Mayo Clinic Radiation Oncology

Phase II Trial of Standard platinum doublet chemotherapy +various proton beam therapy (PBT) doses in order to determine the optimal dose of PBT for unresectable stage 2/3 Non-Small Cell Lung Cancer

Study Co-Chairs: [redacted]

Study Co-Investigators: [redacted]

Statistician: [redacted]

√Study contributor(s) not responsible for patient care.

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]

*No waivers of eligibility allowed

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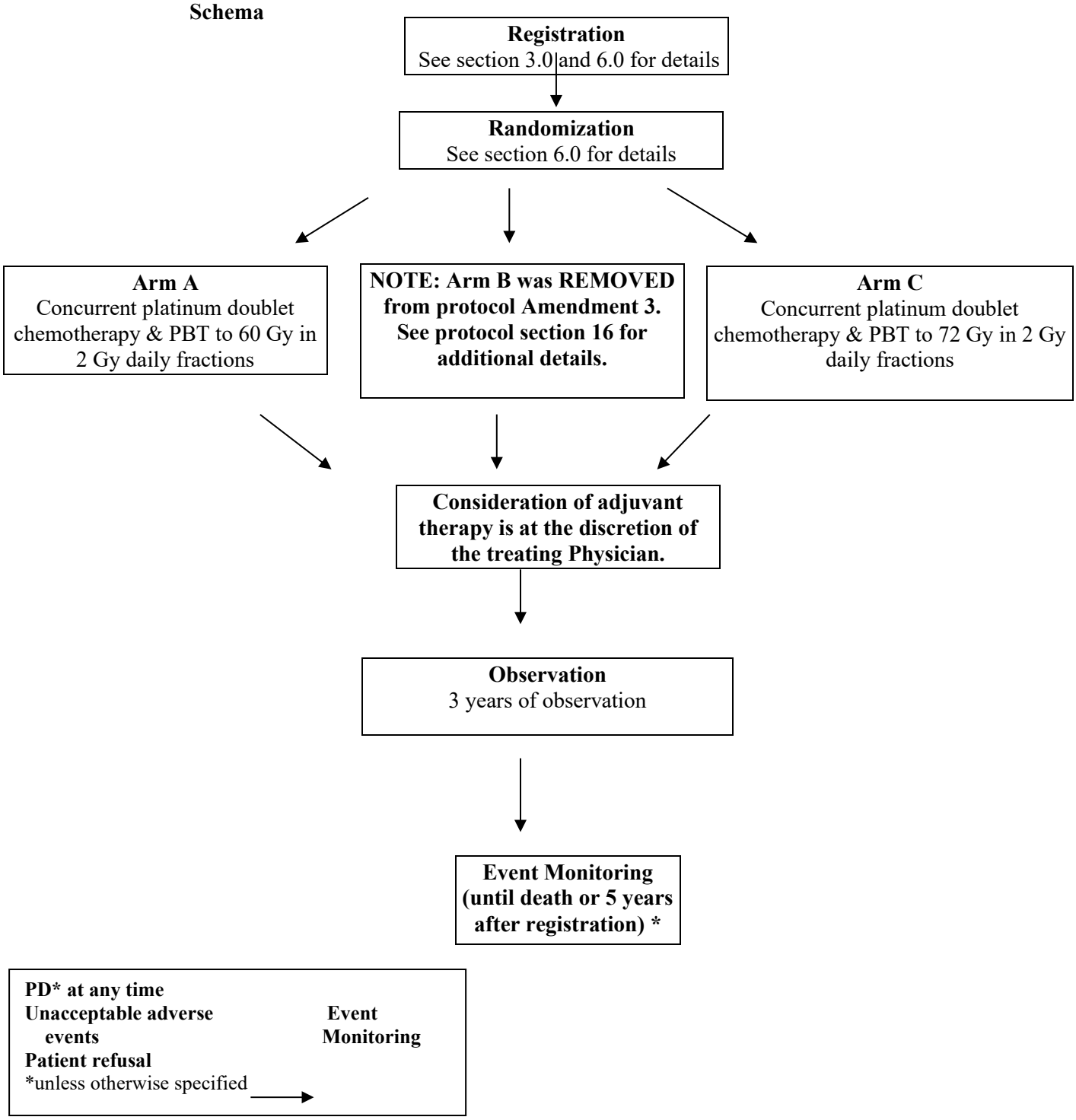
List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncologic Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
PBT	Proton Beam Therapy

Schema


Registration
See section 3.0 and 6.0 for details
Randomization
See section 6.0 for details
Arm A
Concurrent platinum doublet chemotherapy & PBT to 60 Gy in 2 Gy daily fractions
NOTE: Arm B was REMOVED from protocol Amendment 3. See protocol section 16 for additional details.
Arm C
Concurrent platinum doublet chemotherapy & PBT to 72 Gy in 2 Gy daily fractions
Consideration of adjuvant therapy is at the discretion of the treating Physician.
Observation
3 years of observation
Event Monitoring (until death or 5 years after registration) *
PD* at any time
Unacceptable adverse events
Patient refusal
*unless otherwise specified
Event Monitoring

1.0 Background

Protons are used to irradiate and kill tumors by damaging tumor DNA. The chief advantage of proton therapy is the ability to more precisely localize the radiation dosage when compared with conventional types of external beam radiotherapy (photons or electrons). This advantage is specifically due to the relationship between energy deposition within tissues from protons compared to conventional radiotherapy. Protons release the majority of their kinetic energy in a tighter distribution of dose conforming better to a tumor target. The proton beam stops and does not exit beyond the deep edge of a targeted tumor. Protons result in a lower integral dose to the body for a given prescribed dose to the tumor than conventional radiotherapy since they can deliver less radiation to the tissues superficial to the tumor. This has led to fewer second malignancies. [1]

The use of proton therapy is standard practice for pediatric cancer patients. Proton beam therapy has also resulted in very favorable clinical results for some uncommon tumors such as para-spinal & ocular tumors. Proton therapy has been used most often for prostate cancer with very favorable outcomes reported by Mendenhall et al.[2] There are also reports of significantly less toxicity and promising outcomes in patients with unresectable lung cancers.[3]

Concerns regarding proton therapy are not based on the physical advantages but rather on cost. Proton therapy facilities are more expensive to build, as they require huge accelerators to deliver the beam. Though it is considered expensive compared to conventional forms of radiation, cost-benefit studies have suggested cost-effectiveness in the long term due to decreased long-term toxicity.[4, 5] However, much more research is needed to document when the physical dose advantages of proton therapy translate to substantial and lasting improvements in patient outcome in many common clinical situations.

