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RADIATION THERAPY ONCOLOGY GROUP

RTOG Institution # _____

RTOG 0618 **ELIGIBILITY CHECKLIST (12/18/07, 9/3/08, 8/20/09)**

Case # _____

SBRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION.

_____(Y) 1. Non-small cell lung cancer (NSCLC) histologically confirmed by biopsy or cytology within 180 days prior to registration?

_____(N) Does the tumor histology show bronchioloalveolar cell carcinoma subtype?

_____(Y) 2. Is patient T1, T2, or T3 ?

_____(Y) If T2 or T3, is primary tumor less than or equal to 5 cm in greatest diameter?

_____(Y) 12. Have the required pretreatment evaluations and staging studies been obtained as specified in Section 3 and are results compatible with required parameters for registration to this study?

_____(N) 13. Is there evidence of distant metastases, or synchronous primary or prior invasive malignancy within the past 3 years?

_____(N) 14. Any prior radiotherapy for lung cancer?

_____(N) 15. Any prior radiotherapy for any other cancer which would overlap the planned SBRT fields?

_____ (N) 16. Any previous chemotherapy or surgical resection for this lung cancer?

RTOG Institution # _____

RTOG 0618 **ELIGIBILITY CHECKLIST (12/18/07, 2/4/09, 8/20/09, 3/25/10, 4/13/10)**

Case # _____ (page 3 of 3)

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at a VA or military hospital?

_____

1.0 INTRODUCTION

1.1 *Stage I Non-small Cell Lung Cancer*

Lung cancer remains the most frequent cause of cancer death in both men and women in North America. There were 172,570 new lung cancer cases in the United States in 2005, with an estimated 163,510 deaths as a result of this highly lethal malignancy. Lung cancer accounts for approximately 13% of all cancers diagnosed but 29% of all cancer deaths.[1] Seventy-five percent of patients with bronchogenic carcinoma will be diagnosed with non-small cell lung cancer

hypofractionation with markedly increased daily doses and significantly reduced overall treatment time.

The RTOG has completed an extensive dose escalation study of conventionally fractionated radiotherapy for NSCLC for stages I, II, and III disease as long as all detectable tumor can be encompassed by the radiation therapy fields including both primary tumor and regional lymph nodes. No mechanism for minimizing lung and tumor movements was used. Doses escalated as high as 90.3 Gy in the 179 treated patients. Although analysis of this study has not yet been published, the results indicate that the incidence of grade 3 or higher acute toxicity was less than 10%; however, grade 3 or higher late toxicity was approximately 15%.[21] Hayman and co-workers at the University of Michigan[22] reported on 104 patients with stages I-III treated by 3-DCRT with dose escalation as high as 102.9 Gy with acceptable toxicity. Of note is the fact that despite the dose intensification, 53 patients had disease progression, with 52% failing distantly; 8% failing both distantly and in the planning treatment volume (PTV); 2% failing in a distant site, the PTV, and a nodal region outside the PTV; and 35% failing within the PTV alone. Although the volume

= 48 Gy in one T1 patient. Additional patients were treated at each of these levels without further toxicity observed. Twenty-one patients had mild to moderate fibrosis distal to the treated lesion that appeared on chest x-ray after treatment. Nine of these patients had decline of an element of their pulmonary function tests (FEV1, FVC, DLCO

hundred seventy-six patients were enrolled in this randomized trial, all having medical characteristics predicted to allow a lobectomy. Patients were randomized to lobectomy vs. limited resection (segmentectomy or wedge). Lobectomy was superior to limited resection with respect to time to recurrence and survival. The difference in survival was not apparent until 3 years post treatment on actuarial analysis. Despite the fact that margins were mandated to be negative in both groups, excess tumor recurrence was most likely in the involved lobe not completely resected for the limited resection group, indicating a “marginal” recurrence pattern. Furthermore, there was no statistical difference in the operative morbidity or late pullesu9y function. The authors concluded that limited resection is inferior to lobectomy at controlling lung cancer and is not inherently less morbid.

Since these data were presented, wedge resections have been generally considered a compromised operation used only in circumstances in which severe pre-existing pullesu9y dysfunction excludes lobectomy. Recurrences wi

With extremely high rates of primary tumor control in prospective studies treating medically inoperable patients who are poorly tolerant of any therapy, there is ample rationale for testing SBRT in operable patients.

Despite the encouraging results using SBRT in medically inoperable patients, the results

The proposed translational research aims to examine if proteomic or genomic markers in the blood before completion of the last dose of SBRT are predictive of primary tumor control and grade 2 and above radiation toxicity.

2.0 OBJECTIVES

2.1 Primary Objective (3/25/10)

The primary objective of the study is to determine whether radiotherapy involving high biological dose with limited treatment volume (using SBRT techniques) achieves acceptable primary tumor control (i.e., ≥ 90% at 2 years) in operable patients with early-stage NSCLC.

3.1.8 Women of childbearing potential and male participants must use an effective contraceptive method, such as condom/diaphragm and spermicidal foam, intrauterine device (IUD), or prescription birth control pills.

