

## **Cover page**

**Protocol Title:** Phase II Concurrent proton and chemotherapy in locally advanced stage

IIIA/B Non-Small Cell Lung Cancer (NSCLC)

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Phase II Concurrent proton and chemotherapy in locally advanced stage IIIA/B  
Non-Small Cell Lung Cancer (NSCLC)  
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**Core Protocol Information**

<b>Short Title</b>	Phase II Concurrent proton and chemotherapy in locally advanced stage IIIA/B Non-Small Cell Lung Cancer (NSCLC)
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<b>Full Title:</b>	Phase II Concurrent proton and chemotherapy in locally advanced stage IIIA/B Non-Small Cell Lung Cancer (NSCLC)
<b>Protocol Type:</b>	Standard Protocol
<b>Protocol Phase:</b>	Phase II
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Which Committee will review this protocol?

- The Clinical Research Committee - (CRC)

## Protocol Body

### 1.0 Objectives

To assess therapeutic efficacy and toxicities of proton radiotherapy with concurrent chemotherapy for patients with inoperable stages IIIA/B non-small cell lung cancer (NSCLC).

**Primary goal:** Improve median survival.

**Secondary goals:**

1. Improve local control, progression free survival, disease specific survival and disease free survival.
2. Decrease grade 3 and above toxicities.
3. Pre- and post treatment PET/CT in predicting clinic outcome.
4. Biomarker for predicting treatment response and toxicities.

### 2.0 Rationale

1. Uncontrolled local-regional tumor is a major source for continuous seeding to distant organs and causes eventual treatment failure in locally advanced stage IIIA/B NSCLC. With conventional photon radiotherapy, the 2 years local control is only 20% for stage IIIA/B NSCLC. Eradication of local-regional tumor is an essential step for cure.
2. Current literature indicates that there is a dose-response relation for both local tumor control and survival instage III NSCLC. However, toxicities related to high dose of photon treatment limit the potential of dose escalation. For a given level of normal tissue toxicity, the MTD of proton radiotherapy is likely higher than that of conventional photon radiotherapy because of its physical characteristics (the bragg peak). Therefore, proton radiotherapy may have an advantage over conventional photon radiotherapy in attaining local tumor control, improving survival with reduced toxicities.
3. Concurrent chemo/RT has been showed by CALGB and RTOG to improve local control and overall survival compared with radiotherapy alone or sequential chemo/radiotherapy. Adjuvant chemotherapy following concurrent chemo/RT revealed very promising clinical outcome in the recent SWOG studies.
4. Our preliminary data showed that tumor uptake intensity in pre-treatment PET scan predicts poor survival in NSCLC (Komaki et al). Comparison of pre and post treatment PET/CT scans may predict both local control and survival in patients with stage III NSCLC treated with proton radiotherapy and chemotherapy.
5. Certain tumor is resistant to radiotherapy and/or chemotherapy. Each patient may have unique sensitivity for radiotherapy and/or chemotherapy in terms of tumor response and treatment related toxicities. Novel biomarker may help us to identify patients with different radiation and/or chemotherapy sensitivities and individualize patient's treatment in the future.

Data support the concurrent chemoradiotherapy, adjuvant chemotherapy and

radiation dose escalation of stage III NSCLC:

1. In a sequential radiation dose escalation study over a period of 5 years for patients with stage III NSCLC, Choi showed that actuarial 3-year survival rates with a minimum follow-up of 2-year were 28%, 19%, 15%, 5%, and 0% with 60-64 Gy, 56-59 Gy, 50-55 Gy, 46-49 Gy, and 40-45 Gy respectively.
2. Schaake-koning et al. compared radiotherapy alone with radiotherapy plus daily cisplatin or weekly cisplatin. There was no difference in distant failure rates between the groups with or without cisplatin. However, survival in radiotherapy plus cisplatin group was 54%, 26%, and 16% at 1, 2 and 3 years as compared with 46%, 13% and 2 % in radiotherapy alone group respectively,  $p=0.009$ . Therefore, this study showed that a gain in local tumor control seems to have been translated into a gain in survival.
3. CALGB (Dillman et al) conducted a randomized trial to determine whether induction chemotherapy before irradiation improves survival for patients with stage III non-small-cell cancer of the lung. Patients who were randomly assigned to group 1, received cisplatin and vinblastine and began radiation therapy on day 50 (60 Gy over a 6-week period). Patients assigned to group 2 received the same radiation therapy but began it immediately and received no chemotherapy. The median survival was greater for those in group 1-13.8 versus 9.7 months ( $P = 0.0066$  by log-rank test). Rates of survival in group 1 were 55 percent after one year, 26 percent after two years, and 23 percent after three years, as compared with 40, 13, and 11 percent, respectively, in group 2. Those in group 1 had a higher incidence of serious infections requiring hospitalization (7 percent, vs. 3 percent in group 2) and severe weight loss (14 percent vs. 6 percent), but there were no treatment-related deaths.
4. RTOG (Curran et al) conducted a three-arm randomized trial to analyze whether the concurrent delivery of cisplatin-based chemotherapy with thoracic radiotherapy (TRT) improves survival when compared with the sequential delivery of these therapies for patients with locally advanced, unresected stage II-III NSCLC. The sequential arm ((SEQ) included cisplatin (P, 100 mg/m<sup>2</sup>) and Vlb (5 mg/m<sup>2</sup>) with 60 Gray (Gy) radiotherapy beginning day 50, and Arm 2 used the same chemotherapy with 60 Gy TRT beginning day 1 (CON-QD). Arm 3 employed P 50 mg/m<sup>2</sup> day 1, 8, 29, & 36 with oral etoposide 50 mg BID x 10 weeks 1, 2, 5, & 6 with 69.6 Gy in 1.2 Gy BID fractions beginning day 1 (CON-BID). Of the 595 analyzable patients, the rates of acute grade 3-5 non-hematologic (N-H) toxicity rates were higher with concurrent than sequential therapy, but late toxicity rates were similar (18%-27%). With minimum and median potential follow-up times of 4.0 and 6.0 years, the median & 4-yr survivals are 14.6 mo & 12% (SEQ), 17.0 mo & 21% (CON-QD RT), & 15.2 mo & 17% (CON-BID RT). The CON-QD RT arm has better survival than the SEQ arm ( $p=0.046$ ). This report demonstrates the long-term survival benefit of the concurrent delivery of cisplatin-based chemotherapy with TRT as compared with the sequential delivery of these therapies. The local regional failure was 50% (SEQ), 43% (CON-QD) and 34% (CON-BID). The acute toxicities is higher in Con-BID with 68% grade 3 and above toxicities compared with 48% in CON-QD group. There was no significant difference in late toxicities and survival between these two groups. However, radiotherapy in field failure is improved in CON-BID group. Higher toxicities in con-BID group may explain the lack the benefit of survival. In RTOG 94-10, radiotherapy was based on two dimensional planning that is usually associated with higher toxicity.

5. SWOG (Gandara et al) reported their phase II trial consolidation docetaxel after concurrent chemoradiotherapy in patients with pathologically documented stage IIIB non-small-cell lung cancer (NSCLC). Results were compared with those of the predecessor study with identical eligibility, staging criteria, and treatment, except docetaxel consolidation. Median progression-free survival was 16 months, median survival was 26 months, and 1-, 2-, and 3-year survival rates were 76%, 54%, and 37%, respectively. Brain metastasis was the most common site of failure. In the previous SWOG study with same patients group and same concurrent chemoradiotherapy except no consolidation chemotherapy was offered, median survival was 15 months and 1-, 2-, and 3-year survival rates were 58%, 34%, and 17%, respectively. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB NSCLC is feasible and generally tolerable, and results compare favorably with the predecessor trial study.
6. Rosenman et al conducted phase I/II clinical trial using high dose conformal radiotherapy ((60-74 GY) for inoperable stage IIIA/IIIB NSCLC with induction chemotherapy followed by concurrent chemoradiotherapy. They reported 36% 3 years survival and 13% locoregional relapse as the only site of failure. For patients who finished radiotherapy, the 3 years survival was 45%. No grade 3 or above lung toxicities was reported. 8% developed grade 3/4 esophagitis. The same group is conducting higher dose-escalation to up to 90 GY (Morris et al). At 90 GY, cases of broncho-esophageal fistula, bronchial stenosis, and fatal pulmonary hemoptysis were reported although the incidence is still very low. The local control data and survival are not available. Distant metastasis is still the major failure.
7. Recently, Dr. Movsas published RTOG 98-01 using induction chemotherapy with carboplatin and paclitaxel followed by concurrent chemotherapy (same regiment) with radiotherapy to 69.6 GY with 1.2 GY/fraction given as twice a day in patients with stage III NSCLC. In this study, modern 3 dimensional conformal radiotherapy was used. The median survival was about 17 months. The grade 3 and above acute and chronic non-hematological toxicity was about 49% (10% grade 4 and above toxicity). This toxicity data can be used as baseline for toxicity using 3 dimensional radiotherapy in NSCLC.

Since RTOG 9410 was conducted, the chemotherapy for stage III NSCLC has evolved. Paclitaxel and Carboplatin have become standard regiments due to its potential lower toxicities profiles as showed by phase III study of ECOG 1594 (Schiller et al) . In the current study, we will study the efficacy and treatment related toxicities using proton radiotherapy with concurrent chemotherapy followed by adjuvant chemotherapy to treat locally advanced NSCLC. Base on Dr. Rosenman study, 74 GY given with 2 GY/fraction with concurrent chemotherapy is tolerable. Local control and survival are very promising. There are no clear evidence of improved clinical outcome with higher dosage. Therefore, 74 GY with 2 GY/fraction of proton radiotherapy and concurrent chemotherapy using Paclitaxel and Carboplatin will be used. To further reduce the distant metastasis, consolidative full dose chemotherapy will be offered. We will also study the predictive value of pre- and post treatment PET/CT in predicting treatment response. Potential molecular markers for predicting therapeutic effects and toxicities will be explored.

### 3.0 Patient Eligibility

#### Inclusion Criteria:

1. Histologically or cytologically documented NSCLC.
2. Inoperable stage IIIA (T1--3N2MO, T3N1MO) and IIIB (T1-3N3MO, T4NO-3MO) disease excluding malignant pleural effusion.
3. Performance score KPS 70-100, Weight loss: less or equal to 10% in 6 months prior to diagnosis.
4. Patient consented for the protocol.
5. Induction Chemotherapy is allowed.

#### Exclusion criteria:

1. Prior chest radiotherapy.
2. Previous or concomitant malignancy other than (a) curatively treated carcinoma in situ of cervix, (b) basal cell carcinoma of the skin, (c) curatively treated superficial transitional cell carcinoma of the urinary bladder, and (d) early stage tumor treated more than 3 years ago for cure.
3. Pregnancy. Patients (men and women) of child bearing potential should use an effective (for them) method of birth control throughout their participation in this study.

#### Off study criteria:

1. If a patient is found to have distant metastasis during treatment and/or immediate after the treatment (<60 days) indicating inaccurate cancer stage, he or she will be taken off study.
2. If a patient does not follow up at MD Anderson and does not forward his or her medical records such as CT, PET/CT, PFT or pathology report as required by protocol, he or she will be taken off study.
3. If a patient does not have any required post-treatment evaluation such as images, he or she will be taken off study.

### 4.0 Treatment Plan

Patients will receive proton radiotherapy to total dose of 74 GY (cobalt gray equivalents) with 2 GY/fraction for 37 fractions (daily treatment, Monday to Friday, for 7.5 weeks). All patients will receive concurrent chemotherapy using Paclitaxel and Carboplatin followed by possible adjuvant full dose chemotherapy.

#### RT techniques:

All patients will be required to have 4D-CT simulation to take tumor motion into consideration. As part of standard 4-D CT simulation procedure, patients will be evaluated for regularity of breathing, responsiveness to feedback guidance, breath-hold capability, and suitability for implantation of fiducial markers. Based on this evaluation, a treatment delivery technique will be selected:

1. breath-hold (with or without feedback guidance),
2. gated treatment, or
3. free-breathing (with or without feedback guidance).

A 4D-CT study will be required for treatment planning purposes using the technique equivalent to the planned delivery technique.

Breath-hold will be used for patients who can hold their breaths for a minimum of 7 seconds and can do so repeatedly and reproducibly. Patients who do not qualify for the breath-hold delivery, but are able to breath regularly and reproducibly will be treated with gating when available. When gating is not available, they will be treated with a free-breathing technique. Patients who do not qualify for the breath-hold delivery and do not have regular reproducible breathing will be treated with a free-breathing technique.

Feedback guidance, visual and/or audio, will be used for all patients who respond well to training with the feedback devices.

