RADIATION THERAPY ONCOLOGY GROUP

RTOG 0225

A PHASE II STUDY OF INTENSITY MODULATED RADIATION THERAPY (IMRT) +/- CHEMOTHERAPY FOR NASOPHARYNGEAL CANCER

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SCHEMA

Treatment Plan:
Planning target volumes (PTVs) of the primary tumor, lymph node metastases, lymph nodes at risk of metastatic disease, critical organs and the major salivary glands will be outlined on planning CT scans. IMRT technique will be utilized. Gross disease PTV dose will be 70 Gy / 33 fractions and subclinical PTV dose, 59.4 Gy / 33 fractions. The major salivary glands will be spared according to specified criteria (see Section 6.4.5). Saliva output will be measured before and following therapy.

Chemotherapy:
Stage ≥ T2b and/or node positive patients will receive chemotherapy concurrent with IMRT and adjuvant following IMRT

Concurrent with IMRT:
Cisplatin 100 mg/m^2 I.V. on days 1, 22, and 43

Adjuvant following IMRT:
R 5-FU 1,000 mg/m^2 per 24 hours as a 96 hour continuous infusion on days 71-74, 99-102, and 127-130
Cisplatin 80 mg/m^2 I.V. on days 71, 99, and 127

NOTE: Prophylactic use of amifostine and pilocarpine is not allowed (see Sections 3.2.9 and 9.0)

Eligibility: (See Section 3.0 for details) [7/6/04]
- Confirmed histopathologic diagnosis of nasopharyngeal squamous cell carcinoma, types WHO I-III, Stage I-IVB, requiring primary irradiation
- No head and neck surgery of the primary tumor or lymph nodes except for incisional or excisional biopsies
- ≥ 18 years of age
- Zubrod performance status 0-1
- WBC ≥ 4,000/µl, platelets ≥ 100,000/µl; serum creatinine ≤ 1.6 mg/dl or 24 hr. calculated creatinine clearance ≥ 60 ml/min (see Section 3.1.6)
- Must undergo pre-treatment evaluation of tumor extent and tumor measurement
- Nutritional and general physical condition must be considered compatible with the proposed radio-therapeutic treatment
- No prior radiotherapy to the head and neck or any prior chemotherapy ≤ 6 months prior to study entry
- No other malignancy except non-melanoma skin cancer or a carcinoma not of head and neck origin ≤ 5 years
- No evidence of distant metastasis
- Not on any other experimental therapeutic cancer treatment
- No active untreated infection
- No major medical or psychiatric illness
- No pregnant women if node positive or Stage ≥ T2b
- Signed study-specific consent form prior to study entry

Required Sample Size: 64
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the primary tumor site arising from the nasopharynx?</td>
<td>Y</td>
</tr>
<tr>
<td>2. Is the confirmed histology squamous cell cancer?</td>
<td>Y</td>
</tr>
<tr>
<td>3. What is the biopsy proven stage?</td>
<td>I-IVB</td>
</tr>
<tr>
<td>4. Was there surgery on the primary tumor or lymph nodes?</td>
<td>Y</td>
</tr>
<tr>
<td>If yes, was surgery limited to incisional or excisional biopsies?</td>
<td>Y</td>
</tr>
<tr>
<td>5. Is the patient $\geq$ 18 years of age?</td>
<td>Y</td>
</tr>
<tr>
<td>6. What is the Zubrod performance status?</td>
<td></td>
</tr>
<tr>
<td>7. Has the patient undergone pretreatment evaluation of tumor for extent and measurement?</td>
<td>Y</td>
</tr>
<tr>
<td>8. Does the patient have any serious medical or psychiatric illness that would preclude informed consent?</td>
<td>N</td>
</tr>
<tr>
<td>9. Is the patient on any other therapeutic treatment for head and neck cancer?</td>
<td>N</td>
</tr>
<tr>
<td>10. Is there evidence of distant metastases?</td>
<td>N</td>
</tr>
<tr>
<td>11. Did the patient have any previous irradiation for head and neck cancer $\leq$ 6 months prior to study entry?</td>
<td>Y</td>
</tr>
<tr>
<td>12. Is there planned concurrent chemotherapy? (except patients with node positive and/or Stage $\geq$ T2b)?</td>
<td>Y</td>
</tr>
<tr>
<td>13. If node positive or Stage $\geq$ T2b, will the patient receive chemotherapy as per Section 7.0 of the protocol?</td>
<td>N</td>
</tr>
<tr>
<td>14. Has the patient received chemotherapy for any reason $\leq$ 6 months prior to study entry?</td>
<td>Y</td>
</tr>
<tr>
<td>15. Any prior malignancy (other than non-melanomatous skin cancer)?</td>
<td>N</td>
</tr>
<tr>
<td>If yes, has the patient been continuously disease-free for $\geq$ 5 years?</td>
<td></td>
</tr>
<tr>
<td>16. Does the patient have an active, untreated infection?</td>
<td>N</td>
</tr>
<tr>
<td>17. Has the patient taken amifostine or pilocarpine prophylactically?</td>
<td>N</td>
</tr>
<tr>
<td>18. Have all pretreatment studies in Section 4.0 been obtained in the time frame indicated?</td>
<td>Y</td>
</tr>
<tr>
<td>19. Is the WBC $\geq$ 4,000/mm$^3$?</td>
<td>Y</td>
</tr>
<tr>
<td>20. Is the platelet count $\geq$ 100,00/mm$^3$?</td>
<td>Y</td>
</tr>
</tbody>
</table>
21. Is the serum creatinine \( \leq 1.6 \) mg/dl or 24 hour or calculated creatinine clearance \( \geq 60 \) ml/min? (see Section 3.1.6)

22. Is your institution pre-approved for IMRT studies by the Image-Guided Therapy Center (ITC) and the Radiological Physics Center?

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
3. Is the patient eligible for this study?
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Initials
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Ethnic Category (Hispanic or Latino, Not Hispanic or Latino, Unknown)
11. Gender
12. Patient’s Country of Residence
13. Zip Code
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a VA or military hospital?
16. Medical Oncologist
17. Treatment Start Date
18. Is patient Stage \( \geq T2b \) and/or node positive?

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 BACKGROUND

1.1 Treatment of Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is common among Asians, especially the Southern Chinese, but it is rarely seen among the Caucasian population, representing < 1% of all cancers in the United States.1 The standard treatment for nasopharyngeal carcinoma is definitive radiotherapy +/- chemotherapy where chemotherapy is reserved for more advanced lesions.2-3 The local control rate for T1 and T2 tumors ranges from 64-95%; however, the control rate drops to 44-68% in more advanced T3/T4 lesions. Five-year survival is reported between 36-58%.4-10

Tumor control for carcinoma of the nasopharynx is highly correlated with the dose delivered to the tumor.11-12 In a series of 107 patients with nasopharyngeal carcinoma, local control was significantly improved when > 67 Gy was delivered to the tumor target. In another series of 118 patients, the improvement of tumor control was not only attributed to the prescription of higher doses of radiation, but also to improvements in technical accuracy. Because the nasopharynx is surrounded by many normal critical structures, it is absolutely crucial that accuracy in dose delivery is taken into account in any dose escalation studies.

1.2 Intensity Modulated Radiation Therapy

Intensity modulated radiation therapy (IMRT), a type of 3D conformal radiotherapy, has gained its popularity in the treatment of head and neck cancers. With this technique, radiation beams can be modulated such that a high dose can be delivered to the tumor while significantly reducing the dose to the surrounding normal tissue.13-16 Xia et al. compared IMRT treatment plans with conventional treatment plans for a case of locally advanced nasopharyngeal carcinoma. They concluded that IMRT provided improved tumor target coverage with significantly more sparing of sensitive normal tissue structures in the treatment of locally advanced nasopharyngeal carcinoma.17 Two recent papers also substantiated this finding. The authors stated that because there was a lack of a major benefit with conventional 3D planning used only during the boost phase of treatment for nasopharyngeal carcinoma, they are currently using IMRT to deliver the entire course of radiation at their institution.18-19

At the University of California-San Francisco Medical Center, IMRT has been used for the treatment of nasopharyngeal carcinoma. Preliminary clinical experience using IMRT for nasopharyngeal carcinoma with a median follow-up of 31 months showed the local progression-free rate of 97% and the regional progression-free rate of 98% with a four year overall survival rate of 88%.20 Although the results from this single institution are very promising, the use of IMRT for nasopharyngeal carcinoma needs to be tested in a multi-institutional setting.

1.3 Toxicity From the Treatment of Nasopharyngeal Carcinoma

One of the major complaints from patients who undergo conventional external beam radiation therapy to the nasopharynx is xerostomia because standard radiation delivers a high dose to the major salivary glands bilaterally. Salivary flows are markedly reduced following 10-15 Gy of radiation delivered to most of the gland.21,22 The recovery of the salivary function is possible over time even with doses up to 40-50 Gy. However, higher doses to most of the gland will result in irreversible and permanent xerostomia. The degree of xerostomia is largely dependent on the radiation dose and the volume of the salivary gland that is in the radiation field. As a result, patients’ quality of life is compromised as they experience changes in speech and taste. The oral dryness also predisposes the patients to fissures, ulcers, dental caries, infection, and even in worst cases, osteoradionecrosis.23-26 Thus, IMRT has the potential to reduce the dose to the salivary glands while simultaneously delivering a high dose to the tumor target.

In addition, although the intergroup trial using combination chemoradiation followed by adjuvant chemotherapy for the treatment of advanced nasopharyngeal carcinoma demonstrated an improvement in local control and survival, about 1/3 of the patients did not complete the prescribed therapy due to toxicity. Therefore, IMRT may also decrease the toxicities associated with radiation therapy and therefore improve patient compliance to therapy.
1.4 Delineation of Target Volumes
Probably one of the most important issues concerning IMRT is the accurate definition of target volumes. The precise delineation of these volumes, especially the subclinical volumes, is crucial in treatment planning. When compared to standard techniques, the very tight and conformal isodose curves around the outlined target volumes in IMRT increase the risk of missing areas containing subclinical disease when the volumes are not accurately drawn. As a result, there is an increased risk of marginal or out-of-field recurrence. Since there is a significant variation among physicians regarding the definitions of head and neck nodal volumes, efforts to define accurately the location of lymph nodes in the head and neck, using cadaver CT scans, have been described. Although the limited single institution’s results of using IMRT for the treatment of nasopharyngeal carcinoma is very promising, this needs to be verified in a multi-institutional setting.

1.5 Rationale of This Phase II Study
The primary purpose of this study is to test the feasibility of delivering IMRT in a multi-institutional setting for the treatment of nasopharyngeal carcinoma. The rationale is that a potential reduction in radiation side effects using IMRT will increase patient compliance to combined therapy without compromising local-regional control.

2.0 OBJECTIVES
2.1 To determine the transportability of IMRT to a multi-institutional setting.
2.2 To estimate the rate of late xerostomia (defined as one year) associated with this regimen. (see Section 11.2.2)
2.3 To test the hypothesis that a potential reduction of radiation side effects on salivary flow using IMRT will increase patient compliance to combined therapy without compromising local-regional control.
2.4 To estimate the rates of local-regional control, distant metastasis, disease-free and overall survival.
2.5 To assess other acute and late toxicities of this regimen.
2.6 To evaluate chemotherapy compliance with this regimen.

3.0 PATIENT SELECTION
3.1 Eligibility Criteria
3.1.1 Biopsy proven stage I-IVB, (AJCC Staging, 1997, 5th edition) non-metastatic, squamous cell carcinoma of the nasopharynx, types WHO I-III, treated with primary RT. Patients with Stage ≥ T2b and/or node positive patients will receive concurrent chemotherapy followed by adjuvant chemotherapy.
3.1.2 No head and neck surgery of the primary tumor or lymph nodes except for incisional or excisional biopsies.
3.1.3 ≥ 18 years of age
3.1.4 Zubrod performance status 0-1.
3.1.5 All patients must undergo pre-treatment evaluation of tumor extent and tumor measurement. Tumor may be measurable or evaluable.
3.1.6 Nutritional and general physical condition must be considered compatible with the proposed radio-therapeutic treatment.
3.1.7 Patients must have a WBC ≥ 4,000/µl and a platelet count of ≥100,000/µl; patients must have adequate renal function as documented by a serum creatinine of ≤ 1.6 mg/dl or 24 hour or calculated creatinine clearance ≥ 60 ml/min using the following formula:

Estimated Creatinine Clearance = \((140-\text{age}) \times \text{WT(kg)} \times 0.85\) if female
72 \times \text{creatinine (mg/dl)}

3.1.8 Signed study-specific informed consent prior to study entry.

3.2 Ineligibility Criteria
3.2.1 Stage IVC.
3.2.2 Evidence of distant metastases.
3.2.3 Previous irradiation for head and neck tumor ≤ 6 months prior to study entry.
3.2.4 No prior chemotherapy ≤ 6 months prior to study entry.
3.2.5 Patient is on other experimental therapeutic cancer treatment.
3.2.6 Other malignancy except non-melanoma skin cancer or a carcinoma not of head and neck origin and controlled at least 5 years.
3.2.7 Active untreated infection.
3.2.8 Major medical or psychiatric illness, which in the investigators’ opinions, would interfere with either the completion of therapy and follow-up or with full and complete understanding of the risks and potential complications of the therapy.
3.2.9 Prophylactic use of amifostine or pilocarpine is not allowed.
3.2.10 Pregnant women who are node positive or Stage ≥ T2b because of the embryotoxic effects of chemotherapy.

4.0 PRETREATMENT EVALUATIONS (5/26/05)
Each patient must have completed the following studies within six weeks prior to study entry unless otherwise indicated.
4.1 Complete history and physical exam including weight and performance status.
4.2 Complete diagrammatic and descriptive documentation of the extent of the primary and regional disease (if any) following appropriate endoscopic procedures.
4.3 Complete dental and nutritional evaluation. Any required dental repairs must be made and prophylaxis instituted prior to radiotherapy.
4.4 Completion of the following laboratory studies within 14 days of study entry: CBC and platelet count (WBC differential should be obtained if patient is to receive chemotherapy); serum creatinine, creatinine clearance, BUN; serum pregnancy test for women of childbearing potential who will be receiving chemotherapy.
4.5 Completion of the following radiologic studies within 6 weeks prior to study entry:
  ▪ Chest X-ray;
  ▪ An MRI of head and neck with T1 contrast with gadolinium and T2 sequences is required. If an MRI is medically contraindicated (e.g. pacemaker patients), a CT of head and neck with ≤ 3 mm contiguous slices in immobilization system can be substituted (with contrast, unless contraindicated);
  ▪ Liver CT (only in the presence of elevated alkaline phosphatase, AST or bilirubin or other clinical indicator);
  ▪ Bone scan (only in the presence of elevated alkaline phosphatase or other clinical indicator).

NOTE:
  ▪ The use of a PET scan for treatment planning is optional. A PET scan should not be substituted for the required pretreatment and follow-up MRIs of head and neck.
  ▪ A CT scan can be used for treatment planning, but the scan must be within 21 days of start of IMRT. Treatment planning CT scans are not equivalent to diagnostic CT scans, even with contrast. Therefore, if an MRI is medically contraindicated, a diagnostic CT scan of the head and neck should be done and will help to draw volumes on the treatment planning CT.
4.6 Audiogram (if middle or inner ear to be irradiated > 40 Gy).
4.7 Measurement of unstimulated and stimulated whole mouth saliva.
4.8 Objective mucosal assessment; dental evaluation with management according to the guidelines of Daly37 prior to the start of radiation.

5.0 REGISTRATION PROCEDURES (5/26/05)
5.1 Pre-Registration Requirements
The institution must be pre-approved for IMRT studies by the ITC and the Radiological Physics center. See Appendix V.
5.2 Registration
5.2.1 Online Registration
Patients can be registered only after eligibility criteria are met.
Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- The institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event that the RTOG web registration site 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 for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY (CALL DR. LEE FOR QUESTIONS)

6.1 Treatment Planning, Imaging and Localization Requirements

6.1.1 The immobilization device should include neck and shoulder immobilization. A thermoplastic head mask alone may not be sufficient for neck immobilization. Therefore, a thermoplastic head and shoulder mask is strongly recommended for head and neck immobilization. A description of the immobilization system used by each institution and data regarding the range of positioning errors (if data exists) should be provided.

6.1.2 Treatment planning CT scans will be required to define gross target volume, and clinical target volumes. MRI scans (required) aid in delineation of the treatment volume on planning CT scans. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment.

6.1.3 All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 0.3 cm or smaller slices through the region that contains the primary target volumes. The regions above and below the target volume may be scanned with slice thickness 0.5 cm. MRI scans assist in definition of target volumes, especially when targets extend near the base of skull. If possible, the treatment immobilization device should also be used for the MRI scan. If this is not possible, it may be necessary to employ image correlation methods to correlate the MRI and CT scans. Image fusion methods, if available, should be used to help in the delineation of target volumes.

6.1.4 The GTV and CTV (see Section 6.4), and normal tissues must be outlined on all CT slices in which the structures exist.
6.2 **Volume and ICRU Reference Point Definitions**

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

6.2.1 **The Gross Tumor Volume (GTV)** is defined as all known gross disease determined from CT, clinical information, endoscopic findings and MRI which is required in the case of tumors treated after biopsy alone. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center. The gross extent of the tumor should be outlined in conjunction with the neuroradiologist. Whenever possible, fuse the MRI images along with the CT images to more accurately define the gross tumor target.

6.2.2 **The Clinical Target Volume (CTV)** is defined as the GTV plus areas considered to contain potential microscopic disease, delineated by the treating physician. Please refer to section 6.3.1 for details. Three different CTV’s will be defined, namely CTV70 for the gross tumor volume, CTV59.4 for the high risk nodal regions, and CTV50.4 for the low risk nodal regions. Please note that the margin between each GTV and its CTV will have a minimum value of 5 mm except when the clivus is completely infiltrated with GTV and is adjacent to the brain stem. In those situations, the CTV margin can be as small as 1 mm.

6.2.2.1 CTV70 includes the gross tumor volume seen on MRI. CTV59.4 includes the entire nasopharynx, retropharyngeal lymph nodal regions, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus and posterior third of the nasal cavity and maxillary sinuses. Whenever possible, fusion of the diagnostic MRI images and the treatment planning CT images should be performed to accurately delineate the GTV and the surrounding critical normal structures.

6.2.2.2 Regarding lymph nodes, CTV59.4 includes the high risk nodes for all cases, namely:
   a. Upper deep jugular (junctional, parapharyngeal) nodes: bilaterally;
   b. Submandibular lymph nodes: bilaterally;
   c. Subdigastric (jugulodigastric) nodes: bilaterally;
   d. Midjugular: bilaterally;
   e. Low jugular and supraclavicular (level IV): bilaterally;
   f. Posterior cervical nodes (level V): bilaterally;
   g. Retropharyngeal nodes: bilaterally.

6.2.2.3 Examples of the definition of the appropriate nodal groups can be found at the RTOG Image-Guided Therapy Center (ITC) web site at http://itc.wustl.edu.

6.2.3 The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variabilities of treatment set up and internal organ motion. Studies should be implemented by each institution to define the appropriate magnitude of the uncertain components of the PTV. Until the results of that study are available, a minimum of 5 mm around the CTV is required in all directions to define each respective PTV except for situations where the GTV or the CTV is adjacent to the brain stem, where the margin can be as small as 1 mm. Careful consideration should be made when defining the superior and inferior margins in three dimensions.

6.3 **Target and Critical Normal Tissue Definitions (7/6/04)**

6.3.1 **Targets** are defined as primary (requiring higher dose) and secondary (targets at lower risk requiring a lower dose). **Target volumes** are delineated slice by slice on the treatment planning CT images. The gross tumor volume (GTV), also known as CTV70, is defined as the gross extent of the tumor shown by imaging studies and physical examination. This includes the nasopharyngeal primary, retropharyngeal lymphadenopathy and all gross nodal disease. The high risk clinical target volume (CTV) is defined as the GTV plus margin of potential microscopic spread. This is also known as the CTV59.4. It includes the entire nasopharynx, retropharyngeal lymph nodal regions, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus and posterior third of the nasal cavity and maxillary sinuses. The CTV59.4 is a concentric volume that will completely encompass the entire CTV70 in all directions with at least a 5 mm margin except in situations where the GTV is adjacent to a critical normal tissue, i.e., at the clival-brain stem junction. In those cases, there should be at least a one mm margin between the GTV and the brain stem. Please note that in all cases, a recent MRI scan of the nasopharynx to better define the extent of the tumor must be obtained. Whenever possible, fusion of the diagnostic MRI images and the treatment planning CT images should be performed to accurately delineate the GTV and the surrounding critical normal structures.

6.3.2 The lymph node groups at risk (Section 6.2.2.2) will be determined and their volumes (CTVs) will be outlined on the treatment planning CT according to image-based nodal classification.
Alternatively, the surgical neck levels at risk will be determined and will be outlined as CTVs on the planning CT.\textsuperscript{27-9}

A list of the lymph node groups or surgical neck levels outlined for treatment, and the doses prescribed, will be submitted to the ITC. For stage T1-2 N0 patients, the treating physician can elect not to cover level one and/or submandibular lymph nodes.

The ITC will have sample cases of the outlines of the CTVs. Please refer to the ITC web site.

\textbf{6.3.3 Critical Normal Structures}

In addition, surrounding critical normal structures, including the brain stem, spinal cord, optic nerves, chiasm, parotid glands, pituitary, temporo-mandibular (T-M) joints and middle and inner ears and skin, part of tongue, mandible, eyes, lens, brain (temporal lobe will be outlined separately) and glottic larynx should be outlined. The spinal cord contours will be defined at least 5 mm larger in the radial dimension than the spinal cord \textit{(i.e., the cord diameter on any given slice will be 10 mm larger than the cord itself)}. The brain stem and chiasm will be defined as at least 1 mm larger in all directions than the corresponding structure. The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue.

\textbf{6.4 Planning}

\textbf{6.4.1 The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTV (CTV with a 5 mm margin) and critical normal structures. An “inverse” planning using computerized optimization should be used. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of non-involved tissue.}

\textbf{6.4.2 Dose Specifications}

Prescription dose shall be according to the following:

\textbf{6.4.2.1 The gross tumor and lymph node metastasis, PTV\textsubscript{70} (CTV\textsubscript{70} with a 5 mm margin) will receive 70 Gy in 33 fractions at 2.12 Gy per fraction.}

\textbf{6.4.2.2 Primary, subclinical PTV\textsubscript{59.4} (CTV\textsubscript{59.4} with a 5 mm margin - first echelon nodes or dissected neck area containing lymph node metastases) will receive 33 fractions of 1.8 Gy/fraction, total 59.4 Gy.}

\textbf{6.4.2.3 The low neck or supraclavicular field may be treated with conventional AP or AP/PA fields at the discretion of the physician and will receive 28 fractions of 1.8 Gy/fraction, total 50.4 Gy unless there are gross nodes in which all the gross nodes should receive the same dose as the PTV\textsubscript{70}. The midjugular, low jugular, and supraclavicular nodes can be treated either with IMRT or alternatively with an AP field that is beam split to the IMRT fields. This will be at the discretion of the treating physician. If an IMRT approach is not used, then it will not be necessary to submit the DVHs for this PTV. However, if an IMRT approach is used, then it will be necessary to submit DVHs for this PTV.}

If an IMRT approach is used, it is necessary to submit the DVH for his field \textit{(as defined in Section 6.2.2.2, CTV\textsubscript{59.4}}). If a conventional technique (AP or AP/PA field) is used for the low neck and supraclavicular field, it will be treated with 28 fractions of 1.8 Gy/fraction, to a total dose of 50.4 Gy with a depth of 3 cm from the anterior surface for an AP field or midplane for AP/PA fields.

Gross nodes in this field should receive 70 Gy.

Treatment will be delivered once daily, 5 fractions per week, over 6 weeks and 3 days. All targets will be treated simultaneously except for the supraclavicular area that stops after 28 fractions. Breaks in treatment should be minimized. Total treatment times more than 5 days longer will be considered a major violation.

\textbf{6.4.2.4 The reported doses for PTV\textsubscript{70} and PTV\textsubscript{59.4} shall include the prescription dose (Section 6.4.2) as well as the maximum point dose for that PTV, % PTV receiving $\geq 110\%$ and $\geq 115\%$ for that PTV and the PTV receiving $\leq 93\%$ of the prescribed dose for that PTV, and the mean dose for that PTV.}

The prescription dose is the isodose surface that encompasses at least 95\% of the planning target volume (PTV).

- No more than 20\% of any PTV\textsubscript{70} will receive $\geq 110\%$ of the prescribed dose.
- No more than 1% of any PTV\textsubscript{70} and any PTV\textsubscript{59.4} will receive \( \leq 93\% \) of the prescribed dose.
- No more than 1% or 1 cc of the tissue outside the PTVs will receive \( \geq 110\% \) of the dose prescribed to the PTV\textsubscript{70}.

### 6.4.3 Critical Normal Structures

DVH's must be generated for all critical normal structures and the unspecified tissues. Dose constraints to normal tissues will be as follows:

- **Brainstem, optic nerves, chiasm**: 54 Gy or 1% of the PTV cannot exceed 60 Gy
- **Spinal cord**: 45 Gy or 1 cc (if 1% is used, depends on length of the cord outlined) of the PTV cannot exceed 50 Gy
- **Mandible and T-M joint**: 70 Gy or 1 cc of the PTV cannot exceed 75 Gy
- **Temporal lobes**: 60 Gy or 1% of the PTV cannot exceed 65 Gy

Unspecified tissue outside the targets: \( \leq 100\% \) of the dose prescribed to PTV\textsubscript{70}. No more than 5% of the non-target tissue can receive greater than 70 Gy. **Participants are strongly encouraged to remain within these limits.**

### 6.4.4 The method used for tissue heterogeneity calculations shall be reported. The density corrected dose distributions shall be calculated and submitted to the RTOG ITC. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

### 6.4.5 Planning Goals: Salivary Glands and Other Normal Structures

#### 6.4.5.1 Parotid glands:
- Mean dose \( < 26 \text{ Gy} \) (should be achieved in at least one gland) or at least 20 cc of the combined volume of both parotid glands will receive \( < 20 \text{ Gy} \) or at least 50% of the gland will receive \( < 30 \text{ Gy} \) (should be achieved in at least one gland).
- Submandibular/sublingual glands and oral cavity: Reduce the dose as much as possible.

#### 6.4.5.2 Other normal structures:
- **Mean dose less than** 50 Gy
- **Mean dose less than** 35 Gy
- **As low as possible**
- **Mean dose less than** 45 Gy

### 6.4.6 Planning Priorities

Critical normal structure constraints followed by the prescription goals are the most important planning priorities. The priorities in addressing the protocol aims and constraints will be in the following order:

1. Critical Normal Structure Constraints (Section 6.4.3);
2. Dose Specifications (Section 6.4.2);
3. Planning Goals: salivary glands (Section 6.4.5.1);
4. Planning Goals: other normal structures (Section 6.4.5.2).

### 6.5 External Beam Equipment and Beam Delivery Methods

Megavoltage equipment capable of delivering static intensity modulation with a multi-leaf collimator or dynamic intensity modulation (using a multi-leaf collimator or tomotherapy) is required. Other techniques are acceptable as long as dose specifications and constraints are satisfied. The use of three-dimensional conformal radiotherapy (3D-CRT) using forward-planned IMRT treatment planning methods is acceptable. The use of compensators or partial transmission blocks are also acceptable as long as dose specifications and constraints are satisfied.

A conventional anterior low-neck field is allowed. The junction between an IMRT dose distribution and a conventional dose distribution is dependent upon the IMRT technique used and on institutional philosophy. Institutions are required to protect the spinal cord. Dosimetric details regarding the match between this field and the upper neck therapy should be provided.

### 6.6 Treatment Verification

Verification and orthogonal films or images are required. For all forms of IMRT dose delivery, orthogonal films or images that localize the isocenter placement shall be obtained. The length of the treatment field shall be indicated on these films. (See Appendix V)
6.7 **Quality Assurance of Target Volumes and Critical Structure Volumes**

The ITC will facilitate the review of all PTVs and designated critical structures on initial cases submitted by each institution. After an institution has demonstrated compliance with the protocol, future cases will be spot-checked. *(See Appendix V)*

6.8 **Quality Assurance of Field Placement**

6.8.1 **IMRT:** The ITC will review one set of orthogonal *(anterior-posterior and lateral)* prescription images for isocenter *(or IMRT reference point)* localization for each group of concurrently treated beams for the first five cases submitted by each institution. The digital reconstructed radiographs *(DRRs)* from the treatment planning program or, alternatively, a simulation verification radiograph shall be submitted for evaluation except where geometrically impractical. Subsequent cases may be spot checked only.

6.9 **Quality Assurance of Dose Distribution**

6.9.1 The ITC will display, and compare with hard copies, isodose distributions through the planning target volume to verify correct digital submission and conversion.

6.9.2 The ITC will compare the submitted digital dose-volume histograms *(DVHs)* for the PTVs, the designated critical structures, and unspecified tissues with DVHs calculated by the ITC.

6.9.3 Each treatment shall be judged as:

6.9.3.1 **PTV**

1) **No deviation:** the prescription criteria in Section 6.4.2 are fulfilled.
2) **Minor deviation:** the 93% isodose surface covers between 95% to 98% of the PTV, or volumes of overdose exceed those specified in Section 6.4.2 *(115%)* by < 5% of the PTV volume.
3) **Major deviation:** the 93% isodose surface covers < 95% of PTV or > 5% of the PTV receives over 115%.

6.9.3.2 **PTV**

4) **No deviation:** the prescription criteria in Section 6.4.2 are fulfilled.
5) **Minor deviation:** the 93% isodose surface covers between 95% to 98% of the PTV, or volumes of overdose exceed those specified in 6.4.2 by < 5% of the PTV volume.
6) **Major deviation:** the 93% isodose surface covers < 95% of PTV volume.

6.9.3.3 **PTV**

7) **No deviation:** the prescription criteria in Section 6.4.2 are fulfilled.
8) **Minor deviation:** the 93% isodose surface covers between 95% to 98% of the PTV, or volumes of overdose exceed those specified in 6.4.2 by < 5% of the PTV volume.
9) **Major deviation:** the 93% isodose surface covers < 95% of PTV volume.

6.9.3.4 **Parotid Gland Scoring**

1) **No variation:** any of the three criteria specified in section 6.4.5 are met.
2) **Minor variation:** no more than 60% of either parotid gland may receive dose in excess of 30 Gy.
3) **Major deviation:** greater than 60% of each parotid gland receives in excess of 30 Gy.

6.10 **Radiation Therapy Toxicity Adjustments**

6.10.1 **Treatment Interruptions**

Interruptions in radiotherapy may be necessitated by skin reaction, mucositis, ulceration, edema, or other acute complication. The reason for and the length of any such interruption must be documented. If the sum total of such interruptions exceeds five normally-scheduled treatment days, the treatment may be considered in major violation of protocol. Radiation therapy will be continued without interruption if at all possible. Should confluent mucositis, moist desquamation unresponsive to topical dressings, or severe stomatitis resulting in weight loss greater than 15% occur, radiation may be interrupted in order to relieve morbidity. The use of tube feedings in this situation is encouraged; it is anticipated to minimize treatment interruptions.

6.11 **Toxicity Reporting Guidelines (5/26/05)**

6.11.1 For acute radiation effect, through day 90 of treatment, the NCI CTC Version 2.0 will be used.
6.11.2 Late radiation effects will be evaluated and scored per the RTOG Late Effects scale.
6.11.3 See Sections 7.5 and 7.6 for adverse event reporting requirements.
7.0 DRUG THERAPY (CALL DR. KRAMER FOR QUESTIONS)

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

7.1 Cisplatin (Platinol®)

7.1.1 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. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete with only 27 to 45% of the radioactivity excreted in the first five days. The initial fractions of radioactivity are largely unchanged drugs. 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.

7.1.2 Formulation: Cisplatin is available as a dry powder supplied in 10 mg and 50 mg vials.

7.1.3 Preparation: The 10 mg and 50 mg vials should be reconstituted with 10 ml or 50 ml of sterile water for injection USP, respectively. Each ml of the resulting solution will contain 1 mg of cisplatin. Reconstitution as recommended results in a clear colorless solution.

NOTE: Aluminum reacts with cisplatin causing precipitation formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

7.1.4 Storage: The intact vials should be stored under refrigeration. However, once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D51/2NS (precipitate occurs in D5W). Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

7.1.5 Administration: Cisplatin should be given immediately after preparation as a rapid intravenous injection or slow intravenous infusion.

7.1.6 Adverse Effects: Incidence rates of adverse events associated with cisplatin are provided in the product package insert. The following events are expected with the administration of cisplatin:

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

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

7.1.6.3 Hematologic Toxicity: Myelosuppression occurs in 25-30% of patients treated with cisplatin. Nadirs in circulating platelets and leukocytes occur between Days 18 and 23 with most patients recovering by Day 39. Thrombocytopenia, anemia, neutropenia, and fever are also possible adverse events. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

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

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

7.1.6.6 Ocular Toxicity: Optic neuritis, papilledema, and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequency than those recommended in the package insert.

7.1.6.7 Anaphylactic-like Reactions: Anaphylactic-like reactions have occasionally been reported in patients previously exposed to cisplatin. Symptoms include facial edema, wheezing, tachycardia, and hypotension.

7.1.6.8 Hepatotoxicity: Transient elevations in liver enzymes, especially SGOT (AST), and bilirubin, have been reported.
7.1.7 Other Toxicities: Other infrequent toxicities that have been reported include cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, and asthenia. Rare cases of local soft tissue toxicity have occurred.

7.1.8 Supplier: Commercially available.

7.2 5-Fluorouracil

7.2.1 **Mechanism of Action:** Synthesis of 5-fluorouracil was first described by Heidelberger in 1957. 5-FU is considered to act primarily as an inhibitor of thymidylate synthetase.

7.2.2 **Formulation:** 5-FU is commercially available in 500 mg ampules containing 50 mg/cc. It is stable if protected from light. If a precipitate is present, it is to be gently heated to no greater than 140°F in a water bath. In aqueous solution it is colorless to faint yellow, and is pH adjusted with sodium hydroxide to 8.6-9.0.

7.2.3 **Preparation:** An infusion pump should be used to control the infusion flow rate. The volume of diluent is dependent upon the particular type of pump used.

7.2.4 **Storage:** 5-FU should be stored at room temperature and protected from light.

7.2.5 **Administration:** continuous intravenous infusion.

7.2.6 **Adverse Effects:** Toxicities associated with the systemic administration of 5-FU include anorexia, nausea and vomiting, stomatitis, mucositis, phlebitis, diarrhea, myelosuppression, alopecia, rash, photosensitivity, maculopapular eruptions, hyperpigmentation, fingernail changes, neurologic symptoms, cerebellar ataxia *(rare)*, and very occasionally angina with accompanying EKG changes. “Hand and foot syndrome” has been observed in patients receiving continuous infusion 5-FU.

7.2.7 **Supplier:** Commercially available.

7.3 Chemotherapy Dose Schedule for Patients with Stage $\geq$ T2b and/or Node Positive Patients

7.3.1 **Concurrent with radiation therapy:**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
<th>Interval</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>100 mg/m²</td>
<td>I.V.</td>
<td>1, 22, 43</td>
<td>3 weeks (21 days)</td>
<td>Give over 20-30 minutes. See Sections 7.3.1.1-7.3.1.3 for pre and post hydration details</td>
</tr>
</tbody>
</table>

7.3.1.1 *Cisplatin Administration Guidelines:* 
Patients will be pre-hydrated with two liters of 5% D-1/2 NS and 40 mEq KCl/L. This is to be followed by 12.5 gm mannitol immediately before administration of cisplatin.

7.3.1.2 Cisplatin is given over 20-30 minutes followed by 1L of 5% D-1/2 NS and 40 mEq KCl and 25 gm mannitol over four hours, followed by 1L 5% D-1/2 NS and 40 mEq KCl and 8 mEq MgSO₄ over eight hours.

7.3.1.3 Patients should receive at least 3L of fluids over the ensuing 24 hours, either parenterally or orally. The anti-emetic regimen for this combination is to be determined by the local investigator.

7.3.2 **Adjuvant after radiation therapy:**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
<th>Interval</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>80 mg/m²/day</td>
<td>I.V.</td>
<td>71, 99, 127</td>
<td>4 weeks (28 days)</td>
<td>Give over 20-30 minutes. See Sections 7.3.2.1-7.3.2.3 for pre and post hydration details.</td>
</tr>
<tr>
<td>5 FU</td>
<td>1,000 mg/m²</td>
<td>I.V.</td>
<td>71-74, 99-102, 127-130</td>
<td>4 weeks (28 days)</td>
<td>Give in 2000 cc 5% glucose in 1/2 NS per 24 hours as a 96 hour continuous infusion</td>
</tr>
</tbody>
</table>

7.3.2.1 *Cisplatin Administration Guidelines:* 
Patients will be pre-hydrated with two liters of 5% D-1/2 NS and 40 mEq KCl/L. This is to be followed by 12.5 gm mannitol immediately before administration of cisplatin.
7.3.2.2 Cisplatin is given over 20-30 minutes followed by 1L of 5% D-1/2 NS and 40 mEq KCl and 25 gm mannitol over four hours, followed by 1L 5% D-1/2 NS and 40 mEq KC1 and 8 mEq MgSO4 over eight hours.

7.3.2.3 Patients should receive at least 3L of fluids over the ensuing 24 hours, either parenterally or orally. The anti-emetic regimen for this combination is to be determined by the local investigator.

7.3.2.4 5-Fluorouracil Administration Guidelines:
Dose: 5-FU dose = 1,000 mg/m²/24 hr as a 96 hour continuous infusion on days 71, 99, and 127 (4 days) after the second mannitol infusion is completed.

7.4 Dose Reduction Criteria

7.4.1 Patients will be examined and graded for subjective/objective evidence of developing toxicity according to the CTC Version 2.0 each day that chemotherapy is administered and weekly while receiving radiotherapy. Treatment interruptions are allowed if there is symptomatic mucositis or skin reaction that, in the judgment of the clinician, warrants a break. The treatment is completed as per protocol for treatment breaks up to 14 days. If the break exceeds 14 days, the patient will be removed from protocol treatment. The patient will then complete treatment at the discretion of his/her physician but will be followed and included in the analysis.

7.4.2 There will be no dose escalation for concurrent cisplatin or for follow-up therapy with cisplatin and 5-FU.

7.4.3 Chemotherapy dosage modifications are based upon nadir counts and interim non-hematologic toxicities of the preceding cycle for cycles 2-6.

7.4.3.1 Dose Adjustments for Hematologic Toxicity During Concurrent Chemotherapy:

Cisplatin Dose Levels:

<table>
<thead>
<tr>
<th>Level</th>
<th>Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>60 mg/m²</td>
</tr>
<tr>
<td>-1</td>
<td>80 mg/m²</td>
</tr>
<tr>
<td>-</td>
<td>100 mg/m²</td>
</tr>
</tbody>
</table>

Chemotherapy must not be administered until the AGC ≥ 1,500 and platelets are ≥ 100,000. Treatment is based upon the nadir counts as follows:

<table>
<thead>
<tr>
<th>AGC</th>
<th>Platelets</th>
<th>Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,500</td>
<td>≥ 75,000</td>
<td>Full dose</td>
</tr>
<tr>
<td>1,000 – 1,499</td>
<td>50,000 – 74,999</td>
<td>Decrease 1 level</td>
</tr>
<tr>
<td>&lt; 1,000</td>
<td>&lt; 50,000</td>
<td>Hold drug*</td>
</tr>
</tbody>
</table>

* Repeat WBC and platelets until AGC ≥ 1,500 and platelets ≥ 75,000; then decrease by two dose levels. If the patient is at the –1 dose level and the AGC is ≤ 1,500 and/or the platelet count is ≤ 75,000 four weeks following treatment, contact Dr. Kramer.

7.4.3.2 Dose Adjustments for Hematologic Toxicity During Adjuvant Chemotherapy:

Cisplatin Dose Levels:

<table>
<thead>
<tr>
<th>Level</th>
<th>Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>40 mg/m²</td>
</tr>
<tr>
<td>-1</td>
<td>60 mg/m²</td>
</tr>
<tr>
<td>-</td>
<td>80 mg/m²</td>
</tr>
</tbody>
</table>

5-FU Dose Levels:

<table>
<thead>
<tr>
<th>Level</th>
<th>Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>600 mg/m²</td>
</tr>
<tr>
<td>-1</td>
<td>800 mg/m²</td>
</tr>
<tr>
<td>-</td>
<td>1,000 mg/m²</td>
</tr>
</tbody>
</table>

Chemotherapy must not be administered until the AGC ≥ 1,500 and platelets are ≥ 75,000. Treatment is based upon the nadir counts as follows: 
### AGC Platelets Dose Reduction

<table>
<thead>
<tr>
<th>AGC</th>
<th>Platelets</th>
<th>Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,500</td>
<td>≥ 75,000</td>
<td>Full dose of both cisplatin and 5-FU</td>
</tr>
<tr>
<td>1,000 – 1,499</td>
<td>50,000 – 74,999</td>
<td>Decrease 1 level cisplatin; full dose of 5-FU</td>
</tr>
<tr>
<td>&lt; 1,000</td>
<td>&lt; 50,000</td>
<td>Hold cisplatin only* Decrease 1 level 5-FU</td>
</tr>
</tbody>
</table>

* Repeat WBC and platelets until AGC ≥ 1,500 and platelets ≥ 75,000; then decrease cisplatin by two dose levels. If the patient is at the –1 dose level and the AGC is ≤ 1,500 and/or the platelet count is ≤ 75,000 four weeks following treatment, contact Dr. Kramer.

### 7.4.3.3 Dosage Adjustments for Non-Hematologic Toxicity:

#### 7.4.3.3.1 Neutropenic fever
(neutropenic fever is noted after the first or second course of chemotherapy, there should be a 20% reduction of cisplatin and 20% reduction of 5-FU. If neutropenic fever recurs after the initial dose reduction for course #2, the reduction should be 50% for cisplatin and 50% for 5-FU for course #3.

#### 7.4.3.3.2 Gastrointestinal (GI) toxicity
For Grade 2 GI toxicity (other than nausea and vomiting), stomatitis, or skin toxicity, decrease 5-FU at the –1 level (800 mg/m²) for the remaining cycles. For Grade 3 or 4 GI toxicity (other than nausea and vomiting), stomatitis or skin toxicity, hold the 5-FU until recovery and give subsequent doses of 5-FU at the –2 level (600 mg/m²) for the remaining cycles.

#### 7.4.3.3.3 Patients without prior history of angina, who develop angina that appears to be temporarily related to the infusion of 5-FU, must have the drug infusion stopped and the 5-FU permanently discontinued.

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

<table>
<thead>
<tr>
<th>Creatinine</th>
<th>Creatinine Cl ml/min</th>
<th>Dose Reduction of Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>or ≥ 50 cc/min</td>
<td>No change</td>
</tr>
<tr>
<td>&gt; 1.5</td>
<td>and 40-50 cc/min</td>
<td>Decrease 1 level</td>
</tr>
<tr>
<td>&gt; 1.5</td>
<td>and &lt; 40 cc/min</td>
<td>Hold drug*</td>
</tr>
</tbody>
</table>

*Cisplatin must not be administered until creatinine is ≤ 1.5 or creatinine clearance ≥ 60. If creatinine remains > 4 or creatinine clearance remains < 40, the patient must not receive additional cisplatin.

#### 7.4.3.3.5 Neurologic toxicity:
(Refer to NCI CTC version 2.0 for the categories):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>1-2</td>
<td>Hold drug until recovery*, then decrease 1 level. If CNS toxicity recurs, stop drug and continue 5-FU.</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>3</td>
<td>Contact Dr. Kramer before treatment</td>
</tr>
</tbody>
</table>

*Recovery: The patient is once again able to receive chemotherapy according to the treating physician.

#### 7.4.3.6 Ototoxicity: Should patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. Patients with clinically significant hearing loss must not receive additional cisplatin.

#### 7.4.3.7 Dermatitis secondary to 5-FU: For generalized symptomatic macular, papular, or vesicular eruption (grade 3), hold 5-FU until recovery. Resume at 80% of previous dose.
7.5 **Adverse Events (5/26/05)**

This study will utilize the Common Toxicity Criteria CTC version 2.0 for grading adverse events from chemotherapy and other systemic agents prescribed in this protocol. A copy of the CTC version can be downloaded from the CTEP home page ([http://ctep.info.nih.gov](http://ctep.info.nih.gov)). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

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$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.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/members/toxicity/main.html](http://www.rtog.org/members/toxicity/main.html)) for this information.

### 7.5.1 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762 (available 24 hours/day)

**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: Expedited Adverse Event Reporting Requirements. December 2004.]

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 via AdEERS. Use the patient’s case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1). NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting may 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 to RTOG (SAE PHONE: 215-717-2762, available 24 hours/day) within 24 hours of discovery of the event.

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

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE drug experience, 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. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller’s contact information. A Data Manager will return the call the next business day requesting details of the event and also will inform the caller which type of report is required for that study (5 or 10 day AdEERS). The required report must be completed in AdEERS within 5 or 10 calendar days of the initial phone report, as directed by the Data Manager taking the call. SAEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1).

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.
All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTDG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTDG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTDG trial. All forms (and supporting source documentation) submitted to RTDG Headquarters must include the RTDG study/case numbers; non-RTDG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTDG 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 RTDG to the pharmaceutical company/companies supporting the RTDG 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 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)
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTDG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTDG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>
7.6 AdEERS Expedited Reporting Requirements (5/26/05)

Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days\(^1\) of the Last Dose of the Investigational Agents (cisplatin and 5-Fluorouracil) in this Study

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5(^2)</th>
<th>Grades 4 &amp; 5(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected with Hospitalization</td>
<td>Expected with Hospitalization</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>Unlikely</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>Probable</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>24-Hour; 5 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td></td>
<td>Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a non-CTEP IND require reporting as follows:

- AdEERS 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events
  - AdEERS 10 calendar day report:
    - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
    - Grade 5 expected events

\(^2\) Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

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

8.1 Neck Dissection

A neck dissection should be considered if a palpable or worrisome radiographic abnormality persists in the neck eight weeks after radiotherapy ends.

8.2 Cervical Lymphadenectomy

Cervical lymphadenectomy should be comprehensive rather than selective. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle will be at the discretion of the surgeon.
8.3 Operative Report
The operative report must accurately and completely describe the precise location and the extent of the cervical lymph node metastases. Assessment of the completeness of the resection and results of intra-operative frozen section should be included.

9.0 OTHER THERAPY
Prophylactic use of amifostine and pilocarpine is not permitted (Section 3.2.9). These agents and their derivatives are not allowed during radiation or within three months of completion of radiation. Administration of pilocarpine and its derivatives is discouraged before six months post-treatment. However, pilocarpine can be used if there is no salivary flow following the first post-treatment sialometry study. Any use of these agents and their derivatives including start and stop dates must be reported on the case report forms.

10.0 PATHOLOGY
Not applicable to this study.
## 11.0 PATIENT ASSESSMENTS

### 11.1 Patient Assessments (5/26/05)

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Prestudy(^a)</th>
<th>During RT(^i)</th>
<th>CTX</th>
<th>Follow-up(^g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; Physical</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Disease Documentation (including appropriate endoscopic procedures)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Dental Evaluation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional Evaluation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/Platelets</td>
<td>X(^i)</td>
<td>X</td>
<td>X(^i)</td>
<td>X(^n)</td>
</tr>
<tr>
<td>AST, bilirubin, alkaline phosphatase</td>
<td>X(^i)</td>
<td></td>
<td>X(^i)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, creatinine clearance, BUN</td>
<td>X(^n)</td>
<td></td>
<td>X(^n)</td>
<td></td>
</tr>
<tr>
<td>Thyroid function panel ((TSH, T_s, T_d))</td>
<td>X(^n)</td>
<td></td>
<td></td>
<td>X(^n)</td>
</tr>
<tr>
<td>EKG</td>
<td></td>
<td>X(^n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>X</td>
<td></td>
<td></td>
<td>X(^n)</td>
</tr>
<tr>
<td>MRI of H&amp;N(^3)</td>
<td>X</td>
<td></td>
<td></td>
<td>X(^n)</td>
</tr>
<tr>
<td>Liver CT</td>
<td>X(^n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone scan</td>
<td>X(^n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
<td>X(^i)</td>
<td>X</td>
</tr>
<tr>
<td>Toxicity Evaluation</td>
<td>X(^i)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary Flow Measurements</td>
<td></td>
<td></td>
<td></td>
<td>X(^i)</td>
</tr>
<tr>
<td>Audiology</td>
<td>X(^i)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Studies completed 6 weeks prior to study entry.
b. Within 14 days prior to study entry.
c. If patient is to receive chemotherapy, CBC with platelets and differential should be done prior to study entry, weekly during chemoradiation, prior to adjuvant chemotherapy, weekly during chemotherapy; an EKG should be done prior to chemotherapy; serum creatinine should be done weekly during chemoradiation and prior to each cycle during adjuvant chemotherapy; repeat CrCl only if serum creatinine is > 1.5. Alkaline phosphatase, AST or bilirubin prior to each cycle during adjuvant chemotherapy. A serum pregnancy test is required for women of childbearing potential who will be receiving chemotherapy.
d. MRI with T1 contrast with gadolinium and T2 sequences is required ≤ 6 weeks prior to study entry. If MRI is medically contraindicated, a CT with < 3 mm contiguous slices in immobilization can be substituted (with contrast, unless contraindicated).
e. Liver CT must be done in presence of elevated alkaline phosphatase, AST, or bilirubin or other clinical indicator. Bone scan must be done in presence of elevated alkaline phosphatase or other clinical indicator.
f. Weekly during radiotherapy.
g. Follow-up will be performed after IMRT and then every 3 months during the first two years; every 6 months during years 3-5; then annually.
h. These tests will be performed every 6 months during the first 3 years; MRI of nasopharynx (or CT if CT was done pre-study) at 2 months and 4 months after RT and every 6 months during first 3 years.
i. At approximately 3, 6, and 12 months following IMRT.
j. If middle/inner ear to be irradiated > 40 Gy.
k. Prior to each cycle.
l. Yearly if middle/inner ear receives > 40 Gy or if any hearing loss, vertigo, or tinnitus occurs.

### 11.2 Evaluations

#### 11.2.1 Every Follow-up Visit

All patients will enter a common follow-up program commencing one month following completion of radiotherapy. For those patients requiring surgery after radiation, follow-up will begin one month after last protocol treatment was received. Routine follow-up care includes
complete head and neck examination with appropriate endoscopic examination, performance status and weight, and toxicity notation.

11.2.2 Sialometry (before initiation of the first radiation fraction, and at approximately 3, 6, and 12 months after the completion of radiation):

11.2.2.1 Unstimulated Whole Saliva: Patients should refrain from eating, drinking or dental hygiene for at least 60 minutes before collection. During collections, patients should be seated and instructed to minimize orofacial movements and not to attempt to influence salivary flow (such as by sucking or swallowing). Just before the collection, the patient should be instructed to swallow. He/she should then be instructed to allow saliva to accumulate in the floor of mouth for 60 seconds without swallowing. The patient should then spit the accumulated saliva into a pre-weighted 50 ml vial. The patient should repeat this procedure four more times for a total collection time of five minutes. Subjects should be instructed not to swallow during the entire collection procedure.

11.2.2.2 Stimulated Whole Saliva: After the collection of unstimulated saliva, patients will have 2% citrate solution applied with cotton tipped applicators to the lateral tongue bilaterally five times over a two minute period (0, 30, 60, 90 and 120 seconds). The mouth should then be emptied of retained citrate solution. Saliva should then be collected for five minutes, the same as for unstimulated saliva.

11.2.3 Other Studies
- Chest X-ray: For persistent cough, hemoptysis, chest pain, or loss of vocal cord mobility (in addition to routine follow-up chest X-ray, see Section 11.1).
- Biopsy: Any suspicious mucosal lesion in the upper aerodigestive tract; pharyngeal pain referred to the ear; any firm node that persists longer than four weeks; epistaxis; chronic nasal congestion not thought to be due to radiation mucosal changes.
- Audiogram: Pre-RT and yearly if the middle/inner ear receives > 40 Gy, or if any hearing loss, vertigo or tinnitus occurs.

11.3 Criteria for Removal from Protocol Treatment
11.3.1 Progression of disease while on treatment.
11.3.2 Sustained severe radiation mucositis resulting in dehydration and poor nutrition unresponsive to tube feeding or any other toxicity that requires more than a 14 day break from therapy. Every effort should be made to sustain the patient so as to avoid such complications. Should the patient be removed from protocol treatment, surgical removal followed by radiation post-operatively may be attempted.
11.3.3 Patients’ refusal to continue participation (reasons to be clearly specified on data forms).

12.0 DATA COLLECTION (3/7/05)
Data should be submitted to:

RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Sialometric Evaluation Form (L4)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1) (copy to ITC Center)</td>
<td>Within 1 week of end of RT</td>
</tr>
<tr>
<td>Chemotherapy Flow Sheet (TF)</td>
<td>Within 1 week of completing each chemotherapy cycle</td>
</tr>
<tr>
<td>Initial Followup Form (FS)</td>
<td>At 13 weeks</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months during the first two years after RT; every 6 months during years 3-5;</td>
</tr>
</tbody>
</table>
then annually. Also at progression/relapse and at death.

Sialometric Evaluation Form (L4) At 3, 6, and 12 months from end of RT.

Long Term Follow-up Form (FF) Yearly after 5 years in place of the F1 form, as applicable. See FF Form for instructions.

Autopsy Report (D3) As applicable

12.2 Summary of RT QA Requirements (Image-Guided Therapy Center)

Preliminary Dosimetry Information: Within 1 week of start of RT
Digital patient data (CT scans, critical normal structures, all GTV/CTV/PTV contours, doses for all fraction groups, DVHs for total dose plan)

Simulation and port films as defined in Appendix V

Hard copy isodoses for total dose plan as defined in Appendix V

Digital Patient Submission Information Form (T2)

Final Dosimetry Information: Within 1 week of end of RT
Digital patient data for any modified or changed planning data (contours, doses or DVHs)

Hard copy isodoses for total dose plan if any changes made after initial submission.

Simulation and port films for boost and/or field changes as defined in Appendix V

Copy of Daily Treatment Record

Radiotherapy Form (T1)

12.2.1 For Mail or Federal Express

Image-Guided Therapy Center (ITC)
4511 Forest Park Avenue, Suite 200
St. Louis, MO  63108
Phone 314/747-5414; FAX #314/747-5423

12.2.2 To send over Internet or Using Magnetic Tape

Digital data submission may be accomplished using magnetic tape or the Internet. For network submission, the ftp account assigned to the submitting institution shall be used and e-mail identifying the data set(s) being submitted shall be sent to:

itc@castor.wustl.edu

For tape submission, please contact the ITC Center about acceptable tape types and formats.

12.2.3 See the ITC web site at http://itc.wustl.edu for additional helpful information, the current Facility Questionnaire document and the Dry Run Guidelines as necessary for acquiring institutional credentials.
12.3 **Timely Data Submission for Toxicity Evaluation**

Timely data submission is critical in order to meet the study’s objectives for toxicity evaluation and to safely assign treatment levels.

13.0 **STATISTICAL CONSIDERATIONS**

13.1 **Study Endpoints**

13.1.1 Protocol Compliance of IMRT Delivered

13.1.2 Rate of xerostomia at one year (Grade ≥ 2)

13.1.3 Rate of local-regional control at two years

13.1.4 Whole mouth saliva output relative to pre-treatment measurements

13.1.5 Other acute and late toxicities

13.1.6 Compliance to protocol chemotherapy

13.2 **Sample Size Determination (8/19/03)**

The primary endpoint of this study is to determine if the IMRT technique in transportable to the multi-institutional setting. However, we also wish to monitor xerostomia toxicity and local-regional progression. The local-regional failure endpoint requires the most patients and thus determines the total sample size.

The head and neck registry study, RTOG 76-19, and three subsequent RTOG head and neck studies, 7913, 7915, and 8527, included 101 patients with primary disease in the nasopharynx, KPS ≥ 70 (i.e., Zubrod 0-1), presenting with stages I-IV, but no distant disease. All patients were treated with standard RT. Thirty-six percent of these patients failed local-regionally in the first two years. In Stage I/II patients, only about 19% of patients fail local-regionally in the first two years. Lee reported a 4-year local-regional progression-free survival rate of 94% when treating patients with IMRT. Based on the historical data and the reported effectiveness using IMRT on local-regional control, we hypothesize a 2-year local-regional control rate of 80%. Fleming’s one-sample multiple testing procedure is utilized here. The unacceptable local-regional control rate is set at 65% and the acceptable local-regional control rate is set at 80%. We choose Type I error of 0.10 and Type II error or 0.10. Fifty-seven evaluable patients will be needed.

Lee reported a 4-year death rate of only 6%. The sample size will be adjusted by 10% to account for patients that die within the first year and are not evaluable for the toxicity endpoint, and for ineligible or inevaluable (no data) cases. The total target accrual is 64 patients.

13.3 **Evaluation of Primary Endpoint**

With a sample size of 57 patients, the primary endpoint of protocol compliance of IMRT delivered will be evaluated by the study chair or the study co-chair. The cases that are entered from the study chair’s institution will be evaluated by the study co-chair. Protocol compliance will be scored as follows with respect to the protocol prescription: per protocol, acceptable with minor deviation, or unacceptable with major deviation. Patients scored as per protocol or with minor deviation will be considered compliant. Using Fleming’s procedure with two stages, the first evaluation will be made after the first 20 patients have been treated and the final evaluation will be made after all 57 patients have been treated. We set the unacceptable protocol compliance rate at 75%, and the targeted acceptable rate at 90% with Type I and Type II errors of 0.10. If 6 or more out of the first 20 patients are not compliant, the treatment will be considered not transportable and will undergo a review by the study chairs and the RTOG Head and Neck Committee to determine the future course of action. Similarly, if 10 or more patients out of the total 57 are not compliant, the treatment will be deemed not transportable. In addition, the study must not cross any of the unacceptable boundaries as outlined in Sections 13.4 and 13.5.

13.4 **Interim Monitoring for Excessive Xerostomia**

In addition to treatment compliance, late xerostomia (defined as Grade ≥ 2 at one year) will be monitored. Historically, 40% of patients treated with standard RT have persistent xerostomia at one year. Lee reported a one-year rate of xerostomia of 28.5% when treating patients with IMRT. In the U.S. Bioscience Amifostine Trial, patients were treated with standard RT ± Amifostine; the use of Amifostine reduced the rate of xerostomia at one year from 57% to 34%. Late xerostomia is typically underreported. For this reason, we set the unacceptable rate of one-year xerostomia at 55% and the acceptable rate at 30%. If, at any time, the following boundaries are crossed, the study chairs will review all data pertaining to the events and a recommendation will be made to the RTOG Research Strategy Committee for their consideration. The results of this review will determine the future course of action. If accrual has not been completed, it will be
suspended. The following table gives the number of late xerostomia toxicities that are considered unacceptable as calculated by the method of Fleming.

<table>
<thead>
<tr>
<th>Number of Toxicities</th>
<th>Total Number Evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>27</td>
<td>57</td>
</tr>
</tbody>
</table>

### 13.5 Interim Monitoring for Excessive Local-Regional Failure Rate

We do not wish to decrease the toxicity at the expense of increased local-regional failure due to the smaller field used with IMRT. For this reason, local-regional failures will be monitored throughout the study. As outlined in Section 13.2, we set an acceptable local control rate of 0.80 and unacceptable at 0.65. If, at any time, the following boundaries are crossed, the study chairs will review all data pertaining to the events and a recommendation will be made to the RTOG Research Strategy Committee for their consideration. The results of this review will determine the future course of action. If accrual has not been completed, it will be suspended. The following table gives the number of local-regional failures that are considered unacceptable as calculated by the method of Fleming.

<table>
<thead>
<tr>
<th>Number of Local-Regional Failures</th>
<th>Total Number Evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
</tr>
<tr>
<td>15</td>
<td>57</td>
</tr>
</tbody>
</table>

### 13.6 Patient Accrual

It is projected that there will be a period of approximately six months with very slow accrual at the beginning of this study to allow for institutional IRB approval and approval by the QA center. After this initial period, it is projected that this study will accrue approximately 2 patients per month. At this rate, it will take approximately 36-40 months to complete accrual. If accrual is less than 1 patient per month, the study will be re-evaluated with respect to feasibility.

### 13.7 Analysis Plans

**13.7.1 Interim Analysis of Accrual and Toxicity Data**

Interim reports will be prepared every 6 months until the final analysis. In general, these reports will contain information about:

- Accrual rate with projected completion date
- Pretreatment characteristics of patients accrued
- Quality of submitted data with respect to timeliness, completeness, and accuracy
- Protocol compliance rate of treatment delivered with respect to the protocol prescription
- Frequency and severity of toxicity

**13.7.2 Analysis and Reporting of Initial Treatment Results**

The analysis to report the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 12 months. The emphasis of this analysis will be on treatment compliance and toxicity. The usual components of this analysis are:

- Patients excluded from the analysis with reasons for exclusion
- Institutional accrual
- Distribution of important baseline prognostic variables
- Patient accrual rate
- Observed results with respect to the endpoints described in Section 13.1
Further subgroup analyses will not be undertaken because of the relatively small sample sizes. The rates of protocol treatment compliance, salivary gland toxicity, saliva output, and other toxicity rates will be estimated with 95% confidence intervals.

### 13.7.3 Analysis and Reporting of Final Treatment Results

The analysis to report the final results of treatment will be undertaken when each patient has been potentially followed for a minimum of 2 years. The emphasis of this analysis will be on local-regional control. The usual components of this analysis are:

- Patients excluded from the analysis with reasons for exclusion
- Institutional accrual
- Distribution of important baseline prognostic variables
- Patient accrual rate
- Observed results with respect to the endpoints described in Section 13.1

Further subgroup analyses will not be undertaken because of the relatively small sample sizes. The rates of local-regional control at one and two years will be estimated with 95% confidence intervals.

### 13.8 Inclusion of Women and Minorities

In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered the possible interactions (treatment by race and treatment by gender). The study was designed to evaluate salivary gland toxicity and local-regional control under the assumption of the same rates between the gender and among the races. A statistical analysis will be performed to examine the possible differences.

Based on the accrual to the previous intergroup protocol for nasopharyngeal cancer, RTOG 88-17, we project that 75% of patients enrolled on this study will be male, and 25% female; 50% white and 50% non-white; 6% Hispanic and 94% non-Hispanic.

The following table gives the expected number of patients in each race, ethnicity, and gender group.

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>14</td>
<td>46</td>
<td>60</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
<td>16</td>
<td>48</td>
<td>64</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Sex/Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>1</td>
</tr>
<tr>
<td>White</td>
<td>8</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>16</td>
</tr>
</tbody>
</table>
REFERENCES


APPENDIX I

RTOG 0225

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE II STUDY OF INTENSITY MODULATED RADIATION THERAPY (IMRT) +/- CHEMOTHERAPY FOR NASOPHARYNGEAL CANCER

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know”, is available from your doctor.

You are being asked to take part in this study because you have nasopharyngeal cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test whether the use of an advanced radiation therapy delivery technique called intensity modulated radiation therapy (IMRT-see definition below) can spare your normal tissue, including salivary glands, from radiation. Your quality of life will be studied to see if better sparing of healthy tissue can improve your quality of life after radiation.

Definition of IMRT: Many normal tissues, including the salivary glands, are very close to cancers in the nasopharynx, and standard radiation techniques cannot avoid delivering radiation to these normal tissues that do not need to get radiation. IMRT tries to lower the amount of radiation that normal tissues receive, while still delivering the desired amount of radiation to your cancer and to areas that your doctor thinks may have cancer cells, such as lymph nodes in the neck. IMRT does this by using multiple, complicated computer-controlled radiation beams aimed at your cancer.

This research is being done to try to reduce radiation side effects, especially mouth dryness, that occurs with the standard radiation methods.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 64 people will take part in this study.
WHAT IS INVOLVED IN THE STUDY? (3/7/05)

• All patients will receive the following treatment:

  Radiation therapy will be given once a day, five days a week, for six weeks and three days. This will be given as an outpatient. IMRT treatment usually takes longer each day than a "standard" radiation treatment (a "standard" radiation treatment takes 5-15 minutes and an IMRT treatment may take 20-30 minutes) even though the radiation dose to the cancer is the same.

• Depending on the stage of your disease, you may also receive chemotherapy during and after your radiation treatments.