This trial focuses on determining the optimal dose of PBT that can be considered the standard conventionally fractionated dose to use in clinical practice and future trials.

The current standard dose of RT for unresectable stage 2/3 NSCLC is 60 Gy/30 fractions & concurrent carboplatin/paclitaxel followed by 2 cycles of consolidative chemotherapy (RTOG 0617).[6] This study (RTOG 0617) randomly assigned patients to the same chemotherapy plus either 74 Gy or 60 Gy (in 2 Gy daily fractions). Counter to expectations, higher doses of photon RT significantly decreased patient survival likely because of heart and/or lung damage from higher radiation doses. It has been well established that this dose (60 Gy in 30 daily fractions) is insufficient to sterilize most large masses of solid tumors based on the classic dose-response papers of Gilbert Fletcher.[7] Thus, with available modern photon therapy (3-D radiotherapy (3-D RT) and intensity modulated radiotherapy (IMRT), this standard dose-fractionation based treatment regimen is unable to cure the vast majority of unresectable stage II/III lung cancer patients treated. Proton beam therapy can decrease the exposure of normal structures such as the heart and lungs when treating lung cancers, potentially allowing for safe administration of higher doses to the tumor.[8] The current study will evaluate standard chemotherapy doublet therapy plus varying doses of conventionally fractionated proton RT within a range that has already been tested (60-72 Gy) in patients but never directly compared in a randomized trial. An MD Anderson study of chemotherapy (weekly carboplatin (area under the curve=2) and paclitaxel (50 mg/m^2)) plus 74 Gy (in 2 Gy daily fractions) of PBT resulted in median survival of 30 months and 5-year survival of 32% (Dr. Joe Chang, personal communication).[9] No patient experienced grade 4 or 5 proton-related adverse events. The most common non-hematologic grade 3 toxicities were dermatitis (n=5, 11%), esophagitis (n=5, 11%), and pneumonitis (n=1, 2%). This is far less than what would be expected with chemotherapy plus photon RT. Retrospective comparisons

performed at MD Anderson have shown significant decreases in toxicity with proton compared to photons.[3] We have chosen the maximum dose in this study to be 72 Gy due to findings from both proton and photon therapy that 74 Gy does not appear to confer a survival advantage compared to doses up to 72 Gy.[10, 11]

Adult stage II/III NSCLC patients with ECOG PS0-1 will receive concurrent platinum doublet chemotherapy plus proton radiation at 60Gy(RBE) or 72 Gy (RBE) at 2Gy per daily fraction. Dose will be allocated to each patient based on a randomization. The 1-year progression-free survival rates of all groups will be compared and the optimal dose determined by the preponderance of data.

2.0 Goals

2.1 Primary

2.11 To compare the 1-year progression-free survival rates of 72 Gy and 60 Gy conventionally fractionated PBT (as part of concurrent combined modality therapy).

2.2 Secondary

2.21 To assess the adverse events, survival, quality of life, and patterns of failure (local regional, distant metastatic) associated with two dose levels of conventionally fractionated PBT (as part of concurrent combined modality therapy).

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histological confirmation of non-small cell lung cancer

3.13 Forced Expiratory volume in 1 second (FEV1)>1.0 L

3.14 Unresectable or medically inoperable stage 2-3 Non-small cell lung cancer (based on CT/PET, MRI or CT of brain, and Physical exam).

- Eligible if recurrence after surgery and now has the equivalent stage 2-3 NSCLC OR had sub totally resected stage 2-3 NSCLC.

3.15 ECOG Performance Status (PS) 0-1(Appendix I).

3.16 Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.17 The following laboratory values in specified ranges:

- WBC ≥3.0 x 10^9/L,
- ANC ≥1.5 x 10^9/L,
- Hgb ≥9g/dl
- Plts >100 x 10^9/L
- Serum creatinine<1.5 x upper limits of normal(ULN)
- Serum bilirubin <1.5xULN

3.18 Provide informed written consent.

3.19 Willing to return to enrolling institution for follow-up for a minimum of 1 year.

3.19a Ability to undergo potentially curative chemotherapy plus radiotherapy

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Weight loss of >10% in the past 3 months

3.24 Distant metastases (M1 disease)

3.25 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, lupus, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.26 Receiving any investigational agent, that would be considered as a treatment for the primary neoplasm.

3.27 Active second malignancy.

3.28 History of myocardial infarction ≤6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.29 Received Chemotherapy for lung cancer within 6 months of registration.

3.30 Previous chest radiotherapy that would overlap with the proton field.

4.0 Test Schedule (these are all considered standard of care and are not experimental)

Tests and procedures	Active Monitoring Phase			
	≤30 days prior to registration	During course of RT (every 7 days +/- 2 days)	Observation Every 3 months (+/- 1 month) for 3 years post RT[7]	Event Monitoring Every 6 months (+/- 3 months) For a total of 5 years post-registration[7]
History and exam, Wt, ECOG PS	X	X	X	X
Adverse event assessment	X	X	X	X
Height	X			
Pregnancy test[1]	X			
Tumor measurement[2]	X		X	X
Pulm function tests DLCO, FEV1	X[4]		X[6]	
CT (chest preferably with contrast)	X		X	X
MRI, or CT of head	X			
PET /CT	X			
LASA/ QOL (appendix II)	X		X	
CBC/Chemistry panel[3]	X	X	X	
Histologic confirmation of NSCLC[5]	X			

1. For women of childbearing potential only. Must be done ≤7 days prior to registration.
2. Refer to section 11.0 for lesion evaluation and response
3. Glucose, Calcium, Albumin, Total Protein, Sodium, Potassium, CO2 (carbon dioxide, bicarbonate),Chloride, BUN (blood urea nitrogen),Creatinine, ALP (alkaline phosphatase),ALT (alanine amino transferase),AST (aspartate amino transferase),Bilirubin; chemistry and CBC will be monitored during chemotherapy per medical oncology standards
4. PFT's can be up to 90 days prior to registration
5. The biopsy can be older than 30 days but must be done no more than 90 days prior to registration)
6. To be completed at 1 year post only
7. If participant is unable to return to research site then study staff will attempt to obtain outside records

5.0 Stratification Factors:

5.1 Mayo prognostic score[12]: 32-37 vs 38-43 vs 44-47 vs 48-52 (appendix IIb)

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

Patient will be registered to the study when they have consented, met eligibility criteria, and have been logged into Research Participant Tracking (Ptrax).

6.2 Randomization

Performed after registration. Patients will be randomized in equal proportions (1:1) to a single dose level (60 vs 72 Gy) balanced based on the stratification factors in Section 5.0. The balancing algorithm that we will use is a dynamic allocation procedure that is part of Medidata Rave, known as Balance.

7.0 Protocol Treatment

Protocol treatment is to begin within 28 days of registration. Questions regarding treatment should be directed to the Study Chairs.

7.1 Radiation Therapy

7.1.1 Target Dose is based on the arm (60, 72 Gy(RBE) in 2 Gy daily fractions).

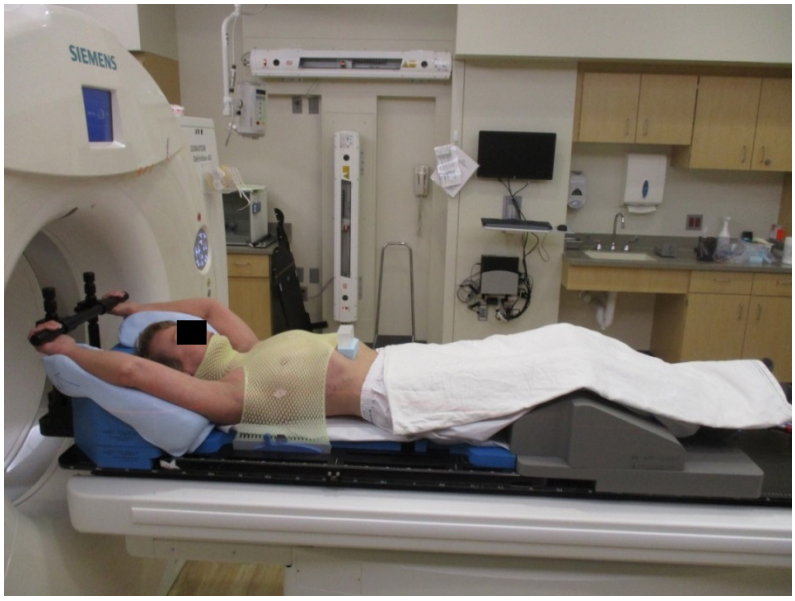
7.1.2 Treatment Technique: PBT

7.1.3 Simulation

Simulation is performed based on the standard of each institution. 4D CT-Simulation will be performed for most patients. The averaged CT and maximum intensity projection (MIP) CT will be generated from the 4D CT. If tumor movement exceeds 8 mm (Mayo Clinic Rochester) or 10 mm (Mayo Clinic Arizona), respiratory management is required (breath hold (BH) or gating). Other advanced techniques will be considered as they become available. For BH patients, the averaged CT will be generated from multiple BH scans, while for gating patients the averaged CT will be generated from the treatment phases. For free breathing, BH, and gating patients, the averaged CT will be used as the **primary planning CT**. For all patients we will conduct plan robustness quantification and motion evaluation. The patients with tumor motion less than 5 mm may also have motion management if the evaluation results show that the plans are not resilient to motions given the thresholds defined in Sec. 7.1.12.

7.1.4 Immobilization

The immobilization as shown below is an example how currently the immobilization is conducted in AZ. The participating institution may have its own established immobilization procedures, which can be adopted for this clinical trial.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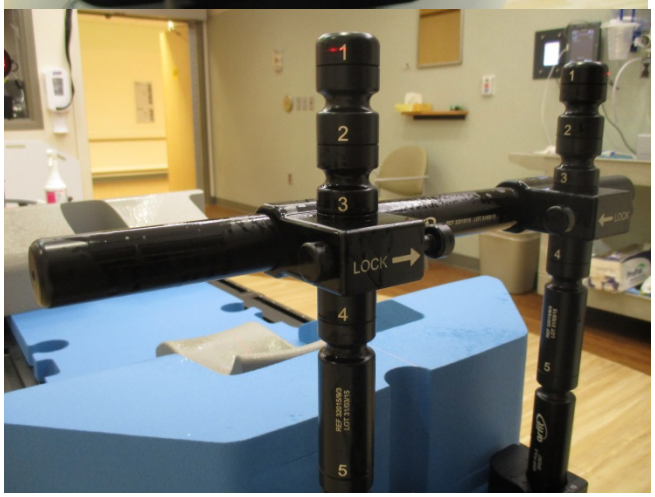
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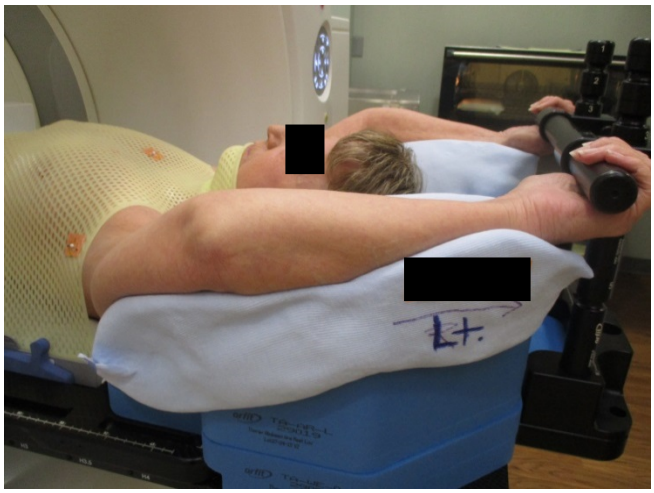

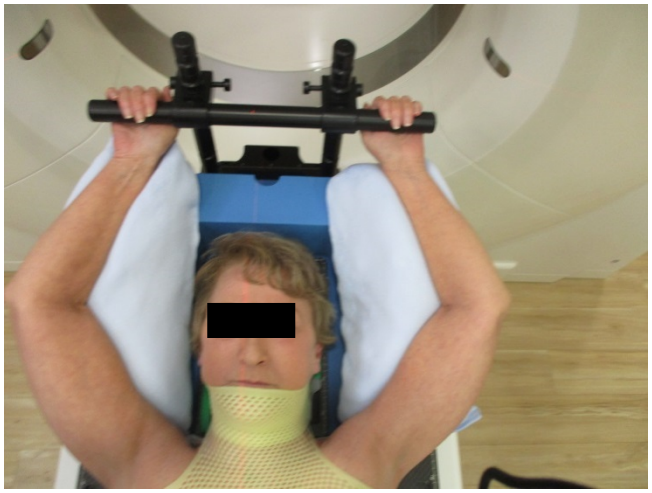

1. We will position the patient as shown in the image below using Orfit board and thermoplastic mask; low arm incline, short poles w/ T-Bar, leg extension, and basic knee wedge
2. The hands should reach the horizontal T bar and rest in an AccuForm cushion as seen in the image below.
3. Localization points (lower 2pt tattoos inferior to mask, 3pt bb's @ iso)
4. Scan the patient – Pre BB 2 mm slice thickness
5. Treatment Iso to be dropped by physician.
6. Wherever the isocenter is dropped, place three points on mask (Triangulation BBs).
7. Record Index of Orfit overlay
8. Record Isocenter (top of overlay)

7.1.5 Image Guidance

The Hitachi Patient Image Alignment System (PIAS) will be used for image guidance. PIAS provides 2D and 3D image guidance (CT on rails). Both are allowed under this protocol. If fiducials are not used, nearby landmarks (such as ribs and spinal column) will be used for image guidance

7.1.6 Contouring and Target Definition

1. For free breathing patients, the internal gross tumor volume (IGTV) will be generated using either a union of GTV on all respiratory phases or MIP and verified through all breathing phases. For BH patients, multiple BH CT scans will be acquired and the IGTV will be generated using a union of GTV defined on all BH scans. If gating is used, IGTV will be generated using a union of GTV on all treatment phases. The IGTV will include all lymph nodes >1.0cm in short diameter and gross tumor (all generally warmer than the mediastinal blood pool on PET).

2. The clinical target volume (CTV) is defined as a margin of 5 to 10 mm (ordinarily 7-8 mm) isotropic expansion of the IGTV and edited clinically based on patterns of tumor spreading and anatomic boundaries such as vertebral bodies, chest wall, heart etc.

3. For free breathing patients, plans will be evaluated on T0 and T50 phases using the CTV on these phases. For BH patients, plans will be evaluated on each BH scan using the CTV on these BH scans. For gating patients, plans will be evaluated on the extreme treatment phases at either end of the respiratory gate, using the CTV on each of those phases.

4. All normal structures will be contoured on the **primary planning CT** scans.

5. Co-registration with contrast enhanced CT scans and/or PET scans may be used in identifying the GTV.

7.1.7 Treatment Planning

i. IMPT plans will be generated on the **primary planning CT**. The prescription iso-dose line definition is up to the treating physician. However, we recommend that in the worst-case scenario the CTV D95% is at least 95% of the prescription dose (please see Sec. 7.1.12).

ii. Beam angles will be selected to minimize the impact of motion and spare normal tissues.

iii. The optimization method can be either multi-field optimization (MFO) or single-field optimization (SFO). SFO, also known as single-field uniform dose (SFUD), optimizes the spots of each proton field individually and creates a more uniform dose distribution from each beam than MFO. MFO is usually referred to as intensity-modulated proton therapy (IMPT). In MFO, spots from all the proton fields are optimized together. The inhomogeneous dose from each field is summed up to create homogeneous target coverage.

iv. 4D treatment planning is the explicit inclusion of the temporal changes

in anatomy during the planning of radiotherapy. Usually it is based on 4D CT.

v. If possible patients will be planned using SFO technique. If SFO cannot meet the dose volume constraints and plan robustness requirement, robustly optimized 3D/4D MFO will be used.

vi. "Verification" dose distributions will be generated by recalculating the dose on the T0 and T50 for the free breathing patients, on all BH scans for BH patients, and on the extreme treatment phases encompassing the respiratory gate for gating patients. The original plan generated on the **primary planning CT** will be adjusted until the verification and original dose distributions all meet the required prescription criteria (see Sec. 7.1.12).

vii. 3D/4D robustness quantification to evaluate the impact of patient setup and proton beam range uncertainties will be performed. The inter-fractional setup uncertainty is assumed to be a minimum of 5 mm and proton beam range uncertainty is assumed to be a minimum of 3%. The intra-field setup uncertainty is assumed to be a minimum of 2 mm. These values are recommended by the PTCOG Thoracic/Lymphoma research subcommittee and are applicable to most patients. However, for some patients with much inhomogeneity, irregular breathing motion, larger values may be applied. For all patients, the plan robustness will be reviewed by a physicist co-chair. We recommend that in the worst-case scenario the CTV D95% is at least 95% of the prescription dose (please see Sec. 7.1.12).

viii. Plans will require 2-3 fields in most cases.

ix. Calculated dose distributions will be verified by comparison to a Monte Carlo calculation. In cases where the CTV mean dose differs by more than 5% between the analytical code and the Monte Carlo algorithm, the Monte Carlo derived dose distribution will be considered the dose of record.

7.1.8 Treatment Delivery

The corresponding treatment delivery techniques as employed in the treatment planning will be used to deliver the plan.

7.1.9 Mitigation of interplay effect: Repainting

Iso-layer repainting will be used to further reduce the impact of interplay effect. The effectiveness of repainting will be evaluated on a patient specific basis using in-house developed software. Dose evaluation software will be used to evaluate the impact of interplay effects by modelling time-dependent spot delivery to incorporate interplay effect with randomized starting phases of each field per fraction for either multiple fractions or single fraction (up to each participating institution's choice). With interplay effects considered, we recommend that in the calculation with multiple fractions the difference of the CTV D95% is within 5%

of the CTV D95% of the original plan and the calculation with single fraction the difference of the CTV D95% is within 15% of the CTV D95% of the original plan (the exact number for the calculation with single fraction will be determined later).

7.1.10 Adaptive re-planning

1. All patients will undergo repeat CT simulation as defined in the CT simulation section (Sec. 7.1.4) weekly during treatment to determine whether adaptive re-planning is needed to maintain target coverage and to avoid overdosing critical structures. The plan will be recalculated on the **primary planning repeat CT scans**. Contours will be deformed from the primary planning CT to the primary planning repeat CT, and the treating physician will review the new contours and doses. The same plan robustness quantification and motion evaluation procedures as defined for the original plan will be conducted. We recommend that in the worst-case scenario the difference of the CTV D95% is within 5% of the CTV D95% of the original plan.

2. If an adaptive plan is deemed necessary, the plan will be developed using the treatment planning guidelines as described for the original plan.

7.1.11 Critical Structures (see Table 7.1 for additional info)

Table 7.1 Dose volume constraints for critical structures

7.1.12 Definitions of Deviations in Protocol Performance

- Prescription Dose: we recommend that in the worst-case scenario the CTV D95% is at least 95% of the prescription dose and the CTV D5% is at most 110% of the prescription dose.
- Minor deviation: CTV D95%: 85-95% of the prescription dose, CTV D5%: 110-120% of the prescription dose in the worst-case scenario
- Major deviation: CTV 95% : <85% of the prescription dose, CTV D5%: >120% of the prescription dose in the worst-case scenario

Critical structure	**Dose limits (Gy[RBE])**
Esophagus	Guideline: 1/3 volume < 65 Gy[RBE]; 2/3 volume < 55 Gy[RBE], whole volume <= 45 Gy[RBE], as low as reasonably achievable, (try to avoid irradiating the full circumference of the esophagus)
Liver*	Whole volume <= 25 Gy[RBE]; 1/2 liver <= 35 Gy[RBE]
Total Normal lung *	V_{20} < 37% of volume is desirable V20>41% is a major deviation
Spinal cord*	Maximum dose ≤ 50 Gy[RBE]
Heart	Guideline: V_{50} < 25% and mean heart dose < 20 Gy (exceeding this is a minor deviation)
Skin	Maximum dose ≤ 55 Gy[RBE] (values will be decided by the treating physician)

- Volume: The GTV and CTV must be specified on any plans with dose – volume histograms for these and all critical organs
- Critical structures with an asterisk in Table 7.1 with the dose volume indices up to 110% of the limit will be considered a minor deviation. Critical structures with an asterisk in Table 7.1 with the dose volume

indices more than 110% of the limit will be considered a major deviation.

7.1.13 Quality Assurance Documentation

All plans will be reviewed by the PI and or the co-PIs and rated as within guidelines (no deviations), minor deviation (any number of minor deviations mentioned above or major deviation (1 or more major deviations present)

7.2 Patient Outcomes Quality of Life Assessment [Database]

7.2.1 A single item quality of life scale (LASA) will be assessed for each patient per the scheduled tests

7.3 Chemotherapy

7.3.1 Patient will receive concurrent platinum based doublet chemotherapy under the direction of the treating medical oncologist. Treatment options can include standard weekly low dose Carboplatin and Paclitaxel, standard etoposide cisplatin or carboplatin or standard pemetrexed with cisplatin or carboplatin., Chemotherapy will be administered in standard doses as per institutional and standard regimen guidelines. Dose modifications will be done as per standard institutional guidelines.

7.3.2 Protocol therapy will consist of radiotherapy given with concurrent chemotherapy for six weeks of weekly chemotherapy. Consideration of adjuvant therapy is at the discretion of the treating Physician.. Patients will also be considered eligible for consolidation therapy clinical trials.

7.3.3 Standard premedications will be employed for chemotherapy according to institutional guidelines.

7.4 For this protocol, the patient must return to the consenting institution for evaluation at least every 7 days during proton treatment and every 3 months(+/-1 month) during observation (Active Monitoring Phase).

8.0 Radiotherapy Dose Modifications Based on Adverse Events

8.1 If a patient develops any grade 3-4 toxicity felt to be due to radiation therapy, the table below will be followed and the patient will have a treatment break as directed and are to resume and complete therapy. This break in treatment is usually no more than 1 week. If the patient suffers neutropenic fever or requires hospitalization for any reason, treatment breaks will be given until the patient is dismissed from the hospital or deemed capable of safely receiving radiotherapy by the care team.

In general, radiation therapy should continue to be delivered for ≤ grade 3 non-hematologic toxicities in or outside the radiation treatment field. The only exception

being grade 3 pulmonary (see table below). RT should be held for all Grade 4 non-hematologic toxicity in or outside the treatment field and resumed only when toxicity ≤ grade 2.

If treatment is interrupted for more than 3 weeks due to toxicity, remove the patient from protocol treatment.

Use the following treatment modification table for toxicities:

In-field AE class	CTCAE Toxicity Grade	Radiation Therapy
Esophagus/Pharynx	4	Hold treatment until ≤ grade 2
Pulmonary	4	Hold treatment until ≤ grade 2
Pulmonary	3	Hold treatment until ≤ grade 2
Skin	4	Hold treatment until ≤ grade 2
Heme (excluding lymphopenia)	4	Hold treatment until ≤ grade 2

8.2 Dose Modifications During Concurrent Chemotherapy will be at the discretion of the treating medical oncologist according to institutional guidelines

8.2.1 Hematologic Toxicities

- Radiation therapy will be held for grade 4 hematologic toxicity until grade <2.(see table above) except lymphopenia.

8.2.2 Non-hematologic Toxicities

Neurotoxicity:

Based on treating oncologists' opinion.

8.3.1 Hematologic Toxicity

8.5 Dosing for Obese Patients will follow published ASCO guidelines

9.0 Ancillary Treatment/Supportive Care

9.1 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as anti-diarrheals, analgesics, and/or anti-emetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

Chemotherapy interruptions will be determined by the Medical Oncology treating physician and will be assessed per standard clinical procedures for the particular chemotherapy being administered (as outlined in 8.2-8.5)

9.2 Skin changes are common complications of radiation therapy. Usual care will be provided. For dry skin, aloe vera based product or aquaphor can be prescribed. If the skin becomes erythematous and/or there is pruritis, topical steroid cream or topical Benadryl can be prescribed. Patients experiencing pain will be prescribed pain medication.

9.3 Antiemetics may be used at the discretion of the attending physician.

9.4 Other toxicities should be treated per standard of care: thrush/candida should be treated with antifungals (preferably nystatin as the first choice). Esophagitis should be treated with pain medications. Pneumonitis would be treated as clinically indicated (cough with anti-tussives (tessalon, dextromethoraphan,) shortness of breath (with inhalers and bronchodilators), poor oxygen saturation (with O2). Patients should be hospitalized when clinically warranted.

9.5 Patients will receive ancillary treatment and supportive care that would otherwise be considered standard of care in the setting of chemotherapy, radiation, and surgery.

9.6 Radiation treatment will be interrupted at the discretion of the treating physician, as per standard of care. Generally, this would be for grade 4 in-field-toxicity (esophagus, pulmonary, skin) and/or grade 4 neutropenia with fever. (see 8.1 for specific recommendations)

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Definitions

Adverse Event- An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event - Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.
All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)- Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Preexisting Condition- A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2 Recording Adverse Events

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
[redacted]

10.21 Adverse event monitoring and reporting are a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the medical treatment or procedure. With this information, determine whether the event must be reported as an expedited report (see Section 10.3).

10.22 Assessment of Attribution
When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
Definite - The adverse event is clearly related to the agent(s).
Probable - The adverse event is likely related to the agent(s).
Possible - The adverse event may be related to the agent(s).

Unlikely - The adverse event is doubtfully related to the agent(s).
Unrelated - The adverse event is clearly NOT related to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

a. Serious Adverse Events will be reported as part of regular adverse event reporting mechanisms via the data capture system and logged for review reporting.
b. General reporting instructions
The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.
Use Mayo Expedited Event Report form [redacted] or investigational agents or commercial/investigational agents on the same arm.

10.31 Investigator Reporting: Notifying the Mayo IRB:

The IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) in early 2007 and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection."

10.311 According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

10.312 Non-UPIRTSO – the investigator reports problems or events that do NOT meet criteria of an UPIRTSO in summary format at the time of the next continuing review. The investigator monitors the severity and frequency of subsequent non-UPIRTSOs.

Consider the following information to collect when developing any forms for documentation of adverse events.
Example
Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

10.4 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Skin and subcutaneous disorders	Radiation dermatitis	X	X
Resp, thoracic & med disorders	Pneumonitis	X	x
GI disorders	Esophagitis	X	x
Blood & lymphatic	Febrile neutropenia	X	x

10.41 Submit via appropriate *reporting mechanisms (i.e., paper or electronic)* the following AEs experienced by a patient and not specified in Section 10.4:

10.4.11 Grade 2 AEs deemed possibly, probably, or definitely related to the radiation.

10.4.12 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.4.13 Grade 5 AEs (Death)

10.4.131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.4.132 Any death more than 30 days after the patients last study treatment or procedure that is felt to be at least possibly treatment related must also be

submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.5 Monitoring and Auditing

The investigator will permit study-related monitoring, audits, and inspections by the IRB, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices

10.51 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10.5 "Monitoring and Auditing"). Medical monitoring will include a regular assessment of the number and type of serious adverse events. "Any serious adverse events will be followed up by the sentinel event reporting procedure"

11.0 Treatment Evaluation

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)[13] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 12-16 weeks during the active phase.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions: to determine local-regional control.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of *12-16* weeks (see Section 11.44).

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-

nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node), which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/ /physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all non-target lesions.

  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the MCCC protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

12.0 Descriptive Factors

- See stratification factors section 5.0

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients found ineligible will be replaced, as will cancels.

13.2 Patients who are stable will continue treatment per protocol.

13.3 Patients who develop PD while receiving therapy or once in observation will go to the event-monitoring phase.

13.4 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

13.5 Observation/Event Monitoring: If the patient has completed therapy and remained stable, the patient will be observed every 3 months (+/- 1 month) for 3 years (observation phase) post RT. Then, every 6 months (+/- 3 months) (event monitoring) for an additional 2 years. For a total of 5 years observation/event monitoring from time of registration

13.6 If a patient fails to complete the entire course of treatment for reasons other than toxicity or PD, the patient will be regarded as inevaluable and will be replaced.

13.7 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event

monitoring will be required per Section 18.0 of the protocol.

13.8 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable, which is to be determined by the Biostatistician and Principal Investigator. All data up until the point of confirmation of a major violation must be submitted. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol. If a treatment deviation occurs wherein a patient is administered an alternative standard of care chemotherapy the patient will be followed and data will continue to be collected according to section 4.0.

13.9 A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

None

15.0 Drug Information

Radiation will be accompanied by concurrent standard platinum doublet chemotherapy under the direction of the treating medical oncologist.

16.0 Statistical Considerations and Methodology

16.1 Overview: This protocol is designed to compare proton beam dose levels of 72 Gy and 60 Gy in patients receiving proton beam therapy for newly diagnosed lung cancer using a flexible "pick the winner" randomized phase II study design (Sargent & Goldberg, 2001). Patients will be randomized to a single dose level using a dynamic allocation procedure (Pocock & Simon, 1975) that balances the marginal distributions of the stratification factors (see Section 5.0) between the treatment regimens.

16.11 Primary Endpoint: The primary endpoint of this trial is progression-free survival (PFS). PFS time is defined as the time from randomization to the earliest date of documentation of disease progression or death due to any cause. If a patient dies without a documentation of disease progression the patient will be censored on the last date the disease was evaluated. In the case of a patient starting treatment and then never returning for any evaluations, the patient will be censored for progression on day 1 post-randomization. All patients meeting the eligibility criteria who have signed a consent form, have begun treatment, and have not been declared a major treatment violation will be evaluable. Analysis will be conducted after all patients have been followed for at least one year.

16.2 Statistical Design:

16.21 The selected design is a flexible "pick the winner" randomized phase II design. . Patients will be randomized to **either 60or 72 Gy** and followed for a minimum of one year This study will randomize 42 evaluable patients (21 per dose level x 2 dose levels If the observed PFS rate at 1 year of one arm is at least 15% greater than the PFS rate of the

other arm, then that arm will be considered the winning arm. This design has a probability of an inconclusive result <8% and an approximate 80% probability of selecting the true winner.

If the difference is <15%, then the trial will be considered stistiatically ambiguous and the selection of a winning arm will be allowed to include other factors (i.e. adverse event data and patient-reported quality of life) in addition to the PFS rate at 1 year.

Based on this flexible "pick the winner" design, if both arms have a PFS rate at 1-year of 48%, then each arm has a 44% probability of being picked the winner based on PFS rate at 1-year and the probability that the trial is statistically ambiguous and selection of a winning arm will be allowed to include other factors in addition to the PFS rate at 1-year is 12%.

If one arms has true PFS rate of 53% and 1 arm has a true PFS rate of 63%, then the arm with 53% PFS rates has a 21% chance of being picked the winner based on PFS rate at 1-year; the arm with the 63% PFS rate has a 69% chance of being picked the winner based on PFS rate at 1-year alone; and the probability that the trial is statistically ambiguous is 10%.

Properties of the proposed "pick the winner" design were computed using the "pselect" function within the "clinfun" package in R.

No interim analyses will be conducted for PFS.

16.211 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.313.

16.22 Sample Size: As of May 16, 2018 7 patients (n_A=3, n_B = 2, n_C=2) have been enrolled in 3 cohorts onto this trial. As of Amendment 3 we remove the 66 Gy (Arm B) dose level, and amend the necessary sample size. In order to sufficiently power this amended protocol, 42 total (n=21 per arm) evaluable patients will need to be accrued onto this randomized phase II study unless undue adverse events are encountered. We anticipate accruing an additional 6 patients (3 per dose level) to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is therefore 48 patients total (including the five patients enrolled prior to Amendment 3). Therefore, we will need to accrue 43 additional patients from the time of Amendment 3. The inclusion of the two patients enrolled into the previously open arm (66 Gy) dictates that a total of 50 patients will be accrued for the duration of this trial.

16.23 Accrual Time and Study Duration: The anticipated accrual rate is approximately 2 patients per month based on physician estimate. Therefore, the accrual period for this randomized phase II study is expected to be 24 months. The final analysis can begin approximately 36 months after the trial begins, i.e., as soon as the last patient has been observed for 12 months.

16.24 Power and Significance Level: For the primary analysis, it is assumed that the 1-year PFS rate for 60 Gy is 48% whereas the 1-year PFS rates for 72 Gy is 63% (the later based on Chang et al., 2015), . It is also assumed that the distributions of PFS times for

each dose group follow an exponential distribution. and the probability of declaring that evidence exists that PFS is superior for 72 Gy relative to 60 Gy is selected for futher studies under various PFS rates is shown in the following table:

N per arm	PFS rate Trt 1	PFS rate Trt 2	Probability of a statistically ambiguous result*	Probability of selecting Trt 1†	Probability of selecting Trt 2†
21	0.48	0.48	0.12	0.44	0.44
21	0.48	0.53	0.12	0.31	0.57
21	**0.48**	**0.63**	**0.08**	**0.12**	**0.80**
21	0.53	0.63	0.10	0.21	0.69

*See section 16.21

† Selection based on PFS rate at 1-year alone.

16.25 Other Considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan: The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair in accordance with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is 3 years after the trial commences.

16.31 Primary Endpoint

16.311 Definition: The primary endpoint of this trial is PFS. PFS time is defined as the time from randomization to the earliest date of documentation of disease progression or death due to any cause. If a patient dies without a documentation of disease progression the patient will be censored on the last date the disease was evaluated. In the case of a patient starting treatment and then never returning for any evaluations, the patient will be censored for progression on day 1 post-randomization. Progression events will be reviewed and confirmed by a central review panel and the primary analysis will be based on these central reads. A patient will be considered censored at the last follow-up date if progression or death had not been observed at that time.

16.312 Estimation: A Cox proportional hazards model stratified by stratification factors (see Section 5.0) will be used to model PFS as a function of dose to test for an overall dose effect (a one-sided p-value<0.10 will be considered as significant evidence of a dose effect). Subsequently, descriptive statistics and separate Cox models stratified by stratification factors (see Section 5.0) will compare PFS between 72 Gy and 60 Gy (for each, a one-sided p-value<0.10 will be considered as significant evidence of superiority). Kaplan-Meier estimates and curves by dose level will also be generated.

16.32 Definitions and Analyses of Secondary Endpoints

16.321 Overall survival time is defined as the time from randomization to death due to any cause. Overall survival will be modeled similarly to PFS as described above using Cox models. Kaplan-Meier estimates and curves by dose level will also be generated. Overall survival will be analyzed at the time of the final PFS analysis. OS will again be analyzed as exploratory analysis after 25 deaths per primary pairwise comparison have occurred or after all patients have completed follow-up (whichever occurs first).

16.323 Adverse events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns by dose level (60 and72 Gy). Additionally, the relationship of the adverse event(s) to dose level will be taken into consideration.