Gross Target Volume (GTV): Primary tumor, all nodal disease documented in image studies, including CT and/or PET Scan. Pulmonary extent of lung tumors should be delineated on lung windows and mediastinal extent of lung tumor should be delineated using mediastinal windows. PET-CT in simulated position is strongly encouraged.

The GTV should be delineated based on 4D-CT images and PET scan should be used as a guide. If PET is positive but there is no CT correlation, physician should consult with diagnostic radiologist. However, if CT image meets the criteria of pathological change (1.5 cm in shortest axis) but PET is negative, physician may include the lesions as a GTV based on his/her clinical judgement. For patient with obstructive atelectasis, PET-CT should be considered to exclude the atelectasis from GTV. Both CT image and PET image can be considered as guide to exclude the atelectasis. Repeat simulation should be considered 3-4 weeks after treatment in case the lung has been expanded.

Contralateral mediastinal or contralateral hilar or S/C lymph nodes should only be included in the GTV when they are positive in the PET and/or CT studies. Ipsilateral hilum should be included as GTV if subcarinal LN or mediastinal LN is involved. Based on Japanese surgical study report, we recommend the following prophylactic treatment for lymph node stations without imaging evidence of involvement (J Thoracic Cardiovasc Surg 1999; 117:1102). For the right mid lobe or right lower lobe, or left lingular, left lower lobe lesion, if mediastinal LN is involved, subcarinal LN should be included as GTV. For left upper lobe lesion, AP window LN should be included as GTV if there is mediastinal LN involvement including subcarinal LN.

For patients who received induction chemotherapy followed by concurrent chemo/RT, GTV should include post-chemo lung extent of GTV, plus pre-chemo abnormal lymphnode stations, plus ipsilateral hilum if mediastinal or subcarinal LN was involved. If patient has CR after chemotherapy, pre-chemo LN station and pre-chemo lung parenchymal disease should be included as CTV and treated to a dose of at least 50 Gy. If disease progress during chemotherapy, the GTV should cover the progressed disease.

Internal Gross Target Volume (IGTV): IGTV is the volume containing the GTV throughout its motion during respiration.

Clinical Target Volume (CTV): GTV plus margin of 8 mm. For patients who received induction chemotherapy, 8 mm margin should be considered. In general, CTVs should not extend beyond anatomic boundaries unless there is evidence of invasion. For example, CTVs should not extend into chest wall or vertebral body without CT/MRI evidence of invasion. Physician should delineate the CTV.

Internal Clinical Target Volume (ICTV): IGTV plus 8 mm margin.

If patient is to be treated using a breath hold or radiation gating technique, the CTV seen on the 4D-CT at the phase corresponding to the radiation delivery plus a margin for residual tumor motion will be used for planning. If the patient is to be treated using free breathing, with or without feedback guidance, the ICTV will be used for planning so that the prescription dose is delivered to the CTV throughout its motion during radiation.

Planning Target Volume (PTV): CTV or ICTV plus margin for daily setup uncertainty. The PTV will be used for evaluation of treatment plans, but not in the design of treatments.

The dose delivered to all important organs should be kept in the dose volume constraints as showed in bellow:

**Dose volume constraints:**

	RT/Chemo
<b>Cord<sup>1</sup></b>	45 Gy
<b>Lung<sup>2</sup></b>	20 Gy (<40%)
<b>Heart</b>	40 Gy (<100%), 50Gy (<50%)
<b>Esophagus</b>	60 Gy (<50%)
<b>Kidney</b>	20 GY (<50% of combined both kidneys or <75% of one side of kidney if another kidney is not functional)
<b>Liver</b>	30 GY (<40%)

1 We should take the treated volume size of spinal cord and dose fraction size to spinal cord into consideration. The chance of spinal cord damage is increased as treated volume or dose fraction size increased. In general, spinal cord should not receive dose of more than 45 GY if dose fraction size to spinal cord is 2 GY and concurrent chemotherapy is given. The dose to spinal cord could be 50 GY if dose fraction size to spinal cord is less than 2 GY or only limited volume (<3cm) is treated to 50 GY.

2 V20 = effective lung volume (total lung volume – GTV) received equal or more than 20 GY.

Criteria for going off proton treatment:

1. Development of distant metastasis during the proton radiotherapy.
2. Development of unpredictable, irreversible, or persistent non-hematological grade 4 toxicity.
3. Patient refusal or non compliance of treatment requirement.