  During your radiation treatments, you will receive three cycles of the chemotherapy drug cisplatin in your vein. This will be done at three-week intervals starting at the time of radiation, on days 1, 22, and 43. This will be given as a 20 to 30 minute infusion. Both before you receive the cisplatin and after you receive the cisplatin, you will receive additional fluids in your vein, and you may also be given additional fluids by mouth.

  When you complete your radiation treatments, you will again receive cisplatin as above, for three cycles. This will be done at four-week intervals on days 71, 99, and 127. Another drug will also be given called 5-FU following the cisplatin. The 5-FU will be given by continuous infusion in your vein over 4 days starting on the day you receive the cisplatin. You will receive the 5-FU on days 71-74, 99-102, and 127-130. In general, this can be done as an outpatient at your institution. However, depending on a number of factors, the chemotherapy treatments may require admission to the hospital.

• Procedures that are part of regular cancer care and may be done even if you do not join the study:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam</td>
<td>Prior to study entry,</td>
</tr>
<tr>
<td></td>
<td>weekly during radiation,</td>
</tr>
<tr>
<td></td>
<td>and at follow-up visits</td>
</tr>
<tr>
<td>Blood Tests</td>
<td>Prior to study entry and every six months for first three years</td>
</tr>
</tbody>
</table>
Chest X-Ray Prior to study entry and every six months for first three years

Thyroid Function Test Prior to study entry and every six months for first three years

Endoscopic Evaluation Prior to study entry and at follow-up

MRI Scan of the head and neck Prior to study entry
(or CT Scan if advised by your doctor)

Dental and Nutritional Evaluation Prior to study entry

Audiogram (if ear is in radiation field) Prior to study entry and yearly if necessary based on side effects and treatment area.

(Pet Scan is optional)

• Standard procedures being done because you are in this study:

CT Scan of Liver Prior to study entry if medically indicated

Bone Scan Prior to study entry if medically indicated

MRI Scan of the head and neck Prior to study entry, at 2 and 4 months after radiation therapy and every 6 months for the first 3 years of follow up
(or CT Scan if advised by your doctor)

EKG Prior to chemotherapy, if you receive chemotherapy

• Quality of Life procedures that are being tested in this study:

Saliva Measurement Prior to treatment start, at approximately 3, 6, and 12 months from the end of radiation treatment.
Blood counts, chemistries, and follow-up visits may be more frequent because you are enrolled in a research study. If you are to receive chemotherapy, more frequent blood tests will be required and if you are a woman of childbearing age, a pregnancy test will be done.

• Follow-up visits with your physician will be scheduled every three months from the end of treatment for two years, then every six months for three years, and then annually for the rest of your life.

HOW LONG WILL I BE IN THE STUDY? (7/6/04)

You will receive radiation therapy for six weeks and three days. If you also receive chemotherapy, your treatment will continue for an additional four to five months after radiation ends. Follow-up visits will continue for the rest of your life according to the schedule above.

The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the radiation is stopped, but in some cases side effects can be serious or long-lasting or permanent.

**Risks Associated with Radiation Therapy**

**Very Likely**
- Redness and irritation of skin within the treatment area
- Difficulty, pain or burning sensation when swallowing
- Dry mouth may remain after treatment
Mouth sores
Hair loss at the treatment area most likely permanent
Nausea and/or vomiting
Loss of appetite and/or taste
Skin in treatment area may remain permanently dry
Decrease in blood counts while undergoing treatment
Fatigue

**Less Likely**
Voice hoarseness may remain after treatment

**Less Likely, But Serious**
Injury to the jaw or tissue of the neck
Thyroid Gland Dysfunction requiring thyroid hormone pills in the future
Irritation of the spinal cord

**Risks Associated with Cisplatin**

**Very Likely**
Decrease in blood counts, which can lead to a risk of infection and bleeding
Loss of appetite and/or taste; metallic taste in your mouth
Nausea and/or vomiting
Fatigue
Hearing loss or ringing in the ears
Numbness or tingling in the hands or feet

**Less Likely**
Muscle cramps or spasm
Loss of coordination
Involuntary movements or shaking
Rash
Loss of hair, which is temporary

**Less Likely, But Serious**
Loss of muscle or nerve function, which may cause weakness or numbness in your hands and feet
Facial swelling
Decreasing ability of the kidneys to handle the body’s waste, which may be permanent
Allergic reactions, which can cause difficulty in breathing, fast heartbeat, and sweating
Decrease in liver function causing temporary elevations in blood tests
Other cancer called Acute Leukemia
Risks Associated with 5-FU (5-Fluourouracil)

**Very Likely**
- Decrease in blood counts, which can lead to a risk of infection and bleeding
- Loss of appetite
- Nausea and/or vomiting
- Diarrhea with cramping or bleeding
- Skin rash
- Fatigue
- Headaches
- Hair loss, which is temporary
- Mouth sores
- Sore throat

**Less Likely**
- Confusion
- Inflammation of the fingers and toes
- Increased sensitivity to sunlight
- Darkening of the skin, nails, or veins
- Loss of coordination or balance
- Inflammation of the veins

**Less Likely, But Serious**
- Damage to the heart that causes chest pain

Risks Associated with Blood Drawing

You may experience some discomfort, bruising and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with head and neck cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) standard radiation therapy delivery with or without chemotherapy during and/or after the radiation; (2) chemotherapy; (3) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your
disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Please talk to your regular doctor about these and other options.

**WHAT ABOUT CONFIDENTIALITY?**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), and other groups or organizations that have a role in this study.

**WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.
We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

A group of experts in head and neck cancer from the RTOG Head and Neck Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?  
(This section must be completed)

For information about your disease and research-related injury, you may contact:

________________________________________  __________________________
Name                                      Telephone Number

For information about this study, you may contact:

________________________________________  __________________________
Name                                      Telephone Number

For information about your rights as a research subject, you may contact:  
(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

________________________________________  __________________________
Name                                      Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615


SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.
I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Patient Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

<table>
<thead>
<tr>
<th>Name of Person Obtaining Consent</th>
<th>Signature</th>
<th>Date</th>
</tr>
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<tbody>
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</tbody>
</table>
APPENDIX II

KARNOFSKY PERFORMANCE SCALE (KPS)

100  Normal; no complaints; no evidence of disease
90   Able to carry on normal activity; minor signs or symptoms of disease
80   Normal activity with effort; some sign or symptoms of disease
70   Cares for self; unable to carry on normal activity or do active work
60   Requires occasional assistance, but is able to care for most personal needs
50   Requires considerable assistance and frequent medical care
40   Disabled; requires special care and assistance
30   Severely disabled; hospitalization is indicated, although death not imminent
20   Very sick; hospitalization necessary; active support treatment is necessary
10   Moribund; fatal processes progressing rapidly
0    Dead

ZUBROD PERFORMANCE SCALE (ZPS)

0    Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1    Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
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 (Karnofsky 50-60).
3    Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4    Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5    Death
APPENDIX III

AJCC STAGING
HEAD & NECK, 5th Edition

Definition of TNM

Primary Tumor (T)

TX  Primary tumor cannot be assessed
T0  No evidence of primary tumor
Tis  Carcinoma in situ

Nasopharynx

T1  Tumor confined to the nasopharynx
T2  Tumor extends to soft tissues of oropharynx and/or nasal fossa
   T2a  without parapharyngeal extension
   T2b  with parapharyngeal extension
T3  Tumor invades bony structures and/or paranasal sinuses
T4  Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit

Regional Lymph Nodes (N)

NX  Regional lymph node metastasis
N1  Unilateral metastasis in lymph node (s), 6 cm or less in greatest dimension, above the supraclavicular fossa
N2  Bilateral metastasis in lymph node (s), 6 cm or less in greatest dimension, above the supraclavicular fossa
N3  Metastasis in a lymph node (s)
   N3a  greater than 6 cm in dimension
   N3b  extension to the supraclavicular fossa

Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
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<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
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<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IIA</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
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<td>T2a</td>
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<td></td>
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<td>M0</td>
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<td>Stage IVA</td>
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</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>T4</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
<tr>
<td>ORGAN TISSUE</td>
<td>GRADE 1</td>
<td>GRADE 2</td>
<td>GRADE 3</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>SKIN</td>
<td>None: Slight atrophy; Pigmentation change; Some hair loss</td>
<td>Patch atrophy, Moderate telangiectasia; Total hair loss</td>
<td>Marked atrophy, Gross telangiectasia</td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>None: Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture; &lt;10% linear reduction</td>
<td>Severe induration and loss of subcutaneous tissue; Field contracture &gt; 10% linear measurement</td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>None: Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; Little mucus</td>
<td>Marked atrophy with complete dryness; Severe telangiectasia</td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None: Slight dryness of mouth; Good response on stimulation</td>
<td>Moderate dryness of mouth; Poor response on stimulation</td>
<td>Complete dryness of mouth; No response on stimulation</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None: Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
</tr>
<tr>
<td>BRAIN</td>
<td>None: Mild headache; Slight lethargy</td>
<td>Moderate headache; Great lethargy</td>
<td>Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)</td>
</tr>
<tr>
<td>EYE</td>
<td>None: Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma</td>
<td>Severe keratitis; Severe retinopathy or detachment Severe glaucoma</td>
</tr>
<tr>
<td>LARYNX</td>
<td>None: Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
<td>Severe edema; Severe chondritis</td>
</tr>
<tr>
<td>LUNG</td>
<td>None: Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade pneumonia</td>
<td>Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes</td>
</tr>
<tr>
<td>HEART</td>
<td>None: Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST Changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes; Low ORS</td>
<td>Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None: Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated</td>
<td>Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required</td>
</tr>
<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None: Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;5 times daily; Excessive rectal mucus or intermittent bleeding</td>
<td>Obstruction or bleeding, requiring surgery</td>
</tr>
<tr>
<td>LIVER</td>
<td>None: Mild tachilude; Nausea, dyspepsia; Slightly abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver function tests; Serum albumin normal</td>
<td>Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None: Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%,Creatinine 1.5-2.0 mg%; Creatinine clearance &gt; 75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt; 36-60mg% Creatinine clearance (50-74%)</td>
<td>Severe albuminuria; Severe hypertension Persistent anemia (&lt; 10%); Severe renal failure; Urea &gt;60 mg% Creatinine &gt;4.0 mg% Creatinine clearance &lt; 50%</td>
</tr>
<tr>
<td>BLADDER</td>
<td>None: Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria</td>
<td>Severe frequency &amp; dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (&lt; 150 cc)</td>
</tr>
<tr>
<td>BONE</td>
<td>None: Asymptomatic; No growth retardation; Reduced bone Density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bone density</td>
<td>Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis</td>
</tr>
<tr>
<td>JOINT</td>
<td>None: Mild joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement</td>
<td>Severe joint stiffness; Pain with severe limitation of movement</td>
</tr>
</tbody>
</table>
APPENDIX V
IMRT for Nasopharyngeal Cancer
Quality Assurance Guidelines

Note: Please visit the Image-Guided Therapy Center (ITC) Website at http://itc.wustl.edu/ to obtain latest version of QA guidelines for this protocol

I. Purpose
To establish quality assurance (QA) guidelines for the radiation oncologist, physicist, dosimetrist, technologist, and data manager pertaining to 3-D conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT) for the purpose of performing national, multi-institutional cooperative studies.

II. Background
A. Radiation therapy treatment planning and treatment delivery are in the process of changing dramatically. This change has been driven in large part by recent advances in computer hardware and software that led to the development of sophisticated three-dimensional radiation treatment planning (3DRTP) and computer-controlled radiation therapy treatment delivery systems. Such planning and delivery systems have made the implementation of 3DCRT practical. The goal of 3DCRT is to conform the spatial distribution of the prescribed dose to the 3D target volume (cancerous cells), while at the same time minimizing the dose to the surrounding normal structures. Currently, the delivery of 3DCRT is typically accomplished with a set of fixed radiation beams, which are shaped using the projection of the target. The radiation beams normally have a uniform intensity across the field, or, where appropriate, have this intensity modified by simple beam fluence modifying devices like wedges or compensating filters.

Now, even before this form of 3DCRT (henceforth referred to as conventional 3DCRT) has been implemented throughout the radiation therapy community, a new type of conformal planning and delivery technology is evolving. This new type of 3DCRT, called IMRT, is based on the use of non-uniform radiation beam intensities within each beam. Preliminary reports of the success of IMRT at generating more conformal dose distributions than achievable with conventional 3DCRT have heightened the interest of the medical community. Controlled, prospective multi-institutional trials to validate and investigate the efficacy of this procedure have become a goal of the RTOG. The ITC has expanded its mission to insure the scientific soundness of these trials. The ITC performs this function through (1) individual and institutional credentialing, (2) establishment of procedural standards, and (3) centralized quality assurance review of case submissions.

B. A partial list of references that provide background information regarding 3-D treatment planning, 3DCRT, and IMRT are listed below.


III. Credentialing Requirements for Participating Institutions

A. **Facility Questionnaire**: The following information must be submitted by each institution prior to enrolling patients in the protocol. Please note that the Facility Questionnaire is available only via the ITC website (http://itc.wustl.edu).

1. **Individual Qualifications**: The training and experience of the 3DCRT/IMRT team is to be documented in the questionnaire.
   a. Radiation Oncologist(s)
   b. Medical Physicist(s)
   c. Dosimetrist(s)
   d. Radiation Therapists

2. **Treatment Equipment**: Documentation of linac model, energies to be used, and description of collimation to be used to define conformal fields (e.g. multileaf, cerrobend) and/or IMRT system.

3. **Immobilization/Repositioning System**: Documentation of immobilization and repositioning system to be used. Submit copy of patient motion study (set-up uncertainty, organ movement) if smaller margins for the Planning Target Volumes than specified by the protocol are to be used.

4. **Treatment Verification Systems**: Documentation of verification imaging system (e.g., film, electronic portal imager).

5. **Computer Planning System**: Information pertaining to the 3DRTP system used for treatment planning and evaluation is to be listed on the credentialing Facility Questionnaire. To participate in this study, the institution's 3DRTP system must have, as a minimum, the following capabilities:
   a. CT data - system must be able to handle the number of axial CT slices required by protocol.
   b. Beam's-eye-view (BEV) display showing tumor and target volumes, critical structures, and beam aperture required for conventional 3DCRT.
   c. Calculate volumetric 3-D dose matrix for photon and electron beam. The minimum dose matrix size shall have a maximum dose point spacing of 3 mm or 10,000 points in axial planes (whichever has least number of dose points). The spacing between axial planes must be such that, at the minimum, a transverse distribution is computed for each axial slice.
   d. Display and hardcopy of superimposed isodose distributions on axial, sagittal, and coronal CT images (multiple axial planes, while not encouraged, are optional).
   e. Calculate dose-volume histograms (DVHs) using dose-volume element sampling at least as fine as the dose calculation grid in axial planes and shall, at the minimum, use spacing in the orthogonal direction identical to the CT slice spacing. These DVHs must identify both absolute volume and absolute dose for the entire structure (irradiated, or not).
   f. Non-coplanar beams -3DRTP system for convention 3DCRT must provide capability of simulating each of the treatment machine motion functions including collimator length, width and angle, gantry angle, couch angle, and couch lateral, longitudinal and vertical position for both beam geometry definition and dose computation.
   g. Calculate and display digital reconstructed radiographs (DRRs) with superimposed target volume, critical structure contours and treatment aperture.
   h. Data transfer: Capability of digital data exchange with the ITC for the data specified in the protocol must be demonstrated. File formats will conform to the latest version of "Specifications for Tape/Network Format for Exchange of Treatment Planning Information". All data will conform to treatment protocol requirements and these Quality Assurance Guidelines.
6. **Quality Assurance Procedures**: Documentation of the 3DCRT/IMRT planning and delivery process as well as the routine QA tests performed to insure the proper functioning should be detailed. The method used to conduct a check of the dose and monitor unit calculations performed by the 3DRTP system must be provided.

B. **Dry Run (Benchmark) Test**: complete test set as specified by the treatment protocol must be submitted to the ITC to demonstrate compliance with 3D technical requirements (see Dry Run Guidelines at http://itc.wustl.edu/).

C. **Phantom Dosimetry Test**: Institutions are required to image, plan, and treat a RPC/RTOG IMRT head and neck phantom to participate in this protocol. (Institutions who have successfully performed this test for H-0022 do NOT have to repeat this exercise.) The IMRT phantom can be requested directly from the Radiological Physics Center (RPC) at 713-745-8989. Information can be found at the RPC’s web site at http://rpc.mdanderson.org

IV. **Protocol Data and Quality Assessment Parameters**

A. **Patient Data Submission**: The following information, in addition to forms T1 and T2, is to be submitted to the ITC for each protocol patient at times specified in Section 12 of the protocol.

1. Hardcopy isodose distribution for the axial, sagittal and coronal planes through the isocenter for the total dose plan must be submitted. If sagittal and coronal hard copy is a problem, five axial distributions may be substituted for them (two cuts that are two slices superior and inferior of the superior and inferior slices containing the PTV, the superior and inferior cuts containing the PTV, and one through the center of the PTV. These dose distributions must include:
   a. A reasonable number of isodose lines should be shown that can be used to determine that the digital dose and anatomy data are properly aligned relative to each other. The prescription dose for the PTV should be displayed. If the hard copy isodose lines are in percentage, the conversion factor to convert them to absolute dose (Gy or cGy) must be indicated.
   b. The above isodoses should be superimposed over the treatment planning CT images. However, if such hard copy presents difficulties, similar plots without the gray scale image may be acceptable if enough critical structure contours are identifiable on the hard copies to allow the ITC to verify correct isodose curve positions relative to the digital data submitted.

2. First day portal films (or images) for each portal (conventional 3DCRT only) and one set of orthogonal (anterior-posterior and lateral) films (or images) for isocenter (or IMRT reference point) localization for each group of concurrently treated beams. If possible, these should be submitted in digital form as described below.

3. Dosimetry and imaging digital data. (To be submitted via the Specifications for Tape/Network Format for Exchange of Treatment Planning Information):
   a. Volumetric CT data for all cuts required by the protocol (required for the initial submission).
   b. Gross tumor volume (GTV), clinical target volumes (CTV), planning target volumes (PTV) and organs at risk contours. They must be contoured on all slices in which each structure exists including skin on ALL CT cuts (required for the initial submission).
   c. Beam geometry specifications (conventional 3DCRT only).
   d. Volumetric 3-D dose distribution data in absolute dose for each set of concurrently treated beams computed with heterogeneity corrections.
   e. Dose-volume histograms for all PTV and critical normal structures (including unspecified tissue).
   f. DRR (or simulation verification radiograph) for each portal (conventional 3DCRT only) and one set of orthogonal (anterior-posterior and lateral) prescription images for isocenter (or IMRT reference point) localization for each group of concurrently treated beams.
   g. Portal images for each portal (conventional 3DCRT only) and one set of orthogonal (anterior-posterior and lateral) images for isocenter (or IMRT reference point) localization for each group of concurrently treated beams.
   h. Any corrections to previously submitted digital data should be discussed with the ITC prior to such submission.
V. ITC Review

A. Quality Assurance of Digital Data Format and CT Scan Data

The format of the digital treatment planning and verification data submitted will be reviewed for compliance with the appropriate exchange specification version. Deviations from compliance will be noted and, depending upon the severity of the deviation, may require a complete resubmission of the digital data set.

The CT Scan set is reviewed to ensure protocol compliance with regard to both interslice spacing as well as the superior/inferior extents of the scan region.

B. Quality Assurance of Target Volumes and Organs at Risk Volumes

The ITC will facilitate the review of all PTVs and designated critical structures on initial cases submitted by each institution. After an institution has demonstrated compliance with the protocol, future cases will be spot-checked.

C. Quality Assurance of Field Shape and Placement

1. Conventional 3DCRT: The ITC will review initial placement films for the first five cases submitted by each institution. At least one port film or pretreatment alignment film per field along with the DRR from the treatment planning program or, alternatively, a simulation verification radiograph shall be submitted for evaluation except where geometrically impractical. Subsequent cases may be spot-checked only.

2. IMRT: The ITC will review one set of orthogonal (anterior-posterior and lateral) prescription images for isocenter (or IMRT reference point) localization for each group of concurrently treated beams for the first five cases submitted by each institution. The DRR from the treatment planning program or, alternatively, a simulation verification radiograph shall be submitted for evaluation except where geometrically impractical. Subsequent cases may be spot checked only.

D. Quality Assurance of Dose Distribution

1. The ITC will display, and compare with hardcopies, isodose distributions for the plans submitted to verify correct interpretation and conversion of the digital patient and dose data.

2. The ITC will calculate DVH's for the sum of all dose distributions submitted (each submitted distribution is for one set of concurrently treated beams) and may compare them with the digitally submitted dose-volume histograms for the PTV and designated organs at risk.

E. Dose Prescription Compliance

1. No Variation
   a. The prescription criteria in Sections 6.4.2-6.4.4 are fulfilled.

2. Minor Variation
   a. The 93% isodose surface covers between 97% to 90% of the respective PTV;

   b. Volumes of overdose exceed those specified in Sections 6.4.3 by < 5% of the PTV volume;

   c. Failure to achieve salivary gland sparing as specified in Section 6.4.5;

   d. Failure to limit the dose to organs at risk as specified in Section 6.4.3.

3. Major Variation:
   a. The 93% isodose surface covers < 90% of the appropriate PTV;

   b. Organs at risk maximum exceeded the specified constraints (Section 6.4.3);

   c. Volumes of overdose exceed those specified in Section 6.4.3 by > 5% of the PTV volume.
APPENDIX VI

MANAGEMENT OF DENTAL PROBLEMS
IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients
Goals for a dental care program include:

1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

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

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

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

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

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

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

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

Causative Factors
The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.
Preventive Program
The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is moulded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

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

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

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

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

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

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