16.324 Local-regional failure time is defined as the time from randomization to the earliest date of documentation of local recurrence (at the site of the original primary tumor and adenopathy, i.e., GTV). The cumulative incidence of local failure will be estimated using Gray's methodology and compared across dose levels using Fine-Gray quadratic regression (with death as a competing risk).

16.324 Distant metastasis time is defined as the time from randomization to the earliest date of documentation of distant metastasis. The cumulative incidence of distant metastasis will be estimated using Gray's methodology and compared across dose levels using Fine-Gray quadratic regression (with death as a competing risk).

16.33 Correlative Research

16.331 Quality of life will be assessed prior to review of disease status and discussions of patient's general health since last treatment evaluation. QOL will be measured using the single item LASA scale described in Sloan et al.[14] The questionnaires will be scored according to published scoring criteria. Descriptive statistics by dose level at each time point will include means, standard deviations, medians, and ranges for each scale. Descriptive graphical techniques will include mean plots by dose over time for each scale. Mixed models will be used to compare each scale across dose levels at each post-baseline time point while adjusting for the baseline value of scale. To handle missing data, we will graphically explore patterns of missing data and will employ pattern mixture models for longitudinal analyses. For interpreting the clinical significance of effects, 0.2, 0.5, and 0.8 standard deviation effects will be considered as small, moderate, and large based on Cohen (1988) throughout.

16.332 **Prior to Amendment 3 there were three arms in this trial.** Patients (n=2) involved in a previously open arm (66Gy) will be followed per protocol and descriptive statistics will be implemented to describe the outcomes associated within the 66Gy arm in congruence with the trial objectives.

16.4 Data & Safety Monitoring:

16.41 The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy either of the following:

- **if 6 or more patients in the first 20 treated patients experience a grade 4 or higher non-hematologic adverse event (excluding skin toxicity which can be significant after proton therapy but does not result in mortality)**
- **if after the first 20 patients have been treated, 30% of all treated patients experience a grade 4 or higher non-hematologic adverse event (excluding skin toxicity).**

This adverse event stopping rule is applied to each arm separately. If the adverse event stopping rule is crossed for any one (or more) arm, accrual to the entire study will be halted to allow for full review of the safety data.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Results Reporting on [redacted]: At study activation, this study will have been registered within the "[redacted]" website. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on [redacted] For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 36 months after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 12 months.

16.6 Inclusion of Women and Minorities

16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.62 There is no information currently available regarding differential effects of these regimens in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look

for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 The geographical region served by MMC has a population that includes approximately 5% minorities. Based on prior MMC studies involving similar disease sites, we expect about 5% of patients will be classified as minorities by race and about 45% of patients will be women. Expected sizes of racial by gender subsets for patients registered to this study are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	2	4
Not Hispanic or Latino	45	68	113
Ethnic Category: Total of all subjects	47	70	**117**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	1	1
Black or African American	2	2	4
Native Hawaiian or other Pacific Islander	0	0	0
White	45	67	112
Racial Category: Total of all subjects	47	70	**117**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

Tissue documenting the presence of non-small cell lung cancer is obtained as per standard institutional practice.

18.0 Records and Data Collection Procedures

CRF completion: this study will use Medidata Rave for remote data capture (rdc) of all study data.

19.0 Study Finances

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: none

20.0 References

Chung, C. S. et al. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys 87, 46-52 (2013).

Mendenhall, N. P., et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. International journal of radiation oncology, biology, physics 88, 596-602 (2014).

Sejpal, S. et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer. Cancer 117, 3004-3013 (2005).

Lundkvist, J. et al. Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. Cancer 103, 793-801 (2005).

Lundkvist, J. et al. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. Acta oncologica 44, 850-861 (2005).

Bradley, J. D. et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 16, 187-199 (2015).

Fletcher, G. H. et al. The interplay of radiocurability and tolerance in the irradiation of human cancers. J Radiol Electrol Med Nucl 56, 383-400 (1975).

Chang, J. Y. et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 65, 1087-1096 (2006).

Chang, J. Y. et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. Cancer 22 (2011).

Nguyen, Q. N. et al. Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II-III inoperable non-small cell lung cancer. Radiother Oncol 115, 367-372 (2015).

Oro, F. et al. Identifying the Optimal Radiation Dose in Locally Advanced Non-Small Cell Lung Cancer (NSCLC) Treated With Definitive Radiation Therapy Without Concurrent Chemotherapy. Int J Radiat Oncol Biol Phys 93, S89 (2015).

Schild, S. et al. A new scoring system for predicting survival in patients with non-small cell lung cancer. Cancer Med 4, 1334-1343 (2015).

Eisenhauer, E. A. et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer 45, 228-247 (2009).

Sloan, J. A. et al. Relationship between deficits in overall quality of life and non-small-cell lung cancer survival. J Clin Oncol 30, 1498-1504 (2012).

Sargent DJ, Goldberg RM. A flexible design for multiple armed screening trials. Stat Med. 2001 Apr 15;20(7):1051-60.

Appendix I

ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Appendix II

Quality of Life Measure

How would you rate your quality of life today?

0 10 20 30 40 50 60 70 80 90 100

As bad as it can be As good as it can be

Appendix IIb

Table 4. Five-year survival rates and the corresponding score.

Variable	Five-year survival, %	Score
QOL		
Non-deficit (>50)	63	6
Deficit (QOL ≤ 50)	30	3
Age, years		
<60	67	7
60–69.999	65	7
70–79.999	48	5
≥80	38	4
Sex		
Female	65	7
Male	51	5
ECOG performance score		
0, 1	62	6
2, 3, 4	24	2
Smoking cessation		
Quit	59	6
Kept smoking	28	3
Tumor size		
≤2 cm	69	7
>2 cm	50	5
Regional nodal involvement		
No nodal metastases	65	7
In ipsilateral peribronchial and/or ipsilateral hilar nodes	46	5
In ipsilateral mediastinal and/or subcarinal nodes	33	3
Metastasis in contralateral mediastinal nodes	13	1
Distant metastasis		
Absence	61	6
Presence	11	1

QOL, quality of life; ECOG, Eastern Cooperative Oncology Group.