RADIATION THERAPY ONCOLOGY GROUP

RTOG 1008

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

Study Chairs (2/27/12)

Co-Principal Investigator/Medical Oncology
Cristina Rodriguez, MD
Oregon Health & Science University
3181 SW Sam Jackson Park Rd., L586
Portland, OR 97239
503-494-8534/FAX503-494-3257
rodrigcr@ohsu.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
875 Blake Wilbur Dr.
650-724-3018/FAX 650-725-8231
Stanford, CA 94305
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
Radiation Therapy Oncology Group/ACR
1818 Market Street, Suite 1600
Philadelphia, PA 19103
215-574-3174/FAX 215-928-0153
jdignam@acr.org

(Continued on next page)

RTOG 1008

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

Title Page (Continued)

Document History

	Version/Update Date	Broadcast Date
Amendment 4	**September 19, 2012**	September 25, 2012
Update	March 6, 2012	March 6, 2012
Amendment 3	February 27, 2012	March 5, 2012
Amendment 2	October 26, 2011	December 1, 2011
Update	August 5, 2011	August 5, 2011
Amendment 1	May 4, 2011	May 12, 2011
Update	November 3, 2010	November 3, 2010
Activation	November 3, 2010	November 3, 2010

RTOG Headquarters
1-800-227-5463, ext. 4189

This study is supported by the NCI Cancer Trials Support Unit (CTSU). [8/5/11]
Institutions not aligned with the RTOG will participate through the CTSU mechanism as outlined below and detailed in Section 5.0.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at http://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to Section 5.0 for specific instructions and forms to be submitted.
- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and RTOG Headquarters.

(Continued on next page)

RTOG 1008
A RANDOMIZED PHASE II STUDY OF ADJUVANT CONCURRENT RADIATION AND CHEMOTHERAPY VERSUS RADIATION ALONE IN RESECTED HIGH-RISK MALIGNANT SALIVARY GLAND TUMORS

Title Page (Continued)

<table>
<tr><th colspan="3">CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION (8/5/11)</th></tr>
<tr><td>To submit site registration documents:</td><td>For patient enrollments:</td><td>Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:</td></tr>
<tr><td>CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone – 1-866-651-CTSU
Fax – 215-569-0206</td><td>Please refer to Section 5.0 of the protocol for instructions on using the OPEN system.</td><td>RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td></tr>
<tr><td colspan="3">The study protocol and all related forms and documents must be downloaded from the protocol-specific web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.

CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.</td></tr>
<tr><td colspan="3">For patient eligibility or treatment-related questions Contact the Study PI of the Coordinating Group</td></tr>
<tr><td colspan="3">For questions 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.</td></tr>
<tr><td colspan="3">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' website https://www.ctsu.org</td></tr>
<tr><td colspan="3">The CTSU web site is located at https://www.ctsu.org</td></tr>
</table>

INDEX (5/4/11)

RADIATION THERAPY ONCOLOGY GROUP

RTOG 1008

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

SCHEMA (2/27/12)

	Histology		
S	1. Intermediate-grade adenocarcinoma	**R**	
T	or intermediate-grade mucoepidermoid	**A**	**Arm 1**
R	carcinoma	**N**	Radiation: 60-66 Gy in 2 Gy daily fractions
A	2. High-grade adenocarcinoma or high-grade	**D**	Cisplatin: 40 mg/m^2 weekly during radiation
T	mucoepidermoid carcinoma or	**O**	for 7 doses
I	salivary duct carcinoma	**M**	
F	3. High-grade acinic cell carcinoma or	**I**	**Arm 2**
Y	high-grade (> 30% solid component) adenoid	**Z**	Radiation: 60-66 Gy in 2 Gy daily fractions
	cystic carcinoma	**E**	
	Nodal Status		
	1. N0		
	2. N1-3		

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: **120**

RTOG Institution #
RTOG 1008 **ELIGIBILITY CHECKLIST (9/19/12)**
Case # **(page 1 of 3)**

_____ (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 ($\leq$ 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 $\geq$ 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?

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

____ (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)

(Continued on next page)

_____(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

_____ 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

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

(Continued on next page)

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____(Y/N) 24. Did the patient agree to participate in the quality of life component?

_____ If no, provide reason:

1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

_____ 25. 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)

_____(Y/N) 27. Use of IMRT

_____(Y/N) 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/RTOG 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

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, Airoldi 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. This randomized phase II study is 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 provides 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.

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, Murphy 2007, 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*

1.4.1.1 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).

1.4.1.2 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.

1.4.1.3 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).

1.4.1.4 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.

1.4.1.5 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

2.1 Primary Objective

2.1.1 Determine the feasibility of conducting a cooperative group prospective clinical trial in patients with resected malignant salivary gland tumors;

2.1.2 Acquire preliminary efficacy data comparing postoperative radiotherapy alone to concurrent chemotherapy and radiation using weekly cisplatin.

2.2 Secondary Objectives

2.2.1 Compare the acute toxicities of these 2 adjuvant treatments;

2.2.2 Compare long-term efficacy results at 5 years and late treatment-related adverse events in patients receiving postoperative radiation to those receiving concurrent chemoradiation;

2.2.3 Investigate quality of life and patient-reported outcomes in patients enrolled in the study;

2.2.4 Identify the histopathology and tumor marker expression from patients enrolled on this trial and assemble a tissue bank for future correlative studies;

2.2.5 Establish an RTOG 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

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

3.1 Conditions for Patient Eligibility (9/19/12)

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:

3.1.3.1 History/physical examination within 8 weeks prior to registration;

3.1.3.2 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 4 weeks prior to registration, with adequate bone marrow function defined as follows:

3.1.6.1 Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3;

3.1.6.2 Platelets ≥ 100,000 cells/mm^3;

3.1.6.3 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 4 weeks prior to registration;, defined as follows:

3.1.7.1 Serum creatinine < 2.0 mg/dl;

3.1.7.2 Total bilirubin < 2 x the institutional ULN;

3.1.7.3 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:

3.2.5.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;

3.2.5.2 Transmural myocardial infarction within the last 6 months;
3.2.5.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
3.2.5.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
3.2.5.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; Note, however, coagulation parameters are not required for entry into this protocol.
3.2.5.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; Note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
3.2.5.7 Pre-existing ≥ grade 2 neuropathy;
3.2.5.8 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 (9/19/12)

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 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);
4.1.4 Dental evaluation within 8 weeks prior to treatment;
4.1.5 Baseline audiogram within 8 weeks prior to treatment for patients randomized to Arm 1 (RT and cisplatin).

4.2 Highly Recommended Evaluations/Management

4.2.1 Nutritional evaluation within 8 weeks prior to treatment

5.0 REGISTRATION PROCEDURES

IMRT and IGRT are optional for this study. If an institution decides to use IGRT (for reduced margins only), that 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)

5.1.1 In order to utilize head and neck IGRT, 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 Advanced Technology Consortium (ATC) web site, http://atc.wustl.edu. The ATC is in part comprised of RTOG RT Quality Assurance, the Image-Guided Therapy Center (ITC) at Washington University, and the Radiological Physics Center (RPC) at MD Anderson Cancer Center.

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 the RTOG 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* **(9/19/12)**

Note: If an institution has been approved for head and neck IGRT credentialing for RTOG 0920 or RTOG 1016, the site will NOT have to be credentialed for this study.

5.1.2.1 Each institution will be required to undergo credentialing for head and neck IGRT (review of at least one case from each institution). The first step is for the institution to complete the IGRT portion of the Facility Questionnaire and/or set up an SFTP account for digital data submission, both of which are available on the ATC web site at http://atc.wustl.edu.

5.1.2.2 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 ATC web site, http://atc.wustl.edu, for 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. Upon approval of these images, the RTOG will notify the institution that they have completed this credentialing step for entering their first patient. The first patient from each institution will be analyzed in the same way before permission is given to enter the second patient. At this point, no additional IGRT data will be gathered.

5.2 Pre-Registration Requirements for IMRT Treatment Approach

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 Radiological Physics Center (RPC) web site. Visit http://rpc.mdanderson.org/rpc 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 RPC web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.2.2 The institution or investigator must complete a new IMRT Facility Questionnaire and send it to RTOG for review prior to entering any cases, and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu. Upon review and successful completion of the "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.3 Pre-Registration Requirements for 3DCRT Treatment Approach

5.3.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients onto this study. 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 Facility Questionnaire (one per institution, available on the ATC web site at http://atc.wustl.edu) is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing.

5.4 Regulatory Pre-Registration Requirements **(8/5/11)**

5.4.1 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 Cooperative Group or a CTSU CICRS site. 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 or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

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.

Requirements for RTOG 1008 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For non-lead group institutions an RT Facilities Inventory From must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

In addition to the requirements noted above, U.S. and Canadian institutions must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), prior to registration of the institution's first case:

- IRB/REB approved consent (English and native language versions*****)
- ***Note**: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number renewal information as appropriate.

5.4.1.1 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 RTOG 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.

5.4.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

5.4.2.1 Prior to clinical trial commencement, 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.

5.4.3 *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS* **(5/4/11)**

5.4.3.1 **For institutions that do not have an approved LOI for this protocol:**
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.aspx .

5.4.3.2 **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.

5.5 OPEN Registration (8/5/11)

5.5.1 Patient registration can occur only after pre-treatment evaluation 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.

All site staff (RTOG and CTSU Sites) will use OPEN to enroll patients to this study. 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 has been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the RTOG, you must have an equivalent 'Registrar' role on the RTOG roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.
- **NOTE**: **If you are enrolling as a non-RTOG site**: Prior to beginning the enrollment, call the RTOG Randomization desk at 215-574-3191 or 215-574-3192 to obtain an RTOG, non-Lead Group, site-specific institution number.

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 or at https://open.ctsu.org.. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.5.2 In the event that the OPEN system is not accessible, participating sites can register a patient by calling RTOG Headquarters, 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, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

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

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).

It is strongly encouraged that the first dose of radiation treatment (RT) 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 PTV1 and one for PTV2. In cases with close or involved surgical margin or with extracapsular nodal extension (ECE), a 3rd boost plan will need to be generated.

6.1.1.1 PTV1 (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.

6.1.1.2 PTV2, 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.

6.1.1.3 PTV3 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, PTV1 and PTV2 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:

- PTV1 will receive 54 Gy at 1.8 Gy/fraction for 30 fractions;
- PTV2 will receive 60 Gy at 2 Gy/fraction for 30 fractions;
- PTV3: 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

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 the ATC 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.

6.2.2.1 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.

6.2.2.2 *Management of Radiation Dose to the Patient from IGRT*

Available peer reviewed literature estimates the patient dose within and outside of the target region when IGRT is used to correct positioning to vary considerably. This is the case when the same imaging hardware is used with x-ray technique and with different data gathering procedures. The dose variation is even greater when different imaging equipment is used. The estimated doses are in the range of 1 mGy for 2D systems such as the BrainLab's ExacTrac system or either the Varian or Elekta kV systems used for orthogonal imaging. These doses are small compared with doses from MV portal imaging and kV or MV cone-beam CT. The doses from helical MV CT scanning with a tomotherapy unit are estimated to be in range from 1 to 3 cGy for head and neck studies, similar to doses reported for kV cone-beam CT on Elekta Synergy machine. The doses for MV cone beam CT were reported to be in range from 10 cGy for a pelvis study to 6 cGy for a head and neck study. Thus, the doses for 3D imaging systems are in the range from 1 to 6 cGy for head and neck imaging and can contribute from 0.5 to 3% to the daily dose of 2.0 Gy. These doses apply each day when image guidance is used, and the numbers double and triple when extra imaging is needed to adjust positioning on a particular day.

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

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 **(2/27/12)**

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.

6.4.1.1 *Parotid Gland Cancer*

CTV1 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, CTV1 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, CTV1 should include the parapharyngeal space to ensure coverage of the deep lobe and regions at risk for microscopic spread. CTV1 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 IIB, IIIB or IVB. The surgical scar should be outlined and also included in CTV1. 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).

6.4.1.2 *Submandibular and Sublingual Gland Cancer*

CTV1 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, CTV1 also should encompass the mandible proximally to the mandibular foramen. In situations where V3 is involved near the skull base, CTV1 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 CTV1. 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).

6.4.1.3 *Minor Salivary Gland Cancer*

CTV1 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, CTV1 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 ispilateral 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).

6.4.1.4 CTV2 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 land marks) and site of involved named nerves +1 cm margin. CTV2 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 (CTV3).

6.4.1.5 CTV3 (defined only for patients with close ($\leq$ 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 land marks) and only the involved nodal bed(s) with pathologic extracapsular extension.

6.4.2 Planning Target Volume (PTV)

6.4.2.1 *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.

6.4.2.2 *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 (5/4/11)

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 OARpharynx
- 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)

6.5.1.1 *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.

6.5.1.2 *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.

6.5.1.3 *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.

6.5.1.4 *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.

6.5.1.5 *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.

6.5.1.6 *Cervical Esophagus:* This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.

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

6.5.1.8 *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.

6.5.1.9 *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 vevin. These cords extent laterally along the axillary vein into the axilla.

6.5.1.10 *Cochlea:* Contour for all cases.

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

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

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

6.5.1.14 *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 **(5/4/11)**

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 $\leq$ 1 mm or involved surgical margins or ECE. The goal is for 95% of the PTV2 to receive ≥ 2 Gy with a minimum dose (cold spot) of no less than 56 Gy. It is recognized that portions of the PTV2 close to the skin may receive significantly less than 56 Gy. This is acceptable as long as cold spots within PTV2 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, PTV2 will be the highest priority target structure. PTV3 and PTV1, if applicable, will be ranked in the IMRT planning as lower priority than PTV2 although higher priority than normal structures other than spinal cord and brain stem.

6.5.3 Dose Constraints to Normal Structures **(5/4/11)**

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.

6.5.3.1 *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.

6.5.3.2 *Brainstem:* The PRVcord (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 CTV1. 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.

6.5.3.3 *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.

6.5.3.4 *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.

6.5.3.5 *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.

6.5.3.6 *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.

6.5.3.7 *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.

6.5.3.8 *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.

6.5.3.9 *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.

6.5.3.10 *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.

6.5.3.11 *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.

6.5.3.12 *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 CTV2. It is recommended that the brain maximal dose should not exceed 66 Gy for all cases.

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

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

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

6.5.3.16 *Unspecified Tissue Outside the Targets:* For the typical case in which there is no CTV3, no more than 5% of unspecified tissue can receive greater than 58 Gy and no more than 1% or 1cc of unspecified tissue can receive 64 Gy or more. When a boost is used to treat CTV3 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)

1. Spinal Cord and brainstem
2. PTV2
3. PTV1
4. PTV3 (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 (11/3/10)

- 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;
- The ITC will display, and compare with hardcopies, isodose distributions for the axial and coronal planes (or multiple axial planes) through the planning target volume to verify correct digital submission and conversion.

6.7 Compliance Criteria

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 PTV2 on the composite plan of PTV1 and PTV2 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 PTV2 on the first phase (PTV1 and PTV2 treated with a single phase) or the evaluation of PTV3 on a composite plan of all phases depending on the total dose prescribed 60 or 66 Gy.

	Per Protocol	**Variation Acceptable**	**Deviation Unacceptable**
Total dose to 95% of PTV2 (60 Gy)	60 Gy	58-61	< 58 or > 61 Gy
Minimum dose ("cold spot" within PTV2, not including portion of PTV2 near (<8 mm) skin)	56 Gy	54-56 Gy	< 54 Gy
Maximum dose ("hot spot") within PTV2*****	< 67 Gy	67-70 Gy	> 70 Gy
Total dose to 95% of PTV3 (66 Gy)	66-70 Gy	64-66 or 70-72	< 64 or > 72
Minimum dose ("cold spot" within PTV3, not including portion of PTV3 near (< 8 mm) skin)	60	59-60	< 59
Maximum dose ("hot spot") within PTV3*****	< 77	77-79.2	> 79.2
Definition of CTV2 and 3	Based on case review by study chair		
Definition of PTV2 and 3	Based on case review by study chair		
Total RT dose to spinal cord PRV (0.03 cc) [for composite plan of PTV2 if there is no boost and PTV 3 is there is a boost]	< 45 Gy	45-48 Gy	> 48
Total RT dose to spinal cord PRV (0.01 cc) [for composite plan of PTV2 if there is no boost and PTV3 if there is a boost]	< 48 Gy	48-50 Gy	> 50 Gy
Total RT dose to brainstem PRV (0.03 cc) [for composite plan of PTV2 if there is no boost and PTV3 if there is a boost]	< 48 Gy if skull base is not included in PTV1 < 52 Gy if skull base is included in PTV1	48-52 Gy if skull base is not included in PTV1 52-55 Gy if skull base is included in PTV1	> 52 Gy if skull base is not included in PTV1 > 55 Gy if skull base is included in PTV1
Definition of Spinal cord and brainstem PRV	Based on case review by study chair		
Overall treatment time 60 Gy only (PTV2) 66 Gy (PTV 3 included)	 45 days 50 days	 46-50 days** 50-54 days**	 > 50 days** > 54 days**
Non-Medically Indicated Treatment Interruptions	0-2 days	2-4	> 4 days

*Not including the region of PTV60 that falls within PTV66 (if applicable

** without a medically appropriate indication for delay

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 (9/19/12)

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 RTOG RTQA.

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

See AdEERS Expedited Reporting Requirements in Section 7.6.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

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/m^2, 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/m^2. (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 (10/26/11)

Refer to the package insert for additional 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.

7.2.6 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/mm^3, 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/mm^3.

If ANC remains < 1000/mm^3 for more than 7 days, all subsequent cisplatin doses will be reduced to 30 mg/m^2, and the next weekly dose only given when the ANC is > 1000/mm^3. In the event of neutropenic fever, reduce all subsequent doses of cisplatin to 30 mg/m^2 and administer only when the ANC is ≥ 1000/mm^3.

If, on the day of scheduled treatment, the patient again experiences an ANC < 1000/mm^3 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/m^2 for all remaining cisplatin doses, which can be given only after recovery of the ANC to ≥1000/mm^3.

Any subsequent ANC < 1000/mm^3 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.

If hematologic recovery requires more than 3 weeks, irrespective of cisplatin dose, all subsequent cisplatin will be discontinued.

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/mm^3.

If the platelets remain < 75,000/mm^3 for more than 7 days, then all subsequent cisplatin doses will be reduced to 30 mg/m^2, and the next weekly dose only given when the platelet count ≥ 75,000/mm^3.

If the platelet count is again < 75,000/mm^3 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/m^2 for all remaining cisplatin doses, which can be given only after recovery of platelet count to ≥ 75,000/mm^3.

Any subsequent platelet count < 75,000/mm^3 on the day of scheduled treatment, after 2 dose reduction will mandate discontinuation of all remaining cisplatin doses.

If hematologic recovery requires more than 3 weeks, irrespective of cisplatin dose, all subsequent cisplatin will be discontinued.

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/m^2. 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/m^2. 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/m^2. 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/m^2. 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 (9/19/12)

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.

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

7.5 Adverse Events (9/19/12)

Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE), MedDRA, v. 12.0 will be utilized for adverse event (AE) reporting. CTCAE, v. 4 is identified and 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 CTCAE, v 4.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.5.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.6 also must be reported via AdEERS.**

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.5.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after 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. Any pregnancy, including a male patient's impregnation of his partner, occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. **Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the "NOT Required" assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note:** Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.5.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) [5/4/11]

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system **within 30 days of AML/MDS diagnosis**. If reporting in CTCAE v. 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

7.6 AdEERS Expedited Reporting Requirements (10/26/11)

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via AdEERS 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 [1, 2]

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

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the 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 AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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

Expedited AE reporting timelines are defined as:

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

[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 AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Additional Instructions or Exceptions to AdEERS 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 enbloc 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

The Surgical Oncology Co-Chair, Ehab Hanna, MD, will perform a modified Quality Assurance Review after complete data for the first 25 cases enrolled has been received at RTOG Headquarters. The quality assurance review will specifically examine the issue related to eligibility and the presence of high risk features. The final cases will be reviewed within 2 months after this study reaches the target accrual or as soon as complete data for these cases has been received at the RTOG headquarters, whichever occurs first.

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

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

In this study, tissue will be submitted to the RTOG Biospecimen Resource 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 (5/4/11)

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 RTOG Biospecimen Resource for retrospective central review:

10.2.1 Representative H & E stained slides from the area with the highest grade within the tumor;

10.2.2 One paraffin block of tumor (recommended); **Note:** If sites are unable to provide the block, then two 2 mm cores of the block taken with a punch tool is acceptable. A specimen plug kit can be requested from the RTOG Biospecimen Resource (see Appendix V for instructions). If the site will not release the block or allow punches to be taken, then a minimum of 17 five micron unstained slides cut onto positive charged slides is an acceptable substitute.

10.2.3 A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the RTOG 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 information must NOT be removed from the report.

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

10.2.5 A Specimen Transmittal Form stating that the tissue is being submitted for Central Review. The Form must include the RTOG 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 (5/4/11)

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 submitted for central review (see Section 10.2.2).

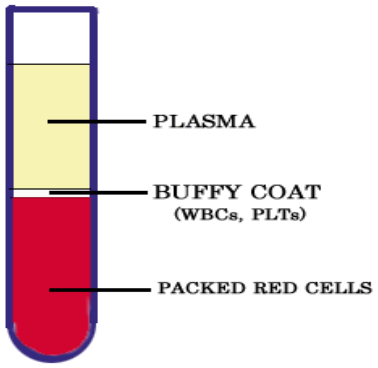
10.3.2 Serum, Plasma, and Whole Blood Collection

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.**

10.3.2.1 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 ~2500g at 4^{o} Celsius (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.



10.3.2.2 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 at least 0.5 ml whole blood into 4-6 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).

10.3.2.3 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 g 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. Tube 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

The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, and whole blood; the RTOG 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 (5/4/11)

Specimens for Tissue Banking/Central Review/Translational Research			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool or a minimum of 17 unstained slides	Pre-treatment	Paraffin-embedded tissue block, punch biopsy, or slides	Block, punch, or slides shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge.	Pre-treatment, week 4 of RT, and 3 mos. post-completion of RT	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Pre-treatment, week 4 of RT, and 3 mos. post-completion of RT	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-treatment (or if missed, at any time)	Frozen whole blood samples containing 1 mL per aliquot in 1ml cryovials	Whole blood sent frozen on dry ice via overnight carrier

10.7 Shipment of Biospecimens (10/26/11)

Submit materials for Central Review and Banking as follows:

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
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
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

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

10.8 Reimbursement (5/4/11)

RTOG will reimburse institutions for submission of protocol-specified biospecimen materials sent to the RTOG Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement & Case Credit Schedule found on the RTOG Web site (http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.9 Confidentiality/Storage (5/4/11)

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

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

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

11.0 PATIENT ASSESSMENTS (9/19/12)

11.1 Study Parameters: See Appendix II for a summary of assessments and timeframes. **Note:** Clarifications of or exceptions to the study parameters are indicated in Appendix II 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 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.

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.

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)**

11.4.1.1 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.

11.4.1.2 The Performance Status Scale for Head and Neck Cancer (PSS-HN) consists of assessment of 3 functional areas (subscales): 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.

11.4.1.3 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/.

11.4.1.4 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.

11.4.1.5 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:

RTOG Headquarters*
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)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Slides/Blocks **(P2)** Operative Report **(S2)**	Within 2 weeks of study entry
Functional Assessment of Cancer Therapy-H &N [FACT] **(FA)** Performance Status Scale for H & N Cancer [PSSHN] **(QP)** EuroQol [EQ-5D] **(HP)** University of Michigan Xerostomia-Related Quality of Life Scale [XeQOLS] **(L4)** PROMIS-Fatigue **(QL)**	
Treatment Form **(TF)**	Upon completion or discontinuation of treatment
Follow-up Form **(F1)**	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
FACT **(FA)** PSS-HN **(QP)** EQ-5D **(HP)** XeQOLS **(L4)** PROMIS-Fatigue **(QL)**	Upon completion or discontinuation of RT, at 3 months post-completion of RT, and at 12 and 24 months from the start of RT

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

Item	Due
Preliminary Dosimetry Information (DD) †Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: • CT data, critical normal structures, all GTV, CTV, and PTV contours • Digital beam geometry for initial and boost beam sets • Doses for initial and boost sets of concurrently treated beams • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan **(DV)**	Within 1 week of start of RT
Digital Data Submission Information Form **(DDSI)** – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/DDSI/ddsi.html)	
Hard copy isodose distributions for total dose plan† **(T6)**	
NOTE: Sites must notify ITC via e-mail (itc@wustl.edu) after digital data is submitted. The	

e-mail must include study and case numbers or, if the data is phantom, "dry run" or "benchmark".

Final Dosimetry Information Radiotherapy Form **(T1) [copy to HQ and ITC]** Daily Treatment Record **(T5) [copy to HQ and ITC]** Modified digital patient data as required through consultation with Image-Guided Therapy QA Center	Within 1 week of RT end

†Available on the ATC web site, http://atc.wustl.edu/

12.2.1 *Digital Data Submission to ITC*

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

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.

13.2 Secondary Endpoints (11/3/10)

13.2.1 Overall survival (OS) rate at 2 years, defined as the event of death from any cause;

13.2.2 PFS rate at 5 years;

13.2.3 OS rate at 5 years;

13.2.4 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;

13.2.5 Treatment related mortality defined as any death during or within 30 days of discontinuation of protocol treatment;

13.2.6 Chemotherapy delivery as measured by percentage of protocol prescription given;

13.2.7 Radiation delivery as measured by elapsed treatment days;

13.2.8 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 (2/27/12)

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 (2/27/12)

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 ≥ 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 uncertainly 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.

13.5 Patient Accrual

During the first 6 months following activation, little accrual is anticipated while the trial is reviewed and approved by site IRBs. After this initial period, it is anticipated that 2-3 patients (average 2.5) will be enrolled per month.

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 rates for each regimen will be directly compared.

13.6.1 Statistical Methods

13.6.1.1 *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. PFS will be compared between treatment arms, using a log-rank test. PFS and OS rates 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.

13.6.1.2 *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.

13.6.1.3 *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 μ_{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 μ_{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 108 patients to complete the baseline evaluations. Assuming 10% attrition by 3 months post enrollment, we expect 96 patients (48 per arm) to still be included though the 3-month assessment period. A between-groups comparison of a given instrument score at that time point would have 84% power at (one-sided) alpha=.15 to detect a difference of one-half standard deviation of the mean. 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 80% 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 RTOG 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

13.6.3.1 *Futility Analysis*

A single interim futility analysis will be conducted when one-half (24) of the requisite events for definitive analysis have been observed. If the observed hazard ratio is equal or greater than 1.10 favoring RT (i.e. in the wrong direction with respect to demonstrating that chemoradiation is more favorable), then early stopping will be considered, with the conclusion being that this regimen would not be a candidate for further evaluation in a definitive phase III trial.

13.6.3.2 *Other Early Termination Considerations*

In relation to early termination, note also that Section 13.6.2 describes a feasibility evaluation, whereby accrual must meet 40% of the intended target in months 7-18, or options including termination will be considered.

13.6.4 Analysis for Reporting the Initial Treatment Results

The analysis reporting these treatment results will be carried out after 48 failure events have been observed. At the specified accrual and event rates, it is anticipated that this analysis will occur approximately 5.25 year after accrual commences. Only eligible patients with both on-study and follow-up information will be included in the primary treatment analysis. The usual components of this analysis are:

- Tabulation of all cases entered and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Observed results with respect to the primary endpoints described above.

The difference in PFS between the 2 arms will be tested 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.

