



NRG ONCOLOGY

RTOG 1008

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

**SCHEMA (11SEP2017)**

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

**Note:** IMRT, IMPT 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](mailto:adelstd@ccf.org)) or Dr. El-Naggar ([anaggar@mdanderson.org](mailto:anaggar@mdanderson.org)) to expedite such a review.

**Patient Population:** (See [Section 3.0](#) for Eligibility) **(2/27/12)**

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

**Required Sample Size: Phase II: 120; Phase III: 252 (includes 120 patients from phase II)**

### 3.0 PATIENT SELECTION (4/22/14)

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

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

**3.1.1** Pathologically proven diagnosis of a malignant major salivary gland tumor or malignant minor salivary gland tumor of the head and neck of the following histologic subtypes:

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

Pathologic interpretation of salivary gland malignancies can be very difficult. Patients with diagnoses such as "undifferentiated or poorly differentiated carcinoma", "carcinoma-ex pleomorphic adenoma", "carcinoma NOS" and others should be considered for this trial. A rapid, anonymous photomicrograph review can be obtained from Dr. El-Naggar to assist in identifying appropriate patients for this trial. Institutions are urged to contact either Dr. Adelstein ([adelstd@ccf.org](mailto:adelstd@ccf.org)) or Dr. El-Naggar ([anaggar@mdanderson.org](mailto: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 ( $\leq 1$ mm) or microscopically positive surgical margin (AJCC, 7<sup>th</sup> ed.; see Appendix IV); patients must be free of distant metastases based upon the following minimum diagnostic workup:

- History/physical examination within 8 weeks prior to registration;
- Radiologic confirmation of the absence of hematogenous metastasis within 12 weeks prior to registration; at a minimum, contrast CT imaging of the chest is required; PET/CT is acceptable.

**3.1.4** Zubrod Performance Status 0-1;

**3.1.5** Age  $\geq 18$ ;

**3.1.6** CBC/differential obtained within 8 weeks prior to registration, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC)  $\geq 1,800$  cells/mm<sup>3</sup>;
- Platelets  $\geq 100,000$  cells/mm<sup>3</sup>;
- Hemoglobin  $\geq 8.0$  g/dl (Note: The use of transfusion or other intervention to achieve Hgb  $\geq 8.0$  g/dl is acceptable.)

**3.1.7** Adequate renal and hepatic function within 8 weeks prior to registration;, defined as follows:

- Serum creatinine  $< 2.0$  mg/dl;
- Total bilirubin  $< 2$  x the institutional ULN;
- AST or ALT  $< 3$  x the institutional ULN.

**3.1.8** Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential;

**3.1.9** Women of childbearing potential and male participants who are sexually active must practice adequate contraception during treatment and for 6 weeks following treatment.

**3.1.10** All patients must have a Medical Oncology evaluation within 4 weeks prior to registration;

**3.1.11** Patients must be deemed able to comply with the treatment plan and follow-up schedule.

- 3.1.12** Patients must provide study specific informed consent prior to study entry, including consent for mandatory tissue submission for central review.
- 3.2 Conditions for Patient Ineligibility (2/27/12)**
- 3.2.1** Patients with residual macroscopic disease after surgery;
- 3.2.2** Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
- 3.2.3** Prior systemic chemotherapy or radiation therapy for salivary gland malignancy; note that prior chemotherapy for a different cancer is allowable;
- 3.2.4** Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
- 3.2.5** Severe, active co-morbidity, defined as follows:
- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
  - Transmural myocardial infarction within the last 6 months;
  - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
  - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
  - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; Note, however, coagulation parameters are not required for entry into this protocol.
  - Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; Note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
  - Pre-existing  $\geq$  grade 2 neuropathy;
  - Prior organ transplant.
- 3.2.6** Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic;
- 3.2.7** Significant pre-existing hearing loss, as defined by the patient or treating physician.