**Chemotherapy:**

During proton radiotherapy patients will receive the following weekly chemotherapy:

Paclitaxel (50 mg/m<sup>2</sup>), followed by Carboplatin (AUC 2 mg/min/mL) given as IV infusion (a total of 7 to 8 weekly doses). For the last week of proton treatment, concurrent last week chemotherapy may be held at the discretion of the physician if proton treatment is less than five fractions. If there is only one fraction of proton therapy in the last week, concurrent last week chemotherapy is not recommended.

Patients may receive the following premedications 30 minutes prior to receiving paclitaxel:  
Dexamethasone 10 mg IV/PO  
Diphenhydramine 25 mg IV/PO  
Cimetidine 300 mg IV  
Patients will receive standard antiemetics at the discretion of the physician.

### **Carboplatin Dosing Standards:**

- 1) A correction factor should NOT be used to calculate creatinine clearance
  - IDMS-measured creatinine (the serum creatinine valued reported in ClinicStation) should be used to in calculations that estimate GFR.
- 2) The maximum value of GFR calculated by the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min .
  - For an AUC of 6, this would mean a maximum dose to be administered would be 900 mg
  - For an AUC of 2 the maximum dose to be administered would be
- 3) Consider adjusting the creatinine to a higher value (i.e. 1 mg/dL) in:
  - elderly patients (those over the age of 70)
  - those with cachexia
  - patients that weigh less than 50 kg
- 4) When concerned about safety in a specific patient, measure the GFR (using 24-hour urine collection).

Both Paclitaxel and Carboplatin are commercially available. Please see package information by the manufacturer recommendations.  
Systemic therapy considered to be equal or superior to paclitaxel/carboplatin may be considered if they become standard treatment for NSCLC at the time when patients are enrolled. However, PI needs to be notified prior to chemotherapy.

### **Weekly Carboplatin and Paclitaxel Dose Modifications During Concomitant Chemoradiotherapy**

#### Hematologic Toxicity

If ANC < 1000 or Plt < 75,000 omit weekly carboplatin and paclitaxel. Restart weekly carboplatin and paclitaxel at same dose if ANC  $\geq$  1000 and Plt.  $\geq$  75,000. Doses that are omitted are not made up.

#### Non-hematologic Toxicity

The management of non-hematologic toxicity and chemotherapy dose modification will be decided at the discretion of the physician based on standard practice. The following recommendations will serve as general guidelines:

#### Dysphagia/Radiation Esophagitis

If radiation is held for grade 3 dysphagia/radiation esophagitis, hold weekly carboplatin and paclitaxel. If radiation is held for grade 3 dysphagia/radiation esophagitis and radiation is to be restarted, it is the investigators decision whether or not to restart chemotherapy. If the decision is made to restart chemotherapy in this setting, weekly carboplatin and paclitaxel may be dose reduced by 50%. If radiation is held for grade 4 dysphagia/radiation esophagitis, should not restart chemotherapy during the radiation treatment even if radiation is restarted.

#### Neurologic Toxicity

Carboplatin and paclitaxel doses should be modified for neurologic toxicity:

If grade 0 or 1 neurologic toxicity, no dose modification

If grade 2 neurologic toxicity, reduce dose 25%.

If grade > 2 neurologic toxicity, delay chemotherapy by 1 week. If neurologic toxicity improves to grade < 2, then reduce doses by 25%. If grade > 2 persists after 2 week delay then discontinue current chemotherapy regimens. Patient may be treated with other agents that have lower neurological toxicity at the discretion of the medical oncologist.

#### **Consolidation (Adjuvant) Chemotherapy following Concurrent Chemoradiotherapy**

Additional "consolidation" or adjuvant chemotherapy may be given  $\geq 4$  weeks after concurrent chemo/RT at the discretion of the treating medical oncologist based upon the patient's performance status and recovery from toxicities of the concurrent chemo/RT. If consolidation chemotherapy is administered, two to four cycles of a carboplatin + paclitaxel regimen is recommended.

Systemic therapy considered to be equal or superior to paclitaxel/carboplatin may be considered if they become standard treatment for NSCLC at the time when patients are enrolled.

## **5.0 Evaluation During Study**

### **Pre-treatment evaluation:**

A complete history and physical to include performance status, recent weight loss, percent of weight loss, usual weight, and concurrent non-malignant disease and its therapy must be recorded.

Laboratory studies will include a CBC with differential, platelet count, LFTs, electrolytes, creatinine within 3 weeks. Additional 10 ml peripheral blood may be collected for the biomarker study for predicting treatment response and toxicities if patient is consented for biomarker study. Separate protocol will be conducted in future for the biomarker study.

Patients should be evaluated by medical oncologist for the suitability for chemotherapy.

Chest X-ray (optional), MRI or CT scans of brain, PET/CT or PET scan to include adrenals are required within 3 months prior radiotherapy. Chest CT is optional if PET/CT is done.

PFTs should be obtained within 3 months prior to radiotherapy.

#### **Treatment evaluation:**

Acute radiation reactions including esophagitis, pneumonitis and other adverse events will be evaluated weekly during the period of treatment. The adverse events will be graded according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 3. Only grade 2 and above toxicity that is directly related to therapy will be required to be documented. Pre-treatment symptoms should not be considered as toxicity related to the treatment and is not required to be documented except it gets worse.

#### **Post-treatment evaluation:**

Patients are recommended to have follow up 6 weeks after completion of concurrent chemoradiotherapy for the evaluation of acute treatment toxicities, then required every 3 months ( $\pm$  1 month) for two years, then every 6 months ( $\pm$  1 month) for three years and then annually for the rest of their lives, that is standard of care. For this protocol purpose, we are going to follow patients for two years to complete current protocol. Patient will be followed continuously according to the standard of care. Follow up will be conducted at MDACC or other clinic facilities. However, follow up at MDACC is strongly recommended. If follow up is performed in other facilities, the information about medical history, physical examination, image and report, lab test report need to be sent to MDACC to be reviewed and documented.

Pulmonary function test will be performed in the second and fourth follow up visit after completion of concurrent radiotherapy and chemotherapy, and then annually for two years. If no 6 week follow-up, then PFT should be down in the first and third visit. Physical examination, medical history, CXR will be performed during every follow up. Chest CT scan will be performed at the second follow up after the completion of concurrent radiotherapy and chemotherapy, and then every three months ( $\pm$  1 month) for two years and then every 6 months ( $\pm$  1 month) for 3 years; then annually. When there is a PET/CT done during a follow-up, chest CT becomes optional.

Median survival and overall survival at 2 years will be analyzed. Progression free survival (PFS) will be evaluated by series CT of chest with contrast for every follow up except 6 weeks after the concurrent chemoradiotherapy for two years. PFS will be calculated. PET scan is required between 2-6 months after finishing treatment including adjuvant chemotherapy. PET scan between 12-24 months is recommended. PET/CT is preferred whenever it is possible. The information of PET scan will be used for the analysis of PFS particularly for distant metastasis and new lesions. If patient develops documented distant metastasis, such as brain metastasis, PET scan may not be needed for re-stage work up. Patients should be followed continually and further work-up and treatment will be determined by treating physician based on standard of care.

Disease specific survival and disease free survival will be evaluated.

Only grade 2 and above toxicity that is directly related to therapy will be required to be documented. Pre-treatment symptoms should not be considered as toxicity related to the treatment and is not required to be documented except it gets worse. Grade 3 and above acute and chronic toxicities by Common Toxicity Criteria will be analyzed.

Response assessment and calculation of PFS at the primary site:

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the largest dimension (LD) of target lesions, taking as reference the baseline sum of LD before the treatment.

Progressive Disease (PD): At least 20% increase in the sum of the LD of target lesions, taking as reference the baseline sum of LD before the treatment, or the appearance of new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the baseline sum of LD before the treatment.

PFS: Patient remains alive without progressive disease (PD) as defined above.

**Evaluation criteria:**

Evaluation before and after proton radiotherapy/chemotherapy:

	Pre-Registration	Weekly During XRT	Every 3 weeks During XRT	Follow-Up (f)	At Relapse
History & PE, KPS	X	X(e)	X	X	X
CBC, Differential, Platelets	X		X	X	X
SMA-12	X(a)				X
PET	X			X(g)	X
Chest X-ray/Chest CT	X(b)			X(g)	X
Brain Scan	X(b)			X(g)	X
PFTs	X(c)			X(c)	
Toxicity Evaluation		X(e)		X(e)	
Pregnancy Test	X(d)				
Biomarker study	X(h)				

- a. SMA-12 = serum creatinine, electrolytes, SGOT(AST) or SGPT (ALT), LDH, Alk Phos, total bilirubin, total protein, albumin, uric acid, phos, calcium, BUN, Mg+ are recommended. Among them, serum creatinine, BUN, electrolytes, SGOT (AST) or SGPT (ALT), Alk Phos, totla bilirubin are required.
- b. Chest X-ray (optional), MRI or CT scans of brain, PET/CT or PET scan to include adrenals are required within 3 months prior radiotherapy. Chest CT is optional if PET/CT is done.