3.1.9 Pretreatment Evaluations Required for Eligibility include:

3.1.9.1 A medical history, physical examination, weight within 45 days prior to study entry;

3.1.9.2

protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no

Organ	Volume	Dose (cGy)
Spinal Cord	Any point	18 Gy (6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral Brachial Plexus	Any point	24 Gy (8 Gy per fraction)

right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

6.5.2.6 Whole Lung

been received. The final cases will be reviewed within 3 months after this study has reached the

6.9.4 *Other Significant Adverse Events*

If other severe adverse events result in withholding therapy, the details will be documented.

6.10 Radiation Adverse Event Reporting

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indicated for resected Stages IIa, IIb and IIIa NSCLC. The role of chemotherapy in resected Stage Ib is controversial based upon the recent update of CALGB 9633. Patients with Stages IIa, IIb and IIIa should be offered adjuvant chemotherapy 92-22.harte ofth istrsia, altshoght chemotherap-

coat; the RTOG protocol number and the patient's case number. **Note**: The method of storage,

Evaluation of Target and Involved Lobe Lesions	
	Disappearance of the target lesion; ideally, this determination will be made based At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD; ideally, this determination will be made based on CT image

Dissemination **(MD)**	of metastatic dissemination from non-small cell lung cancer. Appropriate evaluations for making this determination include physical examination and imaging studies. PET scan OR biopsy to confirm MD is encouraged but not required.

11.2.4 *Criteria for Removal from Protocol Treatment* **(3/25/10)**

All reasons for discontinuation of treatment must be documented. All patients will be followed until death.

11.2.4.1 Disease progression at any time during therapy or the follow-up period; the patient should

1 Unacceptable toxicity1617 0 TDPatient will Re-4 0 TDnot

12.2 Summary of Dosimetry Digital Data Submission for 3D-CRT or IMRT (Submit to ITC; see Section 12.2.1) (9/3/08, 3/25/10)

Item	Due
Preliminary Dosimetry Information (DD)	
†Digital Data Submission – Treatment Plan submitted	

REFERENCES

71.Graham MV, Geitz LM, Byhardt R, et al. Comparison of prognostic factors and survival among black patients and white patients treated with irradiation for non-small cell lung cancer*. J Natl Cancer Inst*. 84:1731-1735, 1992. **PMID: 1331484**

72.Kong FM, Anscher MS, and Jirtle RL, TGFß: 1 plasma tumor marker, In: Hanausek and Walaszek ed, Methods in Molecular Medicine, Vol 14: Tumor Marker Protocols, *Humana Press Inc*., NJ. P417-430, 1997.

APPENDIX I

you medicines to help lessen side effects. Many side effects go away soon after your treatment. In some cases, side effects can be delayed, can be serious, long lasting, or may never go away. Although rare, there also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Stereotactic body radiation therapy (SBRT) to the chest may cause the following side effects:

Very Likely and Serious

- A common effect of this treatment in previous studies was eventual collapse of a portion of the treated lung; this collapse generally affects a limited portion of the lung, but the collapse appears to be permanent. Efforts will be made to reduce this risk and limit its effect. If collapse of a portion of the treated lung occurs, the

these symptoms. You should tell your doctors immediately if you have any of these symptoms. Treatment for this lung damage involves pain medicines, anti-inflammatory medicines (corticosteroids), and rarely, oxygen therapy. Some patients are required to be on oxygen therapy for the rest of their lives.

Reproductive Risks

This study may be harmful to a nursing infant or an unborn child. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), and if you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while you are on this study, you must tell your doctor immediately.

If you are a man able to father children, and if you are unwilling to use adequate birth control measures as approved by your doctor to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone to

- The National Cancer Institute (NCI) and other government agencies, like the Food and

ZUBROD PERFORMANCE SCALE

0 Fully active; able to carry on all predisease activities without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work

2 Ambulatory and capable of all self-care but unable to carry o-0.e1f6ousewo of

APPENDIX IV

AJCC Staging
Lung, 6th Edition, 2002

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumor.

Tis Carcinoma *in situ*

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (i.e., not in the main bronchus)

T2 Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to

APPENDIX IV

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APPENDIX V

CHARLSON COMORBIDITY INDEX (CCI)

Scoring Sheet

RTOG 0618

RTOG Institution Name/Number:_____

APPENDIX V (Continued)

COMORBIDITY RECORDING SHEET

RTOG 0618
RTOG Institution Name/Number:_____
Patient Initials (First Middle Last):_____RTOG Patient Case Number:_____
Name of Person Completing Sheet: _____Phone Number:_____

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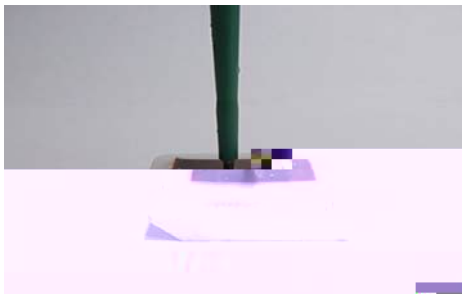

APPENDIX VI (Continued)

Blood Collection Instructions

Blood Sample Drawing and Handling

Samples for TGFb[ý] and other cytokine measurement and proteomic analysis need to be handled gently and carefully to avoid platelet degradation or contamination[72].

(5/7/09) Blood should be drawn in a standard fashion from each individual within 3 days before treatment, at the last day of treatment (before the delivery of the last dose of SBRT), and at the 6 week follow-up visit after completion of SBRT. Needles of large gauge (19-21G) should be used to minimize platelet-contamination from hemolysis. Blood will be collