11.1.1 Radiologic confirmation of the absence of hematogenous metastasis is required within 12 weeks prior to registration; at a minimum, contrast CT imaging of the chest is required. A chest PET/CT is acceptable.

11.1.2 To monitor for metastatic disease: A chest x-ray or CT scan of the chest will be done at 6 and 24 months from the start of radiation therapy, then annually, and a CT scan of the chest will be done at 12 months from the start of radiation therapy. A whole body PET/CT is acceptable.
11.1.3 For tumor evaluation: A CT scan of the neck or an MRI will be done at 3 months post completion of radiation, at 9, 12, and 24 months from the start of radiation therapy, then at the discretion of the treating physician. A whole body PET/CT is acceptable.

11.1.4 All patients must be evaluated by a Medical Oncologist once, within 4 weeks prior to registration.

11.2 Outcome Definitions

11.2.1 No evidence of disease: Absence of clinical or radiographic measurable tumor;

11.2.2 Local recurrence: Recurrent malignancy (preferably histologically proven) in the tumor bed that is not attributable to a second primary tumor;

11.2.3 Regional recurrence: Recurrent malignancy (preferably histologically proven) in regional cervical lymph nodes that is not attributable to a second primary tumor;

11.3.4. Distant recurrence: Recurrent malignancy (preferably histologically proven) in distant organs (such as the lung, bone, or brain) that is not attributable to a second primary tumor.

11.3 Criteria for Discontinuation of Protocol Treatment
Discontinuation of protocol treatment will be required in the following situations:
1. Withdrawal of patient consent;
2. Documented disease progression;
3. Severe debilitating toxicity or unacceptable adverse events;
4. Radiation therapy delay of more than 2 weeks.

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

11.4 Quality of Life (QOL) and Patient-Reported Outcomes (PRO)
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.

QOL and PROs will be assessed at baseline, upon completion of radiation therapy, at 3 months after completion of radiation therapy, and at 12 and 24 months from the start of radiation therapy.

11.4.1 QOL and PRO Instruments (5/4/11)
The Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N) is a multidimensional, patient-self report QOL instrument specifically designed and validated for use with head and neck patients. The patient can complete the assessment in 5-10 minutes. The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. Note: The FACT-H&N has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at http://www.facit.org.

The Performance Status Scale for Head and Neck Cancer (PSS-HN) consists of assessment of 3 functional areas (subscases): Normalcy of Diet, Eating in Public, and Understandability of Speech. The site research nurse or clinical research associate (CRA) will administer the PSS-HN. Interviewers are encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. The interviewer rates the patient on each scale based on the patient’s responses to targeted questions. The PSS-HN takes approximately 5 minutes to complete. The PSS-HN has been translated into 12 languages and is available to institutions at no charge by contacting Marcy A. List, PhD, at mlist@medicine.bsd.uchicago.edu.
PROMIS-fatigue, A Novel Short Form Fatigue Scale is a 7-item questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. This questionnaire can be completed by patients in less than 5 minutes. The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break.

Note: The PROMIS-fatigue is available in validated English and Spanish language formats, and is currently being translated into German and Dutch; is accessible through the PROMIS Assessment Center web site: http://www.assessmentcenter.net/ac1/.

The University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) consists of 15 items covering 4 major domains of oral health-related quality of life: physical functioning, personal/psychological functioning, social functioning, and pain/discomfort issues. The patient can respond to the 15 items in the scale in approximately 5 minutes. The Scale is only available in English.

The EuroQol (EQ-5D) is a two-part questionnaire that the patient can complete in approximately 5 minutes. The EQ-5D has been translated into multiple languages; these translations are available from the EuroQol web site at http://www.euroqol.org/.

The site research nurse or CRA should encourage the patient not to skip questions on the EQ-5D or take breaks during the completion of this questionnaire, as this will invalidate the assessment. If this occurs, sites will document it on the appropriate case report form (see Section 12.1).

12.0 DATA COLLECTION

Data should be submitted to:

NRG Oncology*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

*If a data form is available for web entry, it must be submitted electronically.

