STATUS PAGE

PROTOCOL **05-089**

Closed To New Accrual

Closure Effective Date: 05/22/12

No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

Protocol Number: 05-089

Approval Date: 09/07/06 (IRB meeting date when protocol/consent approved or conditionally approved)

Activation Date: 10/02/06 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

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05-089

A PHASE II STUDY OF PROTON RADIOTHERAPY WITH CHEMOTHERAPY FOR NASOPHARYNGEAL CARCINOMA

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SCHEMA

A Phase II Study of Proton Radiotherapy with Chemotherapy for Nasopharyngeal Carcinoma

Combined Proton-Photon Radiotherapy

Primary site	70 CGE
Nodal Disease > 2cm	70 CGE
Nodal Disease 1 - 2cm	66 CGE
Primary subclinical	60 CGE
High risk nodal region	60 CGE
Low risk nodal region	50 CGE

Chemotherapy

Cisplatin 100mg/msq d1 (cycle 1), 22 (cycle 2), 43 (cycle 3)
5-FU 1000mg/msq 96hr
Cisplatin 80mg/msq

I. Concurrent Radiotherapy and Chemotherapy (Chemoradiation)

RADIOTHERAPY* Days 1 ⟶ 54

CISPLATIN** X

*Administered Monday through Friday, start date may be on a Monday, Tuesday, Wednesday, or Thursday

* *Cisplatin infusion to be given every 21 days during RT. First dose to be administered within the first three days of the start of radiation.

II. Adjuvant Chemotherapy – **to begin 3 - 8 weeks after completion of chemoradiation**

Day	**1**	**2**	**3**	**4**	**29**	**30**	**31**	**32**	**57**	**58**	**59**	**60**
Cisplatin	x				x				x			
5-FU	x	x	x	x	x	x	x	x	x	x	x	x

1.0 Background and Significance

1.1 Background

In the USA and Western Europe, nasopharyngeal carcinoma (NPC) accounts for less than 1% of malignancies. The average incidence increases 80-fold in endemic areas such as Southern China. NPC is a neoplasm that differs from other squamous cell carcinomas of the head and neck with regard to epidemiology, histologic features, treatment strategies, and treatment response. Due to the anatomical location, nasopharyngeal cancers are considered unresectable. The conventional treatment approach has been radiation. Local control rates with conventional once daily radiation are 75% or higher for Stage I and II diseases but decrease to 20 - 70 % for Stage III and IV diseases. For patients with advanced NPC (stage III - IV) treated with radiation alone, the 5-year survival rates are only 10 - 40% (1 - 7).

The predominant patterns of failure for locally advanced NPC are local recurrence and distant metastasis. In a retrospective analysis of 1301 patients with NPC, locoregional recurrence was shown to be an independent prognostic indicator of subsequent distant metastases (8). Achieving local control is therefore important in the treatment of nasopharyngeal carcinoma.

1.2 Combined radiation and chemotherapy is superior to radiotherapy alone

The standard of care of treatment in the United States is concurrent chemoradiation followed by adjuvant chemotherapy, based on the results of the Intergroup study (SWOG/RTOG/ECOG), which showed improved progression-free and overall survival with chemoradiation compared with radiation alone (9). The study compared radiotherapy (70 Gy) alone to chemotherapy concurrent with radiotherapy followed by adjuvant chemotherapy in patients with nasopharyngeal cancer. This revealed a statistically significant increase in 3-year progression-free survival (69% versus 24%) and 3-year overall survival (76% versus 46%) in favor of the chemoradiotherapy arm. Lin et Al recently reported increased progression-free and overall survival rates in patients who received 2 cycles of continuous cisplatin and fluorouracil chemotherapy during radiotherapy compared to radiotherapy alone in patients with locally advanced nasopharyngeal carcinoma in endemic areas (10). Chan et al in a randomized trial of 350 patients, showed that patients who received weekly cisplatin of 40 mg/m² during radiation had a prolonged progression-free survival compared to patients who received radiation alone (11). These studies suggest that concurrent chemoradiation with or without adjuvant chemotherapy is superior to radiotherapy alone in patients with locally advanced NPC in edemic and non-edemic areas.

1.3 Rationale of using proton radiotherapy

In the Intergroup randomized study, only 63% of patients received all three courses of concurrent cisplatin and 55% received all three courses of adjuvant chemotherapy.

Twenty-eight percent of patients in the radiotherapy alone arm experienced grade 3 and 4 mucositis compared to 37% in the chemoradiation arm. Two percent of patients in the radiotherapy arm experienced severe (grade 4) mucositis compared to 12% in the chemoradiation arm (9). In the randomized trial of concurrent weekly cisplatin with radiotherapy versus radiotherapy alone by Chan et al, the progression-free survival was not statistically significant between the two arms (11). The percentage of patients completing at least four cycles of chemotherapy during external radiotherapy was 78%. This number dropped to 60% and 44% for five and six cycles, respectively. In this study, mucositis was the most common reason of discontinuing chemotherapy. These data suggest that if one can reduce acute treatment toxicity from concurrent chemoradiation, one may increase treatment compliance and therefore treatment outcome.

Because of the anatomic location of the nasopharynx, radiation treatment with and without chemotherapy is associated with significant treatment-related toxicity such as brain necrosis, audio-visual toxicity, radiation encephalopathy, radiation myelitis, and cranial nerve paralysis. Xerostomia and swallowing dysfunction are also the major complaints in patients who have undergone conventional external beam radiation therapy to the nasopharynx. Protons are charged particles, with similar biological effect as X-rays. The advantage of protons lies in their physical dose distribution. Due to the defined range of protons (i.e. Bragg peak), dose distribution can be designed that conforms more closely to the tumor volume (12). This superior physical property of proton allowed less radiation to the normal surrounding tissues, therefore expected to result in decreased acute and late toxicities.

The goal of using proton therapy is therefore to: 1) test the hypothesis that reduction of radiation dose to normal tissue can reduce acute toxicity and increase treatment compliance to the combined modality treatment and 2) to decrease late toxicity and improve health related quality-of-life outcomes.

1.4 Preliminary experience of proton radiotherapy for T4 nasopharyngeal carcinoma

At the Massachusetts General Hospital, proton beam radiotherapy has been used to treat locally advanced nasopharyngeal carcinoma. Between 1990 and 2002, 17 patients with newly diagnosed T4 N0-3 nasopharyngeal carcinoma received combined conformal proton and photon radiotherapy. Seventy-one percentage of patients had World Health Organization type 2 - 3 histology The median prescribed dose to the gross target volume was 73.6 Cobalt-Gray-Equivalent (CGE) (range 69 - 76.8). Eleven patients received accelerated hyperfractionated radiotherapy. Ten patients received induction or concurrent chemotherapy. All patients except one completed the planned concurrent radiation and chemotherapy treatments. With a median follow-up of 43 months, 1 and 2 patients developed local and systemic failures, respectively. There was no neck recurrence. The locoregional control and relapse-free survival rates at 3 years were 92% and 79%, respectively. For patients who received chemotherapy, the 3-year

relapse-free survival rate was 91% compared to 50% for those without chemotherapy (p = 0.09). The 3-year overall survival rate was 74%. For patients who received chemotherapy, the 3-year overall survival rate was 91% compared to 40% for those without chemotherapy (p = 0.01). This preliminary experience suggests that combined use of chemotherapy with proton radiotherapy results in improved disease-free and overall survivals in patients with T4 nasopharyngeal carcinoma (13).

2.0 Objectives

2.1 Primary Objectives

(1) To test the hypothesis that reduction of radiation dose to normal tissue can reduce acute toxicity and increase treatment compliance to combined modality treatment.

(2) To assess health related quality-of-life outcomes after proton radiotherapy for nasopharyngeal carcinoma using objective measurements and validated quality-of-life instruments.

2.2 Secondary Objectives

To determine the rate and pattern of locoregional tumor recurrence in patients treated with proton beam radiotherapy and concurrent chemotherapy followed by adjuvant chemotherapy in patients with Stage II - IVA nasopharyngeal cancer.

3.0 Subject Selection

3.1 Patient Eligibility

3.1.1 Biopsy proven stage $\geq$ T2b and/or node positive (American Joint Committee on Cancer Sixth Edition, Stage IIB – IVB) non-metastatic, squamous cell carcinoma of the nasopharynx, types WHO I - III.

3.1.2 No head and neck surgery of the primary tumor or lymph nodes except for incisional or excisional biopsies.

3.1.3 Zubrod performance status 0 - 1 or Karnofsky 70 or above.

3.1.4 All patients must undergo pre-treatment evaluation of tumor extent and tumor measurement.

3.1.5 Nutritional and general physical condition must be considered compatible with the proposed chemoradiation treatment.

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

3.1.7 Patients must have a WBC $\geq$ 4,000/µl and a platelet count of $\geq$ 100,000/µl; patients must have adequate renal function as documented by creatinine clearance $\geq$ 60 ml/min (actual or calculated by the Cockcroft-Gault method).

3.1.8 Age 18 or above

3.1.9 No active alcohol addiction (as assessed by medical caregiver).

3.1.10 Women of childbearing potential must have a negative pregnancy test.

3.2 Exclusion Criteria

3.2.1 Stage IVC or evidence of distant metastases.
3.2.2 Previous irradiation for head and neck tumor.
3.2.3 Patient is on other experimental therapeutic cancer treatment.
3.2.4 Other malignancy except non-melanoma skin cancer or carcinomas not of head and neck origin and have been controlled for at least 5 years.
3.2.5 Active untreated infection.
3.2.6 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.
3.2.7 Prophylactic use of amifostine or pilocarpine is not allowed.
3.2.8 Pregnant or breast feeding women, or women and men of childbearing potential not willing to use adequate contraception while on treatment and for at least 3 months thereafter.
3.2.9 Symptomatic peripheral neuropathy ≥ grade 2 by National Cancer Institute Common Toxicity Criteria (CTCAE)
3.2.10 Symptomatic altered hearing > grade 2 by CTCAE.

4.0 Pre-study Investigations

Each patient must have completed the following studies prior to study entry unless otherwise indicated.

4.1 Complete history and physical exam including weight, height, performance status, neurological examination, and vital signs within 14 days of study.
4.2 Complete descriptive documentation of the extent of the primary and regional disease *(if any)*.
4.3 Completion of the following laboratory studies within 14 days of study entry: Complete Blood Count (WBC, neutrophils, platelet counts); serum creatinine, creatinine clearance, BUN; Chemistry (electrolytes, magnesium, and calcium); serum pregnancy test for women of childbearing. Completion of the following laboratory studies within 14 days of study entry: liver function tests including AST, bilirubin, alkaline phosphatase.
4.4 Completion of the following radiologic studies within 1 month prior to study entry: chest X-ray or CT; CT of head and neck with ≤ 2.5 mm contiguous slices in immobilization system *(with contrast, unless contraindicated)*; or MRI of nasopharynx/base of skull with T1 contrast with gadolinium and T2 sequences required unless contraindicated; liver CT or MRI *(must be done 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)*. The use of PET/CT scan is optional but encouraged. Treatment planning CT can be used but must be within 21 days of start of radiation.

4.5 Thyroid function panel.

4.6 Audiogram.

5.0 Pre-treatment Evaluations

5.1 Dental evaluation
5.2 Nutritional evaluation
5.3 Tobacco and alcohol assessment
5.4 Videofloroscopic Swallowing (VFSS) Evaluation
5.5 Measurement of whole mouth saliva (sialometry)
5.6 EORTC QLQ C30 and EORTC QLQ H&N
5.7 Physician dysphagia log
5.8 Patient swallowing diary
5.9 Speech Assessment/Head and Neck Health Status Assessment Inventory (HNHSAI)
5.10 ChemoSensory Questionnaire (CSQ)
5.11 Trismus Assessment

Subject Enrollment

Patients will be registered through the Quality Control Committee (QCC) at the Dana-Farber Cancer Institute (617-632-3761, fax 617-632-2295) prior to treatment. Any patient not registered to the protocol prior to the initiation of treatment will be ineligible. The following information will be provided to the QCC:

Name and telephone number of primary oncologist
Protocol name
Patient name, date of birth, and ID number
Primary institution
Date of initiation of radiotherapy
Confirmation of eligibility
Copies of consent form with signatures

6.0 Treatment Program

All patients will undergo their radiation planning and radiation treatment at the Massachusetts General Hospital (MGH). Patients may receive chemotherapy at any of the participating institutions.

6.1 Treatment Planning, Imaging, and Localization Requirements

6.1.1 All patients will be immobilized in a custom designed device. Immobilization device should include neck and shoulder immobilization.

6.1.2 Treatment planning CT scans (with contrast, unless contraindicated*)* will be required to define gross target volume and clinical target volume. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 25 mm 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 of 0.5 cm. Treatment planning CT must be within 21 days of start of radiation.

6.1.3 MRI scans (with gadolinium unless contraindicated) are required in assisting the delineation of the treatment volume on planning CT scans.

6.1.4 The GTV, CTV, and normal tissues must be outlined on all CT slices in which the structures exist. GTV and CTV are defined in section 6.2.1.

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, MRI, clinical information, and/or endoscopic findings. Grossly positive lymph nodes are defined as any lymph nodes greater than 1 cm or nodes with a necrotic center.

6.2.2 The Clinical Target Volume (CTV) is defined as the GTV plus areas that are considered to contain potential microscopic disease. Three different CTVs will be defined, namely CTV_{60} for the tumor in the primary site and the high risk nodal regions and $CTV_{50\text{-}54}$ for the low risk nodal regions. Please note that there is no set margin between each GTV and its CTV.

6.2.3 The Planning Target Volume (PTV) will provide a margin of 3 mm around each CTV (namely $PTV_{70,}$ $PTV_{60,}$ PTV_{50-54}) to compensate for the variabilities of treatment set up and internal organ motion.

6.3 Critical Normal Structures

Critical normal structures, including the brainstem, spinal cord, optic nerves, chiasm, retina, eyes, temporal lobes, and frontal lobes should be outlined in all cases. Parotid glands, submandibular glands, oral cavity, cochleas, temporomandibular joints, mandibles, pituitary glands, hypothalamus, and lacrimal glands should also be outlined.

6.4 Treatment Planning

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 and critical normal structures.

6.4.1 Dose Specifications

6.4.1.1 The gross primary tumor and lymph node metastasis of greater than 2 cm, $PTV_{70,}$ will receive 70 CGE in 35 fractions at 2 CGE per fraction. An additional of boost of 6 CGE in 3 fractions to the primary gross tumor volume for patients with large primary tumors is at the discretion of the physician.

6.4.1.2 The lymph node metastasis of 1 - 2 cm, $PTV_{66,}$ will receive 66 CGE in 33 fractions at 2 CGE per fraction.

6.4.1.3 The primary subclinical and the high risk nodal region (PTV_{60}) will receive 30 fractions of 2.0 CGE per fraction, total 60 CGE.

6.4.1.4 The low neck (including) supraclavicular field will be treated with conventional AP field or AP/PA fields at the discretion of the physician, and will receive 25 - 27 fractions of 2.0 CGE/fraction to a total 50 - 54 CGE unless there are gross nodes in which all the gross nodes should receive the same dose as the PTV_{66-70}.

6.4.1.5 PTV_{70} and PTV_{60} of the upper field will be treated with a combination of proton beam and photon radiation. The low neck will be treated with photon only.

6.4.1.6 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_{70} will receive $\geq$ 110% of the prescribed dose. No more than 1% of any PTV_{70} and any PTV_{60} 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_{70}.

Table 1. Radiation dose summary

Target	Dose	Designation
Primary Gross Disease	70 CGE	PTV_{70}
Nodal Disease > 2cm	70 CGE	PTV_{70}
Nodal Disease 1 - 2cm	66 CGE	PTV_{66}
Primary subclinical	60 CGE	PTV_{60}
High risk nodal region	60 CGE	PTV_{60}
Low neck	50-54 CGE	PTV_{50-54}

6.4.2 DVH's must be generated for all critical normal structures and the unspecified tissues.

Table 2. Dose constraints to critical tissues

Normal tissues	Total dose (CGE)	Dose per fraction (CGE)
Brainstem (surface)	$\leq$ 60 - 64	$\leq$ 2.0
Brainstem (center)	<54	$\leq$ 2.0
Spinal Cord (surface)	$\leq$ 50	$\leq$ 2.0
Spinal Cord (center)	$\leq$ 45	$\leq$ 2.0
Optic nerves	$\leq$ 54 - 63	$\leq$ 2.0
Chiasm	$\leq$ 54 - 63	$\leq$ 2.0
Retina	$\leq$ 45	$\leq$ 2.0
Temporal/frontal lobes	$\leq$ 70	$\leq$ 2.0

6.4.3 Other Normal Structures

Parotid glands: Mean dose ≤ 26 CGE *(at least one gland)*, or at least 20 cc of the combined volume of both parotid glands will receive < 20 CGE or at least 50% of the gland will receive < 30 CGE *(should be achieved in at least one gland)*.

Table 3. Dose constraints to normal tissues

Normal tissues	**Total dose (CGE)**
Lacrimal gland	≤ 44
Submandibular glands	reduce the dose as much as possible
Cochleas	reduce the dose as much as possible
Temporomandibular joints	reduce the dose as much as possible
Mandible	reduce the dose as much as possible
Lens	reduce the dose as much as possible
Oral cavity	reduce the dose as much as possible
Pituitary	reduce the dose as much as possible
Hypothalamus	reduce the dose as much as possible
Larynx	≤ 45 CGE
Esophagus	reduce the dose as much as possible
Swallowing Structures	reduce the dose as much as possible
Mastication Muscles	reduce the dose as much as possible

6.4.4 *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 and normal structure constraints

2) Dose specifications

3) Planning Goals: other normal structures

6.5 Chemotherapy

6.5.1 Cisplatin

6.5.1.1 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.

6.5.1.2 Formulation: Cisplatin is available as a liquid (concentration 1 mg/ml) in a 100 ml vial.

6.5.1.3 Preparation: 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.

6.5.1.4 Storage: Cisplatin should be kept at room temperature to avoid precipitation. 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.

6.5.1.5 Administration: Cisplatin should be given immediately after preparation as a slow intravenous infusion.

6.5.1.6 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:

6.5.1.7 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.

6.5.1.8 Ototoxicity: Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2. It is manifested by tinnitus and/or hearing loss in the high frequency range. Deafness has been reported rarely.

6.5.1.9 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 or sooner. 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.

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

6.5.1.11 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.

6.5.1.12 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.

6.5.1.13 Anaphylactic-like Reactions: Anaphylactic-like reactions have occasionally been reported in patients previously exposed to

cisplatin. Symptoms include facial edema, wheezing, tachycardia, and hypotension.

6.5.1.14 Hepatotoxicity: Transient elevations in liver enzymes, especially SGOT *(AST)*, and bilirubin, have been reported.

6.5.1.15 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.

6.5.1.16 Supplier: Commercially available.

6.5.2 Fluorouracil

6.5.2.1 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.

6.5.2.2 Hepatotoxicity: Transient elevations in liver enzymes, especially SGOT *(AST)*, and bilirubin, have been reported.

6.5.2.3 Formulation: 5-FU is commercially available in a liquid (concentration 50 mg/ml) in a 100 ml vial. 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.

6.5.2.4 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.

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

6.5.2.6 Administration: continuous intravenous infusion.

6.5.2.7 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.

6.5.2.8 Supplier: Commercially available.

6.5.3 Chemotherapy Dose Schedule

Three cycles chemotherapy will be given with radiation therapy every 21 days.

Table 4. Dose schedule for cisplatin given with radiation

Agent	Dose	Route		Interval	Notes
Cisplatin	100 mg/m^2	I.V.		3 weeks (21 days)	Administered as per institutional standard

Three cycles of adjuvant cisplatin and 5-fluorouracil will be administrated after radiation therapy. Adjuvant chemotherapy can be given between 3 - 8 weeks after the completion of radiation. If adjuvant chemotherapy is delayed due to treatment related toxicities beyond 8 weeks after the completion of radiation, then adjuvant chemotherapy will be deferred.

Table 5. Dose schedule for adjuvant cisplatin and 5-Fluorouracil given after radiation

Agent	Dose	Route	-	Interval	Notes
Cisplatin	80 mg/m^2/day	I.V.	-	4 weeks (28 days)	Administered as per institutional standard
5-Fluorouracil	1,000 mg/ m^2/day	I.V.		4 weeks (28 days)	Mix according to institutional guidelines. Give as a 96 hour continuous infusion

Chemotherapy can be administered up to two days early or late if necessary for scheduling purposes.

6.5.4 Cisplatin Administration Guidelines:

6.5.4.1 Patients will be pre-hydrated with one liter of D5NS and 20 mEq KCl/L and MgSO4 (2 gm/L). An oral equivalent dose of KCl is an acceptable option.

6.5.4.2 Cisplatin in 1000 ml of NS administered as per institutional standard. Ensure there is adequate urine output prior to cisplatin infusion. Mannitol of 12.5 gm may be given immediately before the administration of cisplatin or it can be given in cisplatin infusion. Furosemide 10 mg may be given as an intravenous bolus before cisplatin infusion. For adjuvant therapy after radiation, the cisplatin dose is 80 mg/m^2.

6.5.4.3 Patients should receive at least 3 liters of fluids over the ensuing 24 hours, either parenterally or orally. The anti-emetic regimens will be administrated per institutional guidelines. In general, the antiemetics should include a 5-HT_3 antagonist (i.e. granisetron 750 mcg IV or 1 - 2 mg orally, or ondansetron 8 - 24 mg IV or orally). Additional antiemetics may include, but are not limited to, lorazepam, aprepitant, metoclopramide and/or prochlorperazine.

6.5.5 5-Fluorouracil Administration Guidelines:

Dose: 5-FU dose = 1000 mg/m^2/24 hr as a 96 hour continuous infusion on days 1-4 of each 28 day cycle.A central intravenous line must be in place for those who receive the continuous 5-FU infusion as outpatients.

6.5.6 Cisplatin Dose Adjustments

6.5.6.1 Neutropenia

Treatment can be delayed for up to 2 weeks until ANC is ≥ 1500/mm3. However, if the counts have not recovered in 2 weeks, the patient should go off chemotherapy. Dose reductions for reduced ANC are not based on a single nadir count. The ANC must remain < 500/mm3 for > 5 days before a dose reduction is made. If the results of the scheduled weekly complete blood count documents an ANC of < 500/mm3, repeat counts are to be obtained every other day until the ANC recovers to a level of > 500/mm3. If chemotherapy must be withheld due to neutropenia, complete blood count should be obtained weekly until the counts reach the lower limits for treatment as outlined.

Table 6. Cisplatin dose modifications in neutopenia

Nadir of last cycle		**% Dose of cisplatin from starting dose**
	ANC* on day 1 of each cycle < 1500	**ANC* on day 1 of each cycle ≥ 1500**
Febrile neutropenia (regardless of duration)	Hold	100%
< 500 for < 5 days	Hold	100%
< 500 for ≥ 5 days	Hold	80%

* ANC = absolute neutrophil count

ANC must be ≥ 1,500/mm3 on day 1 of each cycle. Reduce doses only for ANC is < 500/mm3 for ≥ 5 days.

6.5.6.2 Thrombocytopenia

Chemotherapy must not be administered until platelets are ≥ 100,000. If chemotherapy must be withheld due to thrombocytopenia, platelet counts should be obtained weekly until the counts reach the lower limits for treatment as outlined. Treatment is based upon the nadir count of the last cycle of chemotherapy as follows:

Table 7. Cisplatin dose modifications in thrombocytopenia

Nadir of last cycle		**% Dose of cisplatin from starting dose**
	Platelets on day 1 of each cycle < 100,000	**Platelets on day 1 of each cycle ≥ 100,000**
≥ 50,000	Hold	100%
< 50,000 (1st occurrence)	Hold	80%
< 50,000 (2nd occurrence)	Hold	60%

6.5.6.3 Peripheral neuropathy

A neurological examination must be performed at least before entry into the study and then once every cycle and when the patient goes off chemotherapy. In case of symptoms or signs experienced by the patient, more frequent examinations should be performed and dose modification will be as follows:

Grade 0 - 1: no change

Grade ≥ 2: Decrease cisplatin dose by 50%. Carboplatin at an AUC of 6 may be substituted for cisplatin

6.5.6.4 Otoxicity

Cisplatin is known to cause high frequency hearing loss. If grade 1 or 2 hearing loss occurs, the risk of additional hearing loss versus the potential benefit of continuing cisplatin chemotherapy should be made. If cisplatin is to be continued in the presence of grade 1 or 2 hearing loss, the dose of cisplatin should be decreased by 50%. Grade 3 and 4 hearing loss is an indication to discontinue the drug. In case of grade 3 or 4 toxicity, carboplatin (at dosage of AUC 6) may be used to replace cisplatin in the remaining chemotherapy cycles. The dose of carboplatin AUC 6 will be calculated based on the Calvert formula (table 9).

6.5.6.5 Nephrotoxicity

If, despite adequate rehydration, serum creatinine increases to ≥ grade 1 (> 1.5 x ULN), creatinine clearance should be recalculated before the next cycle and subsequent dose reductions will be considered as follows:

Table 8. Cisplatin dose modifications in kidney impairment

Calculated creatinine clearance (ml/min)		**% Dose of cisplatin from starting dose**
≥ 60		100%
< 60	0% (withhold treatment for a maximum of 2 weeks and repeat serum creatinine weekly after additional hydration), *then*	
	If *CCl was < 60 mL/min and is now:	**The percent dose to give is:**
	> 50 but < 60	80%

	≥ 40 and ≤ 50	50%
	< 40	0%

* CCl = creatinine clearance

If creatinine clearance recovers, the dose of cisplatin for the following cycle should be re-escalated to the previous dose level.

6.5.7 Carboplatin Adminstration and Dose Adjustments

Carboplatin may be substituted for cisplatin if a patient develops 1) grade 3 or higher ototoxicity, 2) grade 2 or higher peripheral neuropathy, or 3) an unacceptable cisplatin-associated nausea and vomiting after receiving 1 or 2 doses of cisplatin. In the event of carboplatin-induced ≥ 3 neurotoxicity, carboplatin is discontinued.

Carboplatin is available commercially. It should be stored and reconstituted according to standard pharmacy operating procedures.

Carboplatin will be infused over 1 to 2 hours. Carboplatin dosage (mg) will be calculated for a target AUC 6 using the Calvert formula (table 9). Creatinine clearance (CrCl) will be calculated using the Cockroft-Gault equation (table 10).

For females, use 85% of the calculated CrCl value. The actual body weight in kilograms will be utilized in the Cockroft-Gault formula (table 10). However, if the calculated creatinine clearance exceeds an upper limit for creatinine clearance, as specified below, then this ceiling value for creatinine clearance, rather than the calculated creatinine clearance, will be used in the Calvert formula to calculate the dose of carboplatin. The maximum creatinine for both male and female patients is 125ml/min. Alternatively, at the treating physician's discretion, a measured 24-hour creatinine clearance can be obtained. In this case, the measured creatinine clearance can be used to calculate the carboplatin dose in the Calvert formula (table 9).

Table 9. Calvert formula for calculation of carboplatin dosage

Dose of carboplatin (mg) = AUC x [CrCl (ml/min) + 25]

Table 10. Cockroft-Gault equation for calculation of creatinine clearance (CrCl)

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) (\text{wt kg})^*}{[72 \times \text{serum creatinine (mg/dl)}]}$$

* For female, the equation needs to be multiplied by 0.85.

6.5.7.1 Thrombocytopenia

Carboplatin must not be administered until platelets are ≥ 100,000/mm3. Treatment is based upon the nadir count of the last cycle of chemotherapy as follows:

Table 11. Carboplatin dose modifications in thrombocytopenia

Nadir of last cycle		**Dose of carboplatin**
	Platelets on day 1 of each cycle < 100,000	**Platelets on day 1 of each cycle ≥ 100,000**
≥ 50,000	Hold	AUC 5
< 50,000	Hold	AUC 4

6.5.7.2 Neutropenia

Carboplatin must not be administered until ANC ≥ 1500/mm3.

Table 12. Carboplatin dose modifications in neutropenia

Nadir of last cycle		**Dose of carboplatin**
	ANC on day 1 of each cycle < 1500	**ANC on day 1 of each cycle ≥ 1500**
Febrile neutropenia	Hold	AUC 6
< 500 for < 5 days	Hold	AUC 6
< 500 for ≥ 5 days	Hold	AUC 4

6.5.8 5-Fluorouracil Dose Adjustments

6.5.8.1 Mucositis

In case of grade 3 mucositis lasting more than 96 hours or grade 4 mucositis, 5-fluorouracil dose will be reduced by 20% from 1000 to 800 mg/m2/day. A mouth rinse should always be allowed.

In case of grade 3 mucositis lasting more than 120 hours as a second occurrence or grade 4 mucositis as a second occurrence, the dose of 5-fluorouracil will be reduced to 800 mg/m2/day for 3 days.

6.5.8.2 Diarrhea

In the case of severe diarrhea, octreotide is recommended. If the patient has a significant diarrhea occurrence again (> 3 loose stools/24 hr), the patient should be treated prophylactically in the subsequent cycles with 2 tablets of loperamide or diphenoxylate in addition to 1 or 2 tablets after each loose stool. The maximum daily dose of loperamide is 16mg and diphenoxylate is 20mg/day.

For grade 4 diarrhea, or grade 3 diarrhea lasting > 7 days despite the prophylactic treatment, 5-fluorouracil will be reduced by 10% per day from 1000 mg/m²/day to 900 mg/m²/day for subsequent cycles. Appropriate symptomatic treatment with loperamide or diphenoxylate hydrochloride with atropine sulfate should be given.

If despite these measures, grade 4 diarrhea or grade 3 diarrhea lasting > 7 days occurs again, the dose of 5-fluorouracil will be reduced 20% from 1000 mg/m²/day to 800 mg/m²/day in the subsequent cycle.

6.5.8.3 Hematologic

For grade 2 or higher hematologic toxicities, 5-fluorouracil dose will be reduced by 20% from 1000 to 800 mg/m2/day. For grade 2 or higher hematologic toxicities as a second occurrence, 5-fluorouracil dose will be reduced from 800 to 640 mg/m2/day.

6.5.8.4 Skin

In case of rash including hand-foot syndrome or moist desquamation of grade 3 lasting > 7 days or grade 4, the dose of 5-fluorouracil will be reduced by 20% from 1000 mg/m²/day to 800 mg/m²/day in the subsequent cycle.

6.5.8.5 Cardiac

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.

6.6 Neck Dissection

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

7.0 Toxicity Measurement

Toxicities will be graded according to the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAE) (Appendix XI).

8.0 Quality of Life Assessment

In patients with head and neck carcinoma, both the disease and its treatment often significantly impact daily functions and activities such as eating, speaking, and socializing. Radiotherapy, particularly combined with chemotherapy, is associated with severe mucositis, sticky saliva, pain, dry mouth, hoarseness, fatigue, skin irritation, and difficulties in swallowing and tasting. Many of these symptoms can persist years after completion of treatment. Dental problems such as radiation caries could develop. Many of these side effects are the results of photon irradiation to the normal tissues, such as the major salivary glands, adjacent to the tumor.

Proton beam radiation has very distinctive physical properties. The beams can be modulated so that the beam stops at the distal edge of the target, resulting in little or no exit dose. This superior dose distribution, when compared to photons, allows high dose conformality and uniform dose distribution around the target and much lower integral dose to the non-target normal tissue. The impact of proton beam irradiation in the health-related quality of life (QOL) of the head and neck cancer patients has not been studied.

8.1 Self-assessment of quality-of-life

The validated 35-item EORTC-QLQ-H&N questionnaire along with the EORTC QLQ-C30 which measures general quality of life will be used (Appendix IV and V). These self-administrated questionnaires will be given pre-radiation treatment, at approximately 1.5, 3, 6, 12, and 24 months post-treatment.

Patients who are found to have serious concerns in quality of life at any time point will be referred to the appropriate sources accordingly. For patients with severe mucositis and pharyngitis, pain medications will be prescribed. Patients with difficulty swallowing or speech dysfunction will be evaluated by speech and swallowing specialists. Patients who have difficulty maintaining their weights will be referred to the nutritional service; gastrostomy tube for feeding will be placed if indicated. Patients with dental problems will be evaluated by the dental service. For patients with difficulties with body image and social interactions, they will be offered to meet with a social worker to discuss their problems. Psychiatric evaluation will be referred if indicated.

8.2 Objective assessment of swallowing function

Improved locoregional control of advanced head and neck cancer has been reported using concurrent radiotherapy and chemotherapy. Concurrent chemoradiation can result in increased acute and long-term dysphagia compared with radiation alone. Late dyshpagia and fibrosis are major factors limiting the intensity of therapeutic regimens for head and neck cancer.

Videofluoroscopic swallowing study (VFSS) (Appendix X) will be used to evaluate swallowing function. VFSS is a validated method of objective assessment of swallowing, allowing viewing and recording of the structures and dynamics of the swallowing process. Each subject will be asked to swallow multiple trials of various food consistencies in varying amounts. The consistencies included thin liquid barium (diluted with water) followed with non-diluted barium, followed with a puree, soft food (fruit mixed with barium), and a solid (shortbread cookie) coated with barium. The examinations are recorded, and analysis of the three phases of swallowing - oral, pharyngeal, and esophageal – is subsequently completed. Assessment will be focused on bolus manipulation and control and bolus passage, including cohesion, motility, and timing.

Evaluation of swallowing function will be performed pre-therapy and at approximately 3, 12, and 24 months after therapy.

8.3 Objective assessment of xerostomia

Sialometry will be performed before initiation of the first radiation fraction, and at approximately 3, 6, 12, and 24 months after the completion of radiation.

8.3.1 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 accumulated saliva should be collected into a pre-weighted container. 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.

8.3.2 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, using the same method as for unstimulated saliva.

8.4 Speech Assessment/Head and Neck Health Status Assessment Inventory (HNHSAI)

Patient self-assessment of speech outcome is an important element in quality-of-life measurements after chemoradiation. Speech assessment questionnaires are from the Head and neck health status assessment inventory (HNHSAI) (14). Nine functional and five attitudinal speech items will be used. The patients' responses to the HNHSAI will be recorded so that the lowest value of 1 represents the most impaired function and the highest value of 5 represents normal or optimal function. "Not applicable" responses are considered appropriate. If the patient responded to the query about problems talking at work with the "not applicable" response (i.e. "I'm not currently employed"), the response will be treated as missing. The speech assessment will be conducted within 14 days of initiation of radiation treatment and at 1.5, 3, 6, 12, and 24 months after treatment completion.

8.5 ChemoSensory Questionnaire (CSQ)

Treatments for head and neck cancer commonly results in smell and taste dysfunction which then can lead to quality-of-life changes. Smell and taste dysfunction can also have a major negative impact on patients' nutrition status.

The Chemosensory Questionnaire (CSQ) developed by Goldberg et al (15) will be used. Four questions each on smell and taste will be used. A minimum score of 4 and a maximum of 20 for the smell scale and taste scale are possible with a higher score indicating better function. If there is a single missing score in a single section, the average of the three remaining scores is used for the missing value. If two questions are missing in a single section, then the survey section is invalid. The chemosensory assessment will be conducted within 14 days of initiation of radiation treatment and at 1.5, 3, 6, 12, and 24 months after treatment completion.

8.6 Trismus Assessment

Trismus or restricted mouth opening is a very common side effect after conventional radiation therapy for nasopharyngeal carcinoma. Radiotherapy involving the structures of the temporomandibular joint or muscles of mastication could result in trimus. The degree of trismus will be measured by serial changes of the maximal inter-incisal distance in the vertical opening, right lateral, and left lateral jaw movements. The trismus assessment will be conducted within 14 days of initiation of radiation treatment and at 1.5, 3, 6, 12, and 24 months after treatment completion.

8.7 Patient Swallowing Diary

Besides the objective assessment of swallowing function by the videofluoroscopic measurements, patient self-assessment of swallowing function is also important. Subjective swallowing dysfunction has been shown to be common after conventional radiation therapy for nasopharyngeal carcinoma (16). In the patient swallowing diary, patients will be ask about their swallowing function with solids and liquids before radiation begins, each day during radiation treatment, and at 1.5, 3, 6, 12, and 24 months after treatment completion.

9.0 Data Collection

Table 13. Evaluations before, during, and after chemoradiation

	Pre-study (timing before study entry)	**Pre-treatment**	**During chemoradiation**[b]	**During chemotherapy alone**	**Follow-up**[c]
History & physical	14 days		X	X	X
Disease	8 weeks				X

documentation	(*EUA)				
Dental evaluation		6 months			
Tobacco and alcohol assessment		14 days			
Nutritional evaluation		1 month			
Patient swallowing diary		14 days	X		1.5, 3, 12, 24 months[i]
CBC/platelets	14 days		X	X[h]	X
Chemistry (alkaline phosphatase[a], AST, ALT, bilirubin, BUN, serum creatinine, creatinine clearance (if indicated), electrolytes (Na, K, Mg, Cl), calcium, protein, albumin, urinalysis (if indicated)	14 days		X (Weekly for BUN and creatinine. Every 3 weeks for the others)	X (Every 3 weeks)	
β-HCG for females at risk for pregnancy	14 days				
Thyroid function panel (TSH, T3, T4)	14 days				X[l]
Chest X-ray or CT	1 month				X[d]
CT/MRI of H&N	1 month				X[d]
PET/CT[f]		1 month			X
Toxicity evaluation			X	X[e]	X
Swallow study		21 days			3, 12, 24 months[i]
Salivary study		21 days			3, 6, 12, 24 months[i]
Speech assessment (HNHSAI)		14 days			1.5, 3, 6, 12, 24 months[i]
Subjective QOL		14 days			1.5, 3, 6, 12, 24 months[i]
Physician dysphagia log		14 days			1.5, 3, 6, 12, 24 months[i]

Audiogram	6 weeks				X[g]
Chemosensory questionnaire (CSQ)		14 days			1.5,3,6,12,24 months[i]
Trismus assessment		14 days			1.5,3,6,12,24 months[i]

* EUA = examination under anesthesia

X denotes the type of evaluation that needs to be performed during the study period.

a. Liver CT or MRI 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.
b. Weekly during radiotherapy.
c. Follow-up will be performed after radiation and then every 3 (+/-3 weeks) months during the first two years; every 6 (+/- 3 months) months during years 3 - 5; then annually (+/- 6 months). After year 5, patients are encouraged to continue with the follow-up appointments and studies annually (+/- 6 months). All follow-up appointments and studies may be performed at non-participating institutions with results sent to the participating institutions for review.
d. These tests will be performed at least every 6 months (+/- 3 months) during the first 3 years; the first CT/MRI of nasopharynx will be performed at approximately 2 months after radiation.
e. Prior to each cycle.
f. PET/CT is optional but encouraged. It will be performed prior to treatment (must be ≤ 21 days prior to study entry), at approximately 2 months after radiation, and every 6 months during the first 3 years.
g. Yearly (+/- 6 months) or clinically indicated. Once patients have reached the 24-month follow-up time point, patients are encouraged but not required to perform these studies at their annual (+/- 6 months) follow-up appointments.
h. Every three weeks, or more frequently as clinically indicated. CBC/platelets must be drawn before treatment, either on day 1 of each cycle or no more than 72 hours in advance of each cycle.
i. The 1.5 month studies will be performed at 1.5 (+/- 1) month after radiation, 3-month studies will be performed at 3 months (+/- 6 weeks), the 6-month studies will be performed at 6 (+/- 3) months, the 12-month studies will be performed at 6 (+/- 3 months), and the 24-month studies will be performed at 24 (+/- 6) months. Once patients have reached the 24-month follow-up time point, Patients are encouraged but not required to perform these studies at their annual (+/- 6 months) follow-up appointments.

10.0 Adverse Events Reports

Adverse events resulting from unanticipated treatment toxicity that is life threatening or fatal will be reported to the IRB within 10 working days.

11.0 Modality Review

Local Recurrence

Local recurrence is defined as: evidence of tumor growth/regrowth in any direction beyond that present on the pre-treatment imaging studies or the appearance of tumor in tissues previously scored as sites of sub-clinical disease. The imaging studies are to be comparable in technical factors. Site of failure will be related to treatment volumes PTV1, 2, and 3.

Nodal Recurrence

Recurrence in regional draining lymph nodes

Compliance to therapy

Defined as the number of courses of concurrent and adjuvant chemotherapy received, as well as the time required to complete the radiotherapy.

Distant Recurrence

Defined as appearance of tumor at sites beyond regional nodal and marginal sites.

Progression-Free and Overall Survival

Measured from the date of registration to the date of progressive disease or death.

12.0 Biostatistical Considerations

The rationale of using protons in the combined modality treatment of locally advanced nasopharyngeal carcinoma is the potential to improve patient outcome if the treatment compliance were improved by reducing acute toxicity. In particular, better tolerance of systemic chemotherapy is expected with the greater degree of normal tissue sparing by the proton beam. Only 55% of the patients on the Intergroup Study completed all 3 concurrent and 3 adjuvant cycles of chemotherapy (9), using the same regimen as in the present protocol. A sample size of 25 patients will provide 80% power to determine an increase in the chemotherapy completion rate to at least 77% at a one-sided significance level of 6%. The error rates correspond to a decision rule that requires a minimum of 18 patients to complete all 6 cycles of protocol-indicated chemotherapy.