- c. PFTs should be obtained prior to the initiation of XRT. In addition, repeat PFTs should be obtained at the second, fourth follow up visit after completion of concurrent chemoradiotherapy, and then annually.
- d. Serum pregnancy test pre-study entry as applicable.
- e. PE including weight, performance status, vital signs. Radiation induced acute reactions including esophagitis, pneumonitis should be evaluated weekly.
- f. Follow-up is at 6 weeks after completion of radiotherapy, then every 3 months ( $\pm 1$  month)x 2 year, then every 6 months ( $\pm 1$  month)x 3 years, then yearly. Long term toxicity for esophagus and lung will be evaluated using CTC criteria.
- g. Obtain chest CT if symptoms. If no symptoms, obtain chest CT at the second follow up after completion of concurrent chemoradiotherapy and then every 3 months ( $\pm 1$  month)during years 1 and 2, then every 6 months ( $\pm 1$  month) for three years and then annually. Brain scan is indicated if patient develops neurological symptoms. PET scan is required between 2-6 months after finishing treatment, including adjuvant chemotherapy. PET scan between 12-24 months is recommended. If patient develops documented distant metastasis such as brain metastasis, PET scan may not be needed for re-stage work up. Patient should be followed continually and further work-up and treatment will be determined by treating physician based on standard of care.
- h. Additional 10 ml peripheral blood may be collected for the biomarker study for predicting treatment response and toxicities if patient is consented for biomarker study.

## 6.0 Statistics

We hypothesize that the median survival time will be increased from a baseline of 16 months (RTOG-9410) to 24 months (50% improvement). Accrual to the trial is expected to be 60 patients per year, and all patients will be followed for two years. Using the normal approximation, we calculate that 65 patients will be required to have an 80% chance of demonstrating improvement using a one-sided test with significance level 0.05.

Duration of the study: Approximately 60 patients per year will be accrued to this study and the expected accrual time is 1.08 years. Total of 3.08 years is needed for the study to take into consideration an additional two years follow up.

Stopping rule for early death:

Based on a 16 month median survival time for patients undergoing standard therapy, we will assume that survival times for these patients can be modeled according to an exponential distribution with rate parameter 23. For patients undergoing experimental therapy, we will also assume an exponential model for survival time. We anticipate that the new therapy will increase the median survival time to 24 months. Based on this assumption, we will assume an inverse gamma prior distribution on the exponential parameter for treated patients that has mean of 24 and standard deviation 24 (i.e., parameters (3,48)). We will stop the trial if the number and time of deaths of study patients imply that the posterior probability that the exponential parameter describing their survival distribution is less than 23 exceeds 80%. In other words, we will stop the trial if the posterior probability that the median survival time of study patients is less than 16 months exceeds 80%. Surviving patients on study will be treated as censored observations in calculating the posterior distribution of the exponential parameter. This stopping rule would trigger if, for example, the mean survival time of the first two patients was 11.5 months, or if the mean survival time of the first three patients was less than 14 months. During this clinical study, we will forward current information on study patients to our statistician collaborator upon the death of a study

patient. The posterior distribution on the exponential parameter describing study patient survival times will then be estimated using a Markov chain Monte Carlo (MCMC) algorithm that accounts for censored observations. The posterior probability that this parameter is less than 23 will be evaluated by examining the proportion of MCMC samples that fell below the target value.

Stopping rule for toxicity:

RTOG 98-01 conducted toxicity analysis using modern 3 dimensional photon radiotherapy to a total dose of 69.6 GY with 1.2 GY given as twice per day (similar biologically effective dose as 74 GY with 2 GY/fraction given once per day) with current chemotherapy (carboplatin and paclitaxel). It reported grade 3 and above non-hematological treatment toxicities happened in 49% patients and grade 4 and above happened in 10% patients.

In the current study, any grade 3 and above treatment toxicities need to be reported to the study chairman. If grade 3 and above non-hematological treatment toxicities is more than 49% or any incidence of unanticipated non-hematological grade 4 treatment toxicity happens, the protocol will be reviewed and decision will be made regarding possible protocol modification.