13.6.5 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 RTOG 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.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	3	5
Not Hispanic or Latino	46	69	115
Ethnic Category: Total of all subjects	48	72	**120**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	1	1
Asian	2	2	4
Black or African American	2	5	7
Native Hawaiian or other Pacific Islander	0	0	0
White	44	64	108
Racial Category: Total of all subjects	48	72	**120**

REFERENCES

Agulnik M, Cohen EW, Cohen RB, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. *J Clin Oncol*. 25: 3978-3984, 2007.

Airoldi M, Pedani F, Succo G, et al. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. *Cancer*. 91: 541-547, 2001.

Armstrong JG, Harrison LB, Spiro RH, et al. Malignant tumors of major salivary gland origin. A matched-pair analysis of the role of combined surgery and postoperative radiotherapy. *Arch Otolaryngol Head Neck Surg*. 116: 290-293, 1990.

Bachaud JM, Cohen-Jonathan E, Alzieu C, et al. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: Final report of a randomized trial. *Int J Radiat Oncol Biol Phys*. 36:999-1004, 1996.

Badia X, Herdman M, Kind P. The influence of ill-health experience on the valuation of health. *Pharmacoeconomics*. 13:687-696, 1998.

Barnes L, Eveson JW, Riechart P, et al. *World Health Organization Classification of Tumors*. Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press; 2005.

Beckmann GK, Hoppe F, Pfreundner L, et al. Hyperfractionated accelerated radiotherapy in combination with weekly cisplatin for locally advanced head and neck cancer. *Head Neck*. 27: 36-43, 2005.

Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *NEJM*. 350:1945-1952, 2004.

Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer.* 36(14): 1796-807, 2000.

Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *NEJM*. 354(6): 567-78, 2006.

Cella DF, et al., The Functional Assessment of Cancer Therapy scale: Development and validation of chemoradiotherapy regimens. *Amer Soc of Clin Onc.* 412, 2000.

Cerezo L, Martín M, López M, Marín A, Gómez A. Ipsilateral irradiation for well lateralized carcinomas of the oral cavity and oropharynx: results on tumor control and xerostomia. *Radiat Oncol.* 4:33, 2009.

Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst*. 97: 536-539, 2005.

Chen AM, Granchi PJ, Garcia J, et al: Local-regional recurrence after surgery without postoperative irradiation for carcinomas of the major salivary glands: Implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys.* 67:982-987, 2007.

Christodoulou C, Junghaenel DU, DeWalt DA, Rothrock N, Stone AA. Cognitive interviewing in the evaluation of fatigue items: Results from the patient-reported outcomes measurement information system (PROMIS). *Qual Life Res*. 17(10):1239-46, 2008. Epub 2008 Oct 12.

Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *NEJM*. 350: 1937-1944, 2004.

Curran D, Giralt J, Harari PM, et al. Quality of life in head and neck cancer patients after treatment with highdose radiotherapy alone or in combination with cetuximab. *J Clin Oncol*. 25(16): 2191-7, 2007. Erratum in: *J Clin Oncol*. 25(24): 3790, 2007.

Diggle PJ, Liang KY, Zeger SL. *Analysis of longitudinal data*. New York: Oxford University Press, 1994.

Frank W. Foote, Edgar L. Frazell. *Tumors of the Major Salivary Glands*. Washington DC: Armed Forces Institute of Pathology; 1954.

Garden AS, el-Naggar AK, Morrison WH, et al. Postoperative radiotherapy for malignant tumors of the parotid gland. *Int J Radiat Oncol Biol Phys.* 37: 79-85, 1997.

Gilbert J, Li Y, Pinto HA, et al. Phase II trial of taxol in salivary gland malignancies (E1394): A trial of the eastern cooperative oncology group. *Head Neck*. 28:197-204, 2006.

Glisson B, Colevas AD, Haddad R, et al. HER2 expression in salivary gland carcinomas: Dependence on histological subtype. *Clin Cancer Res*. 10: 944-946, 2004.

Haddad R, Colevas AD, Krane JF, et al. Herceptin in patients with advanced or metastatic salivary gland carcinomas. A phase II study. *Oral Oncol*. 39: 724-727, 2003.

Hall WH, Guiou M, Lee NY, et al. Development and validation of a standardized method for contouring the brachial plexus; Preliminary dosimetric analysis among patients treated with IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 72(5): 1362-1367, 2008.

Henderson R, Diggle P, Dobson A. Joint modeling of longitudinal measurements and event time data. *Biostatistics*. 1: 465-80, 2000.

Henson BS, Inglehart MR, Eisbruch A, Ship JA. Preserved salivary output and xerostomia-related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. *Oral Oncol*. 37(1): 84-93, 2001. \

Hogan JW, Laird NM. Model-based approaches to analyzing incomplete longitudinal and failure time data. *Stat Med.* 15: 259-72, 1997.

Hotte SJ, Winquist EW, Lamont E, et al. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: A princess margaret hospital phase II consortium study. *J Clin Oncol*. 23: 585-590, 2005.

Johns ME, Goldsmith MM. Incidence, diagnosis, and classification of salivary gland tumors. part 1. *Oncology*. (Williston Park) 3:47-56; discussion 56, 58, 62, 1989.

Karvonen-Gutierrez CA, Ronis DL, Fowler KE, et al. Quality of life scores predict survival among patients with head and neck cancer. *J Clin Oncol*. 26(16): 2754-60, 2008.

List M, Ritter-Sterr C, Baker T, et al. Longitudinal assessment of quality of life in laryngeal cancer patients. *Head Neck*. 18:1–10, 1996.

b) List MA, D'Antonio LL, Cella DF, et al. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale: A study of utility and validity. *Cancer*. 77: 2294-301, 1996.

List MA, Siston A, Haraf D, et al. Quality of life and performance in advanced head and neck cancer (HNC: Comparison between paclitaxel-based (P-CT/XRT) and cisplatin-based (C-CT/XRT) concomitant chemoradiotherapy: A prospective examination. *J Clin Oncol.* 17: 1020-8, 1999.

List MA, Stracks J. Evaluation of quality of life in patients definitively treated for squamous carcinoma of the head and neck. *Curr Opin Oncol*. 12(3):215-20, 2000.

Little RJA. Regression with missing x's: A review. *J Am Stat Assoc*. 87:1227-37, 1992.

Liu CL, Prapong W, Natkunam Y, et al. Software tools for high-throughput analysis and archiving of immunohistochemistry staining data obtained with tissue microarrays. *Am J Pathol*. 161:1557-1565, 2002.

Locati LD, Bossi P, Perrone F, et al. Cetuximab in recurrent and/or metastatic salivary gland carcinomas: A phase II study. *Oral Oncol*. 45: 574-578, 2008.

Logemann JA, Pauloski BR, Rademaker AW, et al. Swallowing disorders in the first year post-radiation and chemoradiation. *Head & Neck*. 30: 148-158, 2008.

Maguire PD, Papagikos M, Hamann S, et al. Phase II trial of hyperfractionated intensity-modulated radiation therapy and concurrent weekly cisplatin for stage III and IVa head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2010 Apr 7. [Epub ahead of print].

Martino R, Ringash J. Evaluation of quality of life and organ function in head and neck squamous cell carcinoma. *Hematol Oncol Clin North Am*. 22(6):1239-56, 2008. Review.