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (11/3/10)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Operative Report (S2)</td>
<td></td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy-H &amp;N [FACT] (FA)</td>
<td></td>
</tr>
<tr>
<td>Performance Status Scale for H &amp; N Cancer [PSSHN] (QP)</td>
<td></td>
</tr>
<tr>
<td>EuroQol [EQ-5D] (HP)</td>
<td></td>
</tr>
<tr>
<td>University of Michigan Xerostomia-Related Quality of Life Scale [XeQOLS] (L4)</td>
<td></td>
</tr>
<tr>
<td>PROMIS-Fatigue (QL)</td>
<td></td>
</tr>
<tr>
<td>Treatment Form (TF)</td>
<td>Upon completion or discontinuation of treatment</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>At 3 mos. post-completion of RT, at 6, 9, 12, 18, and 24 mos. from start of RT, q6 months for years 3-4, then annually; also at death</td>
</tr>
<tr>
<td>FACT (FA)</td>
<td>Upon completion or discontinuation of RT, at 3 months post-completion of RT, and at 12 and 24 months from the start of RT</td>
</tr>
<tr>
<td>PSS-HN (QP)</td>
<td></td>
</tr>
<tr>
<td>EQ-5D (HP)</td>
<td></td>
</tr>
<tr>
<td>XeQOLS (L4)</td>
<td></td>
</tr>
<tr>
<td>PROMIS-Fatigue (QL)</td>
<td></td>
</tr>
</tbody>
</table>

### 12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.4) (11/24/14)

<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><strong>Digital data submission includes the following for 3D-CRT:</strong></td>
<td></td>
</tr>
<tr>
<td>- DICOM CT Image</td>
<td></td>
</tr>
<tr>
<td>- DICOM Structure</td>
<td></td>
</tr>
<tr>
<td>- DICOM Dose (50 Gy)</td>
<td></td>
</tr>
<tr>
<td>- DICOM RT Plan (50 Gy)</td>
<td></td>
</tr>
<tr>
<td>- DICOM Dose (10 Gy)</td>
<td></td>
</tr>
<tr>
<td>- DICOM RT Plan (10 Gy)</td>
<td></td>
</tr>
<tr>
<td>- DICOM Dose (composite 60 Gy)</td>
<td></td>
</tr>
<tr>
<td>- DICOM Dose (6 Gy) – Required when applicable</td>
<td></td>
</tr>
<tr>
<td>- DICOM Plan (6 Gy) – Required when applicable</td>
<td></td>
</tr>
<tr>
<td>- DICOM Dose (composite 66 Gy) – Required when applicable</td>
<td></td>
</tr>
<tr>
<td><strong>Digital data submission includes the following for IMRT:</strong></td>
<td></td>
</tr>
<tr>
<td>- DICOM CT Image</td>
<td></td>
</tr>
<tr>
<td>- DICOM Structure</td>
<td></td>
</tr>
<tr>
<td>- DICOM Dose (60 Gy including 54 Gy)</td>
<td></td>
</tr>
<tr>
<td>- DICOM Plan (60 Gy including 54 Gy)</td>
<td></td>
</tr>
<tr>
<td>- DICOM Dose (6 Gy) - Required when applicable</td>
<td></td>
</tr>
<tr>
<td>- DICOM Plan (6 Gy) – Required when applicable</td>
<td></td>
</tr>
<tr>
<td>- DICOM Dose (composite 66 Gy) – Required when applicable</td>
<td></td>
</tr>
<tr>
<td>- All required structures <strong>MUST</strong> be labeled per the table in Section 6.5.</td>
<td></td>
</tr>
<tr>
<td>- All digital RT data must be in DICOM format.</td>
<td></td>
</tr>
<tr>
<td>- The “RTOG 1008 Datasheet” is available in the Forms section of the RTOG web site, <a href="http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1008">http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1008</a>. Submit via TRIAD with the digital data listed above.</td>
<td></td>
</tr>
<tr>
<td><strong>Upon submission of the digital data via TRIAD, complete a Digital Data Submission Information form (DDSI) located:</strong></td>
<td></td>
</tr>
</tbody>
</table>
13.0 STATISTICAL CONSIDERATIONS (11/5/15)
13.1 Primary Endpoints
13.1.1 Phase II: The primary endpoint is progression-free survival (PFS), defined by the events of local-regional progression or recurrence, distant metastasis, or death from any cause. Primary interest will focus on 2-year PFS because the recurrence/failure rate is highest during this time interval (Schroeder 2008), so as to expedite the design of subsequent clinical trials in this disease.
13.1.2 Phase III: The primary endpoint of interest is overall Survival (OS), defined by the event of death from any cause. Because of the extended period of time required for accrual to this trial, and the natural history of this disease, primary interest will be focus on the difference in 5-year overall survival.
13.2 Phase II/III Secondary Endpoints
13.2.1 PFS rate at 2 and 5 years in both the cohort of patients with pathologically high-risk disease (high-grade adenocarcinoma, high-grade mucoepidermoid carcinoma, salivary duct carcinoma), and the patient cohort with pathologically intermediate risk disease (all other eligible diagnoses);
13.2.2 Treatment related toxicity, defined as any grade 3-4 adverse events (CTCAE, v. 4) deemed to be definitely, probably, or possibly related to protocol treatment;
13.2.3 Treatment related mortality defined as any death during or within 30 days of discontinuation of protocol treatment;
13.2.4 Chemotherapy delivery as measured by percentage of protocol prescription given;
13.2.5 Radiation delivery as measured by elapsed treatment days;
13.2.6 Determine whether quality of life, fatigue, and xerostomia as measured by the FACT-H&N subscale, PSS-HN, PROMIS-fatigue short form, the XeQOLS, and the EQ-5D respectively, differ as a function of treatment assignment (i.e. RT + chemo is worse compared to RT alone) at completion of RT, at 3 months from the end of RT, and at 12 and 24 months from the start of RT.
13.3 Randomization and Stratification
Patients will be randomized to 1 of 2 treatment arms. Additionally, patients will be stratified according to histology (intermediate-grade adenocarcinoma or intermediate-grade mucoepidermoid carcinoma vs. high-grade adenocarcinoma, high-grade mucoepidermoid carcinoma or salivary duct carcinoma vs. high-grade acinic cell carcinoma or high-grade (>30% solid component) adenoid cystic carcinoma) and nodal status (N0 vs. N1-3) prior to randomization.
13.4 Sample Size
Based on the limited published data in chemoradiation for squamous cell carcinomas of the head and neck, and the experience of the study chairs in treating with both regimens, it is hypothesized that the concurrent chemoradiation regimen will improve progression-free and overall survival in this group of high-risk patients. The rarity of the tumor, the limited number of patients in the targeted study population, and the retrospective nature of historical data available for the standard treatment arm (radiation alone), have led to the utilization of a randomized phase II screening trial design (Rubinstein 2005). For the radiation alone regimen, we assume that for the target population (resected T1-2 N0 M0 malignant salivary gland tumor with positive margins), the PFS rate will be similar to that reported by Schroeder, et al. (2008) for the T-3 and T-4a patients, or an estimated 2-year PFS rate of 65%. If the experimental (chemoradiation) regimen results in
at least a 12% higher 2-year PFS rate at 2 years, then this regimen will be considered for further testing. Thus, we specify the following parameters for design of this trial:

- Two-year PFS of 65% in the radiation only arm, or an annual failure rate of 0.215;
- Statistical power of \( \geq 0.80 \) to detect a 12% absolute improvement in PFS at 2 years, which corresponds to an approximate 40% relative reduction in failure rate with the addition of chemotherapy to radiation;
- One-sided alpha of 0.20.

With 54 patients on each treatment arm, power will equal 0.80 for detecting a 12% absolute gain in PFS at 2 years. To account for up to 10% attrition rate for withdrawn consents, ineligible patients, or loss to follow up, **60 patients must be accrued to each treatment arm**. The analysis comparing PFS between treatment groups will be conducted after 48 failure events have been observed.

There is some uncertainty in the PFS rate based on the single institution Schroeder series. The proposed sample size is reasonably robust to deviations from this baseline rate with adequate power for a radiation arm PFS rate as low as 60% and higher power than stated above for a radiation arm PFS rate greater than 65% (assuming the same absolute differences indicated). With respect to the effect size, under the above sample size and control group rate, power exceeds 70% for relative reductions in the annual failure rate of 33% or greater. If the effect size is greater than a 12% absolute gain, then the study will provide more robust evidence for pursuing a chemoradiation regimen in a subsequent phase III trial.

Prior to completion of the accrual goal described above, it was determined that this trial offers an opportunity to evaluate the worth of chemotherapy in both intermediate-risk and high-risk patients. It also was determined that given the low frequency of this disease, a trial that directly informs evaluation of a definitive endpoint (overall survival) would be the most efficient approach. After that determination, a protocol-specified futility analysis was conducted and presented to the NRG Oncology Data Monitoring Committee. It was determined that the trial surpassed criteria for continuation (no futility stopping) and that furthermore, the protocol-specified criterion for evaluating the regimen in a phase III trial would likely be met.

To meet the goals of a) evaluating PFS benefit in both intermediate- and high-risk patients and b) evaluating overall survival (the phase III endpoint), the patient cohort to be enrolled will be expanded, and a phase II/III design will be conducted. The expanded sample size will permit phase II testing for PFS improvement in intermediate-risk patients and support the phase III evaluation in all patients.

As in the original design, for statistical power of \( \geq 0.80 \) to detect a 40% relative reduction in failure rate with the addition of chemotherapy to radiation, and one-sided alpha of 0.20, 48 events are required. During accrual to the phase III trial, futility evaluation for PFS will be conducted for intermediate-risk patients (see Section 13.6.3 below). The expected PFS annual failure rate for the intermediate-risk group is 0.197 and is 0.236 for both risk groups combined, based on estimates from the control arm of this study.

The primary endpoint for the phase III trial is OS, defined as time from randomization to death from any cause. The expected OS annual failure rate is 0.16, based on assumed 5-year survival of 45%. The phase III trial aims to detect a 33% reduction in mortality hazard with 80% power at one-sided alpha = 0.05, i.e. an improvement of 14% in 5-year overall survival. Analysis will occur after 156 deaths have been observed.

To date, the trial has accrued 115 eligible patients with approximately 50% representation of each risk class. To meet the above described requirements for events, an additional 125 eligible patients will be accrued for a total of 240 patients. To account for consent withdrawals, ineligible patients, and other losses, **up to 252 patients will be accrued**.
13.5 **Patient Accrual**
Accrual reached 3 patients per month in the most recent 12 months, and it is anticipated that this rate can be maintained. We conservatively assume the same 2.5 patients/month accrual to account for the closure time and ramp-up upon resumption of accrual. Accrual to the phase III portion is assumed to be at the same rate.

13.6 **Analysis Plans**
The principal comparison will be between the 2 protocol arms, since there is no prospective cooperative group experience using post-operative adjuvant radiation therapy alone in patients with resected high-risk malignant salivary gland tumors. The PFS and OS rates for each regimen will be directly compared.

13.6.1 **Statistical Methods**

*Primary Efficacy Endpoints*
Results will be analyzed using all eligible patients with follow up based on the treatment arm to which they were randomized, regardless of whether they started the assigned treatment.

For the phase II trial, analyses will be conducted using all eligible patients with follow up based on the treatment arm to which they were randomized, regardless of whether they started the assigned treatment. PFS will be compared between treatment arms, using the log-rank test. PFS curves will be estimated using the Kaplan-Meier method (1958) for graphical presentation. All failure times will be measured from the date of study registration to the date of failure, or last follow up. Analyses will be conducted separately within intermediate-risk and high-risk patients.

For the phase III trial, OS will be compared between treatment arms, using a log-rank test. OS curves will be estimated using the Kaplan-Meier method (1958). All failure times will be measured from the date of study registration to the date of death or last follow up. The hazard ratio with 95% confidence interval will be estimated using the Cox proportional hazards model. If there is strong evidence of nonproportionality of the failure hazards, then alternative models and summaries may be used.

All patients (intermediate-risk and high-risk) will be included in the primary phase III evaluation. If the primary treatment effect evaluation indicates a benefit for the experimental group, then treatment effect testing within each risk group will be carried out.

*Adverse Event Endpoints*
For the endpoints related to adverse events (AEs), AEs assessed to be definitely, probably, or possibly related (if relationship is missing, it will be assumed to be definitely, probably, or possibly) to protocol treatment will be considered. The rates of any ≥ grade 3 toxicity 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 groups.

*Quality of Life (QOL) and Patient-Reported Outcome (PRO) Endpoints*
For these investigations, the primary analysis will focus on treatment group differences at 3 months post-radiation and patterns of scores over time points (radiation therapy completion, 3 months, 12 months, and 24 months) for the QOL and PRO instruments. Following descriptive statistics on assessments, tests of the exploratory study hypotheses will involve the use of repeated measures analysis of covariance (ANCOVA) on scores for the assessment measures, in which time points are considered the within-patient factor and treatment (group) is considered the
between-patient factor (Diggle 1994). While scales for the individual instrument questions are quantitative, they represent ordinal values on a bounded range rather than continuous quantities. Nonetheless, in aggregate, these approximate continuous distributions and appropriate transforms will be applied to improve consistency with model assumptions. The hierarchical analytic approach described below permits tests of omnibus hypotheses that control for multiple comparisons among time points and treatment groups. The analysis will be conducted as follows:

1. The ANCOVA model will be used to carry out an omnibus test of the hypothesis that there is a common mean score across time points within the treatment groups: \( H_0: \mu_{it} = \mu_i \), where \( i = \) treatment group 1 or 2, \( t = \) time point (baseline, post-RT, 3, 12, and 24 months) and \( \mu_{it} \) is the mean score in treatment group \( i \) at time \( t \).

2. If the hypothesis in (1) is rejected, then individual comparisons of the post-RT and subsequent scores will be conducted within treatment groups. Additional modeling and graphical methods to determine trends or patterns of change in scores over time points will be conducted.

3. The ANCOVA model will be used to carry out an omnibus test of the hypothesis that there is a common mean score at each time point among the treatments: \( H_0: \mu_{it} = \mu_{t} \), where again \( \mu_{it} \) is the mean score in treatment group \( i \) at time \( t \).

4. Assuming the result of the hypothesis test in (3) is significant (\( H_0 \) rejected), individual tests will be carried out to determine differences between treatment groups at specific time points. If there are no significant treatment differences identified in (3), then an overall test of trend in scores can be aggregated over treatment groups. Additional modeling to characterize patterns of change over time will be conducted.

Although treatments are randomly assigned, there may be potentially confounding factors, and these may be incorporated into the above hypothesis tests via the ANCOVA model. The effects of these covariates on QOL/PRO scores also may be evaluated separately in exploratory analyses. Also note that baseline scores will be analyzed in relation to subsequent impairment or decline for both treatment groups [hypothesis (1) above]. The use of change scores (relative to baseline) for the main analysis also may be explored to account for the influence of per patient conditions prior to undergoing treatment.

Based on prior trials in head and neck cancer, about 87-90% of eligible patients are expected to participate in the QOL/PRO component at baseline; thus, we expect approximately 216 patients to complete the baseline evaluations. Assuming 10% attrition by 3 months post enrollment, we expect 194 patients (97 per arm) to still be available through the 3-month assessment period. For enrollment of 180 patients (90/arm), a between-groups comparison of a given instrument score at that time point would have over 90% power at \( \alpha = .05 \) to detect a one-half standard deviation difference. At 12 months, the QOL/PRO completion rate may be as low as 50% (although it is anticipated to be greater than that based on the more favorable prognosis of these patients compared to other head and neck cancer sites), in which case, the power would remain over 85% for a two-thirds (.67) standard deviation difference in means.

As described above, a certain degree of attrition from the study, due to both patient withdrawal and mortality, is expected. Efforts will be made to minimize attrition due to avoidable factors, such as investigator oversight. Characteristics of patients with missing data will be evaluated to identify imbalance in factors such as treatment, baseline scores, and other clinical and demographic features. In the absence of apparent systematic missing data patterns, data will be analyzed assuming that the
observations are missing at random, employing appropriate methodology for this purpose (Little 1992). In the case of evidence for systematic patterns of missing data (‘informative’ missingness), alternative strategies for analyzing such data, depending on the pattern (e.g. intermittent versus complete dropout pattern) will be investigated (Wu 1988, Little 1992). Furthermore, methodology developed in the area of combined longitudinal measurements and event-time data may be applied (Hogan 1997, Henderson 2000).

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

The study team will evaluate feasibility via the accrual rate in months 7-18 compared to the projected rate of 2.5 patients per month. If the rate is 40% or less of that projected or ≤12 patients are enrolled in this time period, then the study team will re-evaluate whether a) the accrual situation is rectifiable and likely to improve, and b) if useful information is likely to be obtained from the trial and consider termination if warranted.

13.6.3 Significance Testing for Early Termination and Reporting

Significance Testing for Early Termination and Reporting

Futility Analysis for the Phase II Trial: The planned futility analysis for the originally planned phase II trial has been executed. For the phase II trial with increased sample size, the same rule will be applied to the intermediate-risk cohort only: this interim futility analysis will be conducted when one-half (24) of the requisite events for definitive analysis have been observed. If the observed experimental/control hazard ratio is equal or greater than 1.00 (i.e. favoring RT, in the wrong direction with respect to demonstrating that chemoradiation is superior), then early stopping for the intermediate-risk cohort will be considered, with the conclusion being that this regimen would not be a candidate for further evaluation in a definitive phase III trial. Accrual of these patients will cease (if applicable).

Futility Analysis for the Phase III Trial: When 25% of requisite events for the phase III trial have occurred, efficacy and futility monitoring for the phase III endpoint will commence. Futility monitoring will follow the approach of Freidlin, et al. (2010) and if the boundary is crossed, then accrual may be stopped (if ongoing) or the trial results may be reported due to it being unlikely that the trial would find in favor of the experimental arm. Efficacy monitoring will follow the approach of Harrington, et al. (1984).
Efficacy and futility monitoring for the phase III endpoint (OS) will be carried out as described in the table below:

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Time (mos.) (from phase III open)</th>
<th>Proportion Total events</th>
<th>Cumulative Total Events (Both Arms)</th>
<th>Efficacy boundary</th>
<th>Futility boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z&gt;</td>
<td>P&lt;</td>
</tr>
<tr>
<td>Interim 1</td>
<td>24</td>
<td>0.25</td>
<td>39</td>
<td>2.57</td>
<td>0.005</td>
</tr>
<tr>
<td>Interim 2</td>
<td>42</td>
<td>0.50</td>
<td>78</td>
<td>2.51</td>
<td>0.006</td>
</tr>
<tr>
<td>Interim 3</td>
<td>56</td>
<td>0.75</td>
<td>117</td>
<td>2.41</td>
<td>0.008</td>
</tr>
<tr>
<td>Final</td>
<td>90</td>
<td>1.00</td>
<td>156</td>
<td>1.70</td>
<td>0.044</td>
</tr>
</tbody>
</table>

**Note**: boundary values for efficacy based on one-sided 0.05 test.

13.6.4 Analyses and Reporting of Phase II and Phase III Trial Findings

The definitive analysis determining phase II results will be carried out after 48 failure events have been observed in each risk cohort. At the specified accrual and event rates, it is anticipated that this analysis will occur approximately 9-10 years after the initial accrual start (November 2010) for both risk cohorts. The difference in PFS between the 2 arms will be evaluated within each risk cohort using a log-rank test at the significance level of 0.20 and interpreted as a one-sided evaluation of whether the chemoradiation arm is more favorable than radiation alone in that cohort.

For the phase III trial, accrual will proceed to a total of 240 eligible patients as described above, and follow up will continue until the observation of 156 deaths. At the planned accrual and event rates, this analysis is anticipated to occur approximately 4 years after completion of phase III accrual (phase II and III, totaling 9.0 years). The difference in OS will be evaluated as described above.

Analyses for the 2 trial phases will be performed using eligible patients with follow-up information. The usual components of an analysis report are:

- Tabulation of all cases entered and any excluded from analysis with reasons for exclusion;
- Information on patient accrual and follow-up;
- Accrual by institution;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Results for the primary endpoint (interim and definitive analysis) and secondary endpoints (definitive analyses) described above.

13.6.6 Clinical Data Update System (CDUS) Monitoring

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.
13.7 Gender and Minorities
In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we also have considered the possible interaction between race and treatments. The projected gender and minority accruals are provided in the table below. While men and women are approximately equally represented in the population for this disease, previous NRG Oncology studies have tended to accrue more men even in these circumstances. With respect to ethnic and racial categories, distributions similar to previous head and neck cancer trials are expected.

<table>
<thead>
<tr>
<th>Projected Distribution of Gender and Minorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic Category</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
</tr>
<tr>
<td>Racial Category</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Black or African American</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
</tr>
</tbody>
</table>
REFERENCES (11/5/15)


REFERENCES (Continued)


REFERENCES (Continued)


REFERENCES (Continued)


REFERENCES (Continued)


### APPENDIX I, STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (11/24/14)

*See Section 11.1 for details and exceptions*

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Prior to Registration</th>
<th>Prior to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>History/Physical</td>
<td>Within 8 weeks</td>
<td></td>
</tr>
<tr>
<td>Tissue submission for central review</td>
<td></td>
<td>Within 2 weeks after study entry</td>
</tr>
<tr>
<td>Chest CT</td>
<td>Within 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CBC with diff</td>
<td>Within 8 weeks</td>
<td>Within 2 weeks prior to treatment (Arm 1 patients only)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Within 8 weeks</td>
<td>Within 2 weeks prior to treatment (Arm 1 patients only)</td>
</tr>
<tr>
<td>Total bilirubin; AST or ALT</td>
<td>Within 8 weeks</td>
<td>Within 2 weeks prior to treatment (Arm 1 patients only)</td>
</tr>
<tr>
<td>Serum pregnancy test</td>
<td>Within 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Medical Onc. exam</td>
<td>Within 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Surgical Eval</td>
<td></td>
<td>Within 6 weeks</td>
</tr>
<tr>
<td>Dental eval</td>
<td></td>
<td>Within 8 weeks</td>
</tr>
<tr>
<td>Audiogram</td>
<td></td>
<td>Within 8 weeks for Arm 1 patients only</td>
</tr>
<tr>
<td>Nutrition eval</td>
<td></td>
<td>Recommended within 8 weeks</td>
</tr>
<tr>
<td>QOL/PROs: FACT-H&amp;N; PSS-HN; PROMIS; XeQOLS; EQ-5D</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Tissue/ blood, for research-if patient consents</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT (11/24/14)
*See Section 11.1 for details and exceptions

<table>
<thead>
<tr>
<th>Assessments</th>
<th>During Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekly</td>
</tr>
<tr>
<td>History/Physical</td>
<td></td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
</tr>
<tr>
<td>CBC with diff</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td></td>
</tr>
<tr>
<td>Adverse event eval</td>
<td>X</td>
</tr>
<tr>
<td>QOL/PROs: FACT-H&amp;N; PSS-HN; PROMIS; XeQOLS; EQ-5D</td>
<td></td>
</tr>
<tr>
<td>Tissue/ blood, for research-if patient consents</td>
<td></td>
</tr>
</tbody>
</table>

Week 4: Blood
**APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP**
*See Section 11.1 for details and exceptions*

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Follow Up</th>
<th>Long-Term Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mos. post completion of RT</td>
<td>6, 9, 12 &amp; 18 mos. from start of RT</td>
</tr>
<tr>
<td>History/Physical</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td></td>
<td>At 6 mos. X</td>
</tr>
<tr>
<td>Chest CT</td>
<td></td>
<td>At 12 mos.*</td>
</tr>
<tr>
<td>Tumor evaluation (CT of neck or MRI)*</td>
<td>X*</td>
<td>X*</td>
</tr>
<tr>
<td>Performance Status</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC with diff</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Total bilirubin; AST or ALT</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse event eval</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>QOL/PROs: FACT-H&amp;N; PSS-HN; PROMIS; XeQOLS; EQ-5D</td>
<td>X</td>
<td>At 12 mos. only</td>
</tr>
<tr>
<td>Tissue/ blood, for research-if patient consents</td>
<td>Blood</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX II: ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours

4 Completely disabled. Cannot carry on self-care. Totally confined to bed

5 Death
APPENDIX III: AJCC STAGING SYSTEM


HEAD & NECK

Major Salivary Glands
(Note: Minor salivary gland cancers of the head and neck are staged using the TNM staging criteria for the anatomic site of origin i.e. oral cavity, oropharynx, etc.)

T groups for major salivary gland cancers
TX: The main (primary) tumor cannot be assessed; information not known.
T0: No evidence of a primary tumor.
T1: Tumor is 2 cm (about ¾ inch) across or smaller. It is not growing into nearby tissues.
T2: Tumor is larger than 2 cm but no larger than 4 cm (about 1½ inch) across. It is not growing into nearby tissues.
T3: Tumor is larger than 4 cm across and/or is growing into nearby soft tissues.
T4a: Tumor is any size and is growing into nearby structures such as the jaw bone, skin, ear canal, and/or facial nerve. This is known as moderately advanced disease.
T4b: Tumor is any size and is growing into nearby structures such as the base of the skull or other bones nearby, or it surrounds the carotid artery. This is known as very advanced disease.