Mucositis was the most common reason for discontinuing chemotherapy in the Intergroup study, with 37% of patients experiencing grade 3 or 4 events on the chemoradiation arm. If grade 3 or 4 mucositis were observed among no more than 5 of the 25 patients treated by proton radiotherapy, 80% power will be available to detect a decrease in the rate to 16%. The decision rule is associated with a one-sided significance

level of 6% under the null hypothesis assuming no difference from the Intergroup data. In general, 25 patients will provide 90% confidence interval widths that are no more than 35% for estimating the rate of acute and late effects. As all other toxicities are expected to be less common than mucositis, interval widths will be much narrower in practice.

A secondary objective will investigate the rate and pattern of loco-regional recurrence. In addition to progression-free survival, the rate of loco-regional failure first will be estimated by allowing for competing risks due to distant failure and death from other causes. The subgroup sample size will be limited for each of the T1-T2 and T3-T4 tumor categories, especially as the patient distribution cannot be projected definitively for the accrual of only 25 patients with a rare cancer. Thus the goal will be mainly to show the null hypothesis cannot be rejected, that is, the local control rate in tumor subgroups will not be lower than that observed using conventional radiotherapy in combined modality treatment. The accrual goal of 25 patients is anticipated to be reached in about 3 years. The referral pattern of tumor stage to proton treatment suggests the expected accrual distribution will be approximately 6 patients with T1 - 2 tumors and 18 patients with T3 - 4 tumors. Assuming the local-regional control rate was 70% for T1-T2 tumors at 3 years based on conventional radiotherapy regimens, the probability is 7% for at least 4 of 6 patients to have experienced local-regional failure within 3 years. If the local-regional control rate of T3 - 4 tumors using protons were the same as the historical 50% rate using conventional radiotherapy, the probability is 5% for 13 or more of 18 patients to have failed locally or in the regional lymph nodes.

13.0 References

1. Chu A, Flynn MB, Achino E, et al. Irradiation of nasopharyngeal carcinoma: Correlations with treatment factors and stage. Int J Radiat Oncol Biol Phys 1984;10:2241–2249.

2. Hoppe RT, Goffinet DR, Bagshaw MA. Carcinoma of the nasopharynx: Eighteen years' experience with megavoltage radiation therapy. Cancer 1976;37:2605–2612.

3. Mesic JB, Fletcher GH, Goepfert H. Megavoltage irradiation of epithelial tumors of the nasopharynx. Int J Radiat Oncol Biol Phys 1981;7:447–453.

4. Sanguineti G, Geara F, Garden A, et al. Carcinoma of the nasopharynx treated by radiotherapy alone: Determinants of local and regional control. Int J Radiat Oncol Biol Phys 1997;37:983–996.

5. Bailet JW, Mark RJ, Abemayor E, et al. Nasopharyngeal carcinoma: Treatment results with primary radiation therapy. Laryngoscope 1992;102:965–972.

6. Vikram B, Strong EW, Manolatos S, et al. Improved survival in carcinoma of the nasopharynx. Head Neck Surg 1984;7:123–128.

7. Wang CC. Carcinoma of the nasopharynx. In: Wang CC, editor. Radiation therapy for head and neck neoplasms: 3rd ed. Wiley-Liss Publishers; 1997. p. 257–280.

8. Kwong D, Sham J, Choy D: The effect of loco-regional control on distant metastatic dissemination in carcinoma of the nasopharynx: An analysis of 1301 patients. Int J Radiat Oncol Biol Phys 1994;30:1029–1036.

9. Al-Sarraf M, LeBlanc M, Giri PGS, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup Study 0099. J Clin Oncol 1998;16:1310–1317.

10. Lin JC, Jan JS, Hsu CY, et al. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol. 2003;21:631–637.

11. Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol. 2002;20:2038–2044.

12. Suit HD. Protons to replace photons in external beam radiation therapy? Clin Oncol (R Coll Radiol). 2003;15:S29–31.

13. Chan AW, Liebsch LJ, Deschler DG, et al. Proton radiotherapy for T4 nasopharyngeal carcinoma. American Society of Clinical Oncology 40th Annual Meeting 2004; New Orleans, Louisiana.

14. Karnell LH, Funk GF, Tomblin JB, et al. Quality of life measurements of speech in the head and neck cancer patient population. Head and Neck. 1999;21:229-238.

15. Goldberg AN, Shea JA, Deems DA, et al. A chemosensory Questionnaire for patients treated for cancer of the head and neck. Laryngoscope. 2005;115:2077-2086.

16. Ku PK, Yuen EH, Cheung DM, et al. Early swallowing problems in a cohort of patients with nasopharyngeal carcinoma: Symptomatology and videofluoroscopic findings. Laryngoscope. 2007;117(1):142-6.

14.0 Regulatory Requirements

14.1 Declaration of Helsinki

The PI will ensure that this study will be conducted in full conformity with the current version of the declaration of Helsinki and with U.S. FDA requirements.

14.2 Informed Consent

The PI and Co-PIs will obtain witnessed informed consent of the patients (or patients' parents or guardians if appropriate) after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study to the patient (or patients' parents or guardians if appropriate). The patient will be given a copy of the informed consent which is stamped 'Patients Reference Copy'. The original signed copy informed consent will be retained in the patient's radiation oncology record.

14.3 Patient Confidentiality

The investigators will ensure that patient anonymity is maintained.

APPENDIX I - PERFORMANCE STATUS

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)*.

APPENDIX II - STAGING SYSTEM

NASOPHARYNX, AJCC STAGING, 6th Edition, 2002

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
- T2a tumor extends to the oropharynx and/or nasal cavity without parapharyngeal extension*
- T2b any tumor 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, orbit, or masticator space

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor beyond the pharyngobasilar fascia.

Regional Lymph Nodes (N)

NX Regional lymph node metastasis
N0 No 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) *, greater than 6 cm and/or to supraclavicular fossa
- N3a greater than 6 cm in dimension
- N3b extension to the supraclavicular fossa**

*Note: Midline nodes are considered ipsilateral notes

**Note: Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder (see figure below). Note this would

include caudal portions of Levels IV and V. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

Stage Grouping: Nasopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
Stage III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	N0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1