Medina JA, Rueda A, de Pasos AS, et al. A phase II study of concomitant boost radiation plus concurrent weekly cisplatin for locally advanced unresectable head and neck carcinomas. *Radiother Oncol*. 79: 34-38, 2006.

Mendenhall WM, Morris CG, Amdur RJ, et al. Radiotherapy alone or combined with surgery for salivary gland carcinoma. *Cancer.* 103: 2544-2550, 2005.

Murphy BA, Ridner S, Wells N, Dietrich M. Quality of life research in head and neck cancer: A review of the current state of the science. *Crit Reviews Oncol/Hemat*. 62:251–267, 2007.

Ostman J, Anneroth G, Gustafsson H, Tavelin B. Malignant salivary gland tumours in Sweden 1960-1989--an epidemiological study. *Oral Oncol*. 33(3): 169-76, 1997.

Reeve BB, Hays RD, Bjorner JB, Cook KF, Crane PK, Teresi JA, Thissen D, Revicki DA, Weiss DJ, Hambleton RK, Liu H, Gershon R, Reise SP, Lai JS, Cella D; PROMIS Cooperative Group. Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). Med Care. 2007 May;45(5 Suppl 1):S22-31.

Ringash J, Bezjak A, O'Sullivan B, Redelmeier DA. Interpreting differences in quality of life: The FACT-H&N in laryngeal cancer patients. *Qual Life Res*. 13(4): 725-33, 2004.

Ringash J, Warde P, Lockwood G, O'Sullivan B, Waldron J, Cummings B.Postradiotherapy quality of life for head-and-neck cancer patients is independent of xerostomia*. Int J Radiat Oncol Biol Phys*. 1;61(5): 1403-7, 2005.

Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer*. Jul 1;110(1):196-202, 2007.

Rogers SN, Johnson IA, Lowe D. Xerostomia after treatment for oral and oropharyngeal cancer using the University of Washington saliva domain and a Xerostomia-Related Quality-of-Life Scale. *Int J Radiat Oncol Biol Phys*. 77(1): 16-23, 2010. Epub 2009 Aug 11.

Rubinstein LV, Korn EL, Freidlin B et al. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol*. 23(28): 7199-206, 2005.

Schroeder U, Groppe D, Mueller RP, et al. Parotid cancer: Impact of changes from the 1997 to the 2002 American Joint Committee on cancer classification on outcome prediction. *Cancer.* 113: 758-764, 2008.

Schulz MW, Chen J, Woo HH, et al. A comparison of techniques for eliciting patient preferences in patients with benign prostatic hyperplasia. *J Urol.* 168:155-159, 2002.

Siddiqui F, Pajak TF, Watkins-Bruner D et al. Pretreatment quality of life predicts for locoregional control in head and neck cancer patients: a radiation therapy oncology group analysis. *Int J Radiat Oncol Biol Phys*. 70(2): 353-60, 2008.

Spiro RH: Salivary neoplasms: Overview of a 35-year experience with 2,807 patients. *Head Neck Surg*. 8:177-184, 1986.

Spiro RH, Armstrong J, Harrison L, et al. Carcinoma of major salivary glands. recent trends. *Arch Otolaryngol Head Neck Surg*. 115: 316-321, 1989.

Spiro RH. Management of malignant tumors of the salivary glands. *Oncology*. (Williston Park) 12:671-80; discussion 683, 1998.

Tanvetyanon T, Qin D, Padhya T, et al. Outcomes of postoperative concurrent chemoradiotherapy for locally advanced major salivary gland carcinoma. *Arch Otolaryngol Head Neck Surg*. 135: 687-692, 2009.

Terhaard CH, Lubsen H, Van der Tweel I, et al. Salivary gland carcinoma: Independent prognostic factors for locoregional control, distant metastases, and overall survival: Results of the dutch head and neck oncology cooperative group. *Head Neck.* 26: 681-92; discussion 692-3, 2004.

Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: Results of a nonrandomized prospective study using a standardized follow-up program. *Int J Radiat Oncol Biol Phys*. 74(1):1-8, 2009. Epub 2008 Dec 26.

Vermorken JB, Verweij J, de Mulder PH, et al. Epirubicin in patients with advanced or recurrent adenoid cystic carcinoma of the head and neck: A phase II study of the EORTC head and neck cancer cooperative group. *Ann Oncol*. 4:785-788, 1993.

Weymuller EA, Yueh B, Deleyiannis FW, et al. Quality of life in patients with head and neck cancer: Lessons learned from 549 prospectively evaluated patients. *Arch Otolaryngol Head Neck Surg*. 126(3): 329-35; discussion 335-6, 2000.

Wu AW, Jacobson KL, Frick KD, et al. Validity and responsiveness of the EuroQol as a measure of health related quality of life in people enrolled in an AIDS clinical trial. *Qual Life Res.* 11: 273-282, 2002.

Wu MC, Bailey K. Analyzing changes in the presence of informative right censoring caused by death and withdrawal. *Stat Med*. 7:337-46, 1988.

APPENDIX I

RTOG 1008

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

Informed Consent Template for Cancer Treatment Trials
(English Language)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have cancer of the salivary gland that is at high risk to come back after surgery.

Why is this study being done?

The standard treatment for cancer of the salivary gland is surgery, and all patients will have had surgery before taking part in this study. Although the surgery may have removed your cancer, features of your disease suggest that you are at an increased risk for your cancer to return.

In patients at risk for disease recurrence after surgery, radiation therapy to the head and neck is frequently recommended after surgery. The purpose of this study is to test whether the use of chemotherapy with radiation will improve the results after surgery and radiation alone.

The study will compare the effects, good and/or bad, of radiation and chemotherapy with radiation alone on you and your salivary gland cancer to find out which is better at reducing the chance that your cancer will come back.

How many people will take part in the study?

About 120 people will take part in this study.

What will happen if I take part in this research study? (10/26/11)

If you agree to participate in this study, your study doctor will send some of your tumor tissue (obtained when you had surgery) to a central office to confirm your type of tumor. This tissue submission for testing is required for this study.

Eligible participants will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in Group 1 (often called "Arm 1"), you will receive radiation therapy once a day, Monday through Friday for about 6 to 7 weeks. Each treatment may take up to 30 minutes depending on the technique used. You will also receive a chemotherapy drug, cisplatin, through the vein, every week (before or after radiation), and you will receive a total of 7 treatments. The chemotherapy will take about 4 hours, including administration of medications to prevent nausea and to replace body fluids.

If you are in Group 2 (often called "Arm 2"), you will receive radiation therapy once a day, Monday through Friday for about 6 to 7 weeks. Each treatment may take up to 30 minutes depending on the technique used.

Before you begin the study: You will have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical examination by several doctors
- A chest CT (Computed Tomography) scan, a study using x-rays to look at one part of your body or a whole body CT/PET (Positron Emission Tomography) scan; A PET scan is a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer's signal as it travels through your body.
- Evaluation of your ability to carry out daily activities
- Blood tests (about 2 teaspoons of blood will be taken from your vein)
- For women able to have children, a pregnancy test
- A dental evaluation before receiving radiation
- For Group 1 patients: A hearing test
- If your study doctor recommends: An evaluation of your diet and your ability to chew and swallow

(5/4/11) During the study: If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care and will be performed weekly during radiation therapy.