N groups for major salivary gland cancers
NX: Nearby (regional) lymph nodes cannot be assessed; information not known.
N0: No spread to regional lymph nodes.
N1: The cancer has spread to 1 lymph node on the same side of the head or neck as the primary tumor. The lymph node is smaller than 3 cm (about 1¼ inch) across.
N2: This group includes 3 subgroups:
  • N2a: The cancer has spread to 1 lymph node on the same side as the primary tumor. The lymph node is larger than 3 cm but not larger than 6 cm (about 2½ inches) across.
  • N2b: The cancer has spread to more than 1 lymph node on the same side as the primary tumor, none of the lymph nodes are larger than 6 cm across.
  • N2c: The cancer has spread to 1 or more lymph nodes, none larger than 6 cm across, either on the side opposite the primary tumor or on both sides of the neck.
N3: The cancer has spread to a lymph node that is larger than 6 cm across.

M groups for major salivary gland cancers
MX: Presence of distant spread (metastasis) cannot be assessed; information not known.
M0: The cancer has not spread to tissues or organs far away from the salivary glands.
M1: The cancer has spread to tissues or organs far away from the salivary glands

Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T, N, M</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 or T1-3, N1 M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a N0-N1 M0 or T1-T4a N2 M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b any N M0 or any T, N3 M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>any T, any N M1</td>
</tr>
</tbody>
</table>
APPENDIX IV: FFPE SPECIMEN PLUG KIT/INSTRUCTIONS (11/5/15)

This kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank-San Francisco. The plug kit contains a shipping tube and a punch tool.

**Step 1**
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

**Step 2**
Label punch tool with proper specimen ID and block ID. **DO NOT remove specimen from the punch.**

Use a separate punch tool for every specimen. Call or e-mail the Biospecimen Bank if you have any questions or need additional specimen plug kits.

**Step 3**
Embed punches into one block and submit with both a H&E slide from the original block that is marked with where the punches were taken, as well as an H&E slide of the punch block. Label block and slides with pathology accession number and block ID. If site is unable to embed the punches then make sure the punch tool is labeled, place in shipping tube, and mail to address below with 2 H&E slides described above. Please do not mix specimens in the same tube.

For sites that unable to embed the punches, the Biospecimen Bank will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID and block ID. **NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank-San Francisco and the Bank will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

**Ship the punch block and matching H&E OR the specimen plug kit, specimen in punch tool, and all paperwork as follows:**

**US Postal Service Mailing Address:** For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

**Courier Address (FedEx, UPS, etc.): For Frozen Specimens or Trackable shipments**
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu
APPENDIX V: BLOOD COLLECTION KIT/INSTRUCTIONS (11/5/15)

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

This kit contains: (Note: Sites are expected to provide their own blood draw tubes.)
- Thirty-five (35) 1 ml cryovials for all time points
- Biohazard bags (7)
- Absorbent shipping material (7)
- 1 Styrofoam container (inner)
- 1 Cardboard shipping (outer) box
- 1 Pre-paid shipping label for batch shipping of all time points
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal (ST) Form
- Instructions

Serum (if requested): Red Top Tube
- Label as many 1ml cryovials (up to 5) as serum collected. Label them with NRG Oncology study and case number, collection date, 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 ~1.0 ml serum into as many cryovials as serum collected (up to 5) 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 with cryovials upright 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.

Plasma (If requested): Purple Top EDTA tube #1
- Using four to five (4-5) 1 ml cryovials, label them with the NRG Oncology study and case number, collection date and time, 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 greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot ~1.0 ml plasma into each cryovial labeled with NRG Oncology study and case numbers, collection date, time point, and clearly mark specimen as “plasma”.
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.
Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- Using three to five (3-5) 1 ml cryovials, label them with the NRG Oncology study and case number, collection date and time, and clearly mark cryovial(s) “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 cryovials labeled “blood” (3-5 tubes). Clearly mark the tubes with date/time of collection and time point collected.
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80°C Celsius.
4. Store blood samples frozen until ready to ship on dry ice. See below for storage conditions.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

**Freezing**

- Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.

**Storage**

- 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).
    - **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).
    - **OR**
    - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only [U.S.] and for Canada, Monday-Tuesday).

- 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 and tape to the outside top of the Styrofoam box.
- 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 NRGBB@ucsf.edu or call (415)476-7864.

**Ship specimens and all paper work as follows:**

- **Courier Address (FedEx, UPS, etc.)**
  - NRG Oncology Biospecimen Bank-San Francisco
  - University of California San Francisco
  - 2340 Sutter Street, Room S341
  - San Francisco, CA 94115
- **Questions:** 415-476-7864/NRGBB@ucsf.edu