Based on RTOG 98-01, we assume a prior probability of 0.49 for developing a Grade 3 and above toxicities using photon radiotherapy and two patients worth of "prior" data. To trigger a protocol review based on toxicities, the probability that a Grade 3 and above toxicities from the current proton treatment is greater than 0.49 must be 0.80 or greater. Using this criteria, we calculate the number of patients developing grade 3 and above toxicities (label as C) among patients treated with current proton radiotherapy (label as N) that should trigger protocol review and modification consideration as follow:

	N	C
[1,]	2	2
[2,]	3	3
[3,]	4	3
[4,]	5	4
[5,]	6	5
[6,]	7	5
[7,]	8	6
[8,]	9	6
[9,]	10	7
[10,]	11	7
[11,]	12	8
[12,]	13	8
[13,]	14	9
[14,]	15	10
[15,]	16	10
[16,]	17	11
[17,]	18	11
[18,]	19	12
[19,]	20	12
[20,]	21	13
[21,]	22	13
[22,]	23	14
[23,]	24	14
[24,]	25	15
[25,]	26	15
[26,]	27	16

[27,]	28	16
[28,]	29	17
[29,]	30	18
[30,]	31	18
[31,]	32	19
[32,]	33	19
[33,]	34	20
[34,]	35	20
[35,]	36	21
[36,]	37	21
[37,]	38	22
[38,]	39	22
[39,]	40	23
[40,]	41	23
[41,]	42	24
[42,]	43	24
[43,]	44	25
[44,]	45	25
[45,]	46	26
[46,]	47	26
[47,]	48	27
[48,]	49	27
[49,]	50	28
[50,]	51	29
[51,]	52	29
[52,]	53	30
[53,]	54	30
[54,]	55	31
[55,]	56	31
[56,]	57	32
[57,]	58	32
[58,]	59	33
[59,]	60	33
[60,]	61	34
[61,]	62	34
[62,]	63	35
[63,]	64	35
[64,]	65	36

### Toxicity Monitoring Rule for Surgical and Post-operative Complications

Throughout the phase I and phase II part of this study we will monitor patients for grade 3 or higher surgical and/or post-operative complications through 4 weeks post surgery. We will start monitoring toxicity beginning with the 10th patient enrolled in the study using the following rule. We will enroll a maximum of 52 patients. We will continue to enroll and evaluate patients for toxicity (grade 3 or higher surgical and/or post-operative complications through 4 weeks post surgery) as long as we are sure that the toxicity rate is not more than 20%.

We will stop the trial if  $P(\text{toxicity rate} > 20\% \mid \text{data from the trial}) > 0.80$ . That is, given the outcomes from the patients who have already been evaluated, if we determine that there is more than an 80% chance that the toxicity rate is more than 20% we will stop the trial. This decision rule gives the following stopping rule. We assume a  $\text{beta}(0.4, 1.6)$  prior distribution for the toxicity rate. This prior distribution has mean 20% and standard deviation of 23%. Stop the trial if

$$[ \# \text{ of pts with toxicity} / \# \text{ of pts evaluated} ]$$

> 4/10, 5/13, 6/17, 7/21, 8/26, 9/30, 10/34, 11/39, 12/43, 13/48

The operating characteristics of this rule are shown in Table 8.

Toxicity Rate	Probability of Stopping	Sample Size		
		P <sub>25</sub>	P <sub>50</sub>	P <sub>75</sub>
0.15	0.173	52	52	52
0.20	0.421	18	52	52
0.25	0.722	11	23	52
0.30	0.898	10	12	27
0.35	0.975	10	11	16
0.40	0.997	10	10	12
0.45	0.999	10	10	11

Once we have completed the study we will estimate the toxicity rate with a 90% credible interval. If we have toxicity in 6 of the 52 patients, then our 90% credible interval for the toxicity rate will be 5.6% to 19.7%. If we have toxicity in 8 of the 52 patients, then our 90% credible interval for the toxicity rate will be 8.3% to 24.3%.

We will also report the posterior probability that the toxicity rate is 20% or less. For example, if we have toxicity in 6 of the 52 patients, then the probability that the toxicity rate is 20% or less is 0.954. If we have toxicity in 8 of the 52 patients, then the probability that the toxicity rate is 20% or less is 0.822.

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