- If you are in Group 1, blood tests (about 2 teaspoons of blood will be taken from your vein)
- For Groups 1 and 2, evaluation of any side effects from treatment you may be having

(9/19/12) When you have finished radiation therapy: You will need the following tests and procedures. These are done to see how you and your cancer was affected by the treatment you received.

At the end of treatment:

- A physical examination
- Evaluation of your ability to carry out daily activities
- Evaluation of any side effects from treatment you may be having

At 3 months from the end of treatment and at 6, 9, 12, 18, and 24 months from the start of treatment:

- A physical examination
- Evaluation of your ability to carry out daily activities
- Blood tests (about 2 teaspoons of blood will be taken from your vein)
- Evaluation of any side effects from treatment you may be having

At 3 months from the end of treatment and at 9, 12, and 24 months from the start of treatment, then as your doctor recommends: A CT scan of the neck or an MRI to monitor for any recurrence of the cancer

At 6 and 24 months from the start of treatment, then yearly: A chest x-ray

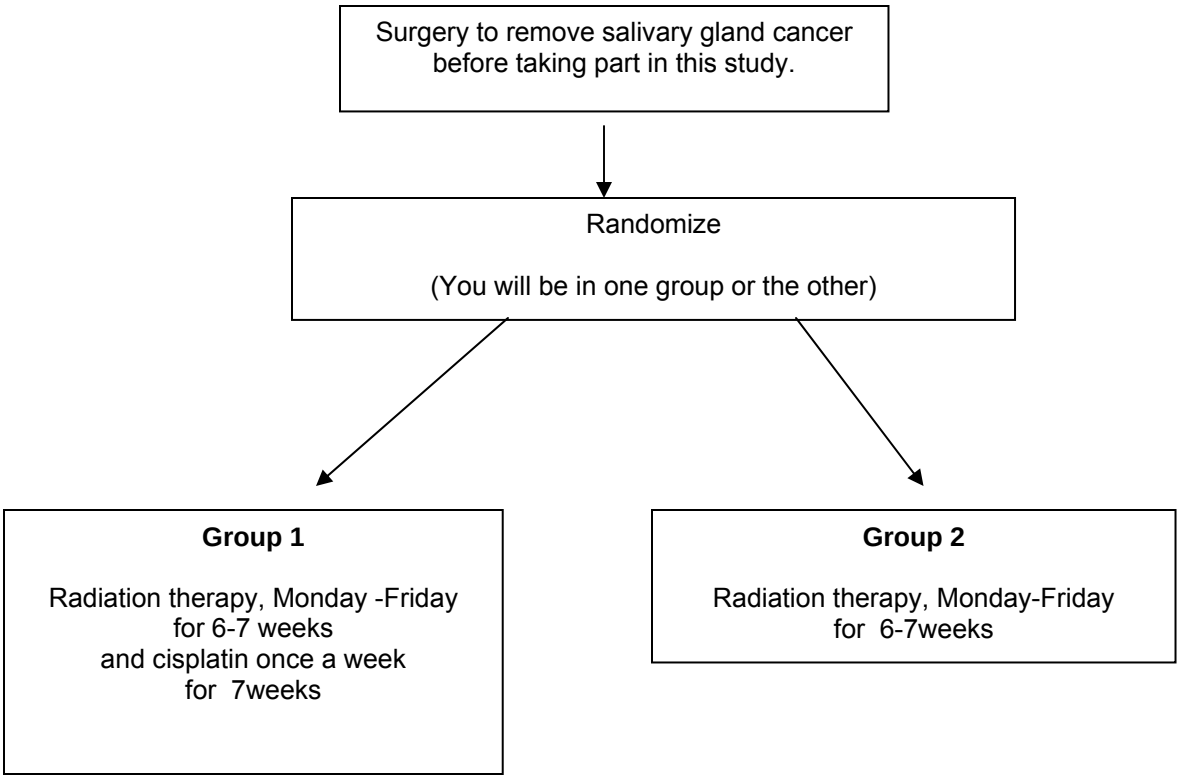
At 12 months from the start of treatment: A CT scan of your chest

Twice a year during years 3-4: Evaluation of your ability to carry out daily activities

If your doctor recommends: Blood tests (about 2 teaspoons of blood will be taken from your vein) when you are seen in follow-up visits every 6 months for years 3-4, then yearly

Study Plan (5/4/11)

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study? (5/4/11)

You will receive radiation therapy with or without chemotherapy for 6 to 7 weeks. You will be seen in a follow-up visit at 3 months following radiation therapy. Then you will be seen at 6, 9, 12, 18, and 24 months from the start of radiation for years 1 and 2, every 6 months for years 3 and 4, and then yearly for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the radiation and chemotherapy, if you receive chemotherapy, can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop radiation and chemotherapy, if you receive chemotherapy. In some cases, side effects can be serious, long lasting, or may never go away. As in any treatment with side effects, there also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

(5/4/11) Risks and side effects related to radiation therapy include those which are:

Likely
- Sores in the mouth and or throat that can be painful and make it difficult to chew or swallow food
- Mouth dryness and changes in your ability to taste food that may be permanent
- Thick saliva
- Hoarseness
- Tanning or redness and irritation of the skin exposed to radiation
- Ear pain or pressure
- Tiredness
- Weight loss
- Permanent loss of hair in skin areas exposed to radiation
- Loss of teeth or cavities in the teeth if strict dental care is not followed

Less Likely, but serious
- Decrease in the function of the thyroid gland, which may require pills for thyroid replacement
- Serious ear infections or hearing loss
- Breathing problems
- Difficulty with swallowing food that may require placement of a long term or permanent feeding tube and the possibility of inhaling food or liquids into the lungs, which may result in pneumonia
- Temporary pain or scarring around nerves in the shoulder that can cause numbness or weakness

Rare, but serious
- Serious damage to the spinal cord, nerves in the neck, jawbone, voice box, skin, or other parts of the head and neck that may require surgery to correct
- Damage to the spinal cord leading to permanent weakness

Sores in the mouth and painful swallowing are the most common side effects experienced by patients who receive radiation therapy for cancers of the head and neck. Before starting treatment, your doctor may recommend that your diet and your ability to chew and swallow be evaluated and ways of maintaining your nutrition be discussed with you. If sores in your mouth and/or painful swallowing become severe during treatment, your doctor may recommend a feeding tube, which will be inserted through your nose or through a small cut in the skin of your abdomen. This feeding tube will help you receive nutrition and fluids during treatment and is not meant to be permanent. The feeding tube will prevent excessive weight loss and dehydration. Most patients who have feeding tubes placed during treatment have them removed once they recover from side effects in the weeks to months after radiation is completed. It is uncommon for patients to permanently require feeding tubes after treatment.

Risks and side effects related to cisplatin (Group 1 patients)

Very likely:
- Decrease in white blood cells, which can lead to an increased risk for infection
- Decrease in red blood cells (anemia), which could lead to weakness, fatigue, or shortness of breath
- Loss of appetite and taste and/or a metallic taste in your mouth
- Nausea and vomiting

- Tiredness
- Generalized loss of strength
- Hearing loss or ringing in the ears
- Loss of muscle or nerve function that can cause weakness or numbness in your hands and feet
- Weight loss
- Temporary decrease in kidney function, which could lead to changing the dose of your chemotherapy
- Low potassium in the blood which could result in muscle weakness, cramping, muscle limpness, and/or irregular heartbeat

Less likely
- Allergic reactions
- Muscle cramps or spasm
- Facial swelling
- Restlessness
- Loss of hair
- Low blood pressure

Rare but serious
- Seizures
- Kidney damage, which may be permanent
- A severe drop in the blood potassium levels that may affect heart function

Reproductive risks: You should not become pregnant or father a baby while on this study because the radiation treatment and/or cisplatin in this study can affect an unborn baby. Women who are able to have children will have a pregnancy test before beginning treatment. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope that the combination of radiation and cisplatin or radiation treatment alone will help stop your cancer from growing back or occurring again after surgery, there is no proof of this yet. We do know that the information from this study will help researchers learn more about salivary gland cancer and treatment after surgery. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:
- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no further treatment

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private? (10/26/11)

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Monitoring Committee will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to taking part in this additional research.

You can say "yes" or "no" to each of the following studies. Below, please mark your choice for each study.

Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This "quality of life" study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete 5 questionnaires at the following times: before starting treatment, 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. It takes about 5 to 10 minutes to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the 5 questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the Quality of Life Questionnaires.

YES NO

Consent Form for Use of Tissue and Blood for Research (10/26/11)

About Using Tissue and Blood for Research

You have had surgery to remove your cancer. Your doctor has removed some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. In addition to the tumor tissue, we would like to collect 2 teaspoons of your blood before treatment, at week 4 of radiation therapy, and at 3 months after the completion of radiation. Blood for research will be collected at the same time your blood is collected for other tests required in the main part of this study.

If you agree, your tissue and blood will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How Is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm.

Your tissue and blood may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue and blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue or blood. Then any tissue or blood that remains will no longer be used for research and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the doctor/institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue or blood is used for genetic research (about diseases that are passed on in families). Even if your tissue and blood is used for this kind of research, the results will not be put in your health records.

Your tissue or blood will be used only for research and will not be sold. The research done with your tissue and blood may help develop new treatments for cancer and other diseases in the future, and this may help other patients.

Benefits

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at _____ [IRB's phone number].

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

3. Someone may contact me in the future to ask me to take part in more research.
   ☐Yes ☐ No

Where can I get more information? (2/27/12)

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://www.cancer.gov/cancertopics/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II (9/19/12)

STUDY PARAMETER TABLE: *SEE SECTION 11. 1 FOR DETAILS

Assessments	Pre-Treatment			During Treatment		Follow Up			Long-Term Follow Up
	Within 12 wks prior to registration	Within 8 wks prior to registration	Within 4 wks prior to registration	Weekly	At end of RT	3 mos. post completion of RT	6, 9, 12 & 18 mos. from start of RT	24 mos. from start of RT	q6 mos. for years 3-4, then annually
History/Physical		X			X	X	X	X	X
Tissue submission for central review	Within 2 weeks of study entry								
Chest x-ray							At 6 mos.	X	Annually
Chest CT	X (or PET/CT)*						At 12 mos.		
Tumor evaluation (CT of neck or MRI)*						X*	X*	X*	At physician's discretion
Performance Status	Pre-treatment				X	X	X	X	X
CBC with diff			X	For Arm 1		X	X	X	At physician's discretion
Serum creatinine			X	For Arm 1		X	X	X	At physician's discretion
Total bilirubin; AST or ALT			X			X			At physician's discretion
Serum pregnancy test			Within 2 wks prior to registration						
Medical Onc. exam			X						
Surgical Eval			Within 6 wks prior to tx						
Dental eval	Within 8 weeks prior to treatment								
Audiogram	Within 8 weeks prior to treatment for Arm 1 patients only								
Nutrition eval	Recommended: Within 8 wks prior to tx								
Adverse event eval				X	X	X	X	X	X
QOL/PROs: FACT-H&N; PSS-HN; PROMIS; XeQOLS; EQ-5D	Pre-treatment				X	X	At 12 mos. only	X	
Tissue/ blood, for research-if patient consents	Pre-treatment			Week 4: blood		Blood			

APPENDIX III

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 IV (2/27/22)

AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

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

Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0 or T1-3, N1 M0
Stage IVA	T4a N0-N1 M0 or T1-T4a N2 M0
Stage IVB	T4b any N M0 or any T, N3 M0
Stage IVC	any T, any N M1

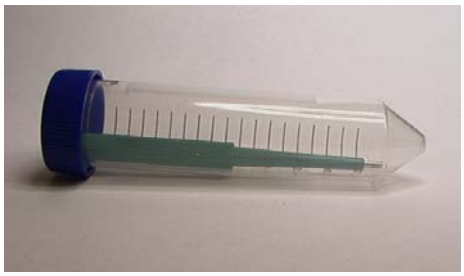
APPENDIX V (10/26/11)
RTOG FFPE SPECIMEN PLUG KIT/INSTRUCTIONS

This kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. 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. DO NOT remove specimen from the punch.

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



Step 3
Once punch tool is labeled, place in shipping tube, and mail to address below. Please do not mix specimens in the same tube.

The Biospecimen Resource will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

*NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and the Resource 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 specimen plug kit, specimen in punch tool, and all paperwork as follows:

US Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
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
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

APPENDIX VI (10/26/11)
RTOG BLOOD COLLECTION KIT/INSTRUCTIONS

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

This kit contains:

- One Red Top tube for serum
- One Purple Top EDTA tube for plasma
- One Purple Top EDTA tube for Whole Blood
- Twenty (20) 1 ml cryovials
- Biohazard bags (3)
- Absorbent shipping material (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form
- Instructions

Serum (if requested): Red Top Tube

- ❑ Label as many 1ml cryovials (up to 10) as serum collected. Label them with the RTOG study and case number, collection date and time, 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 STF.
3. Aliquot 0.5 ml serum into as many cryovials as serum collected (up to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

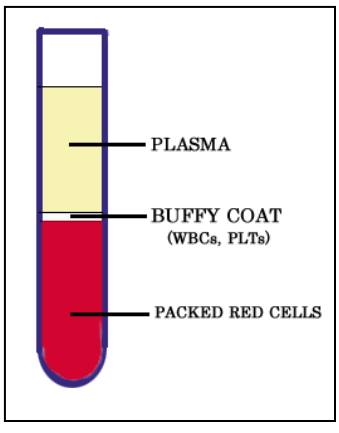
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma (If requested): Purple Top EDTA tube #1

- ❑ Using four (4) or more 1 ml cryovials, label them with the RTOG 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 STF.
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 0.5 ml plasma into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected 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 four (4) or more 1 ml cryovials, label them with the RTOG 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 as many cryovials labeled "blood" as possible. 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° 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 -80C 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 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 RTOG 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 RTOG@ucsf.edu or call (415)476-7864.

Ship specimens and all paper work as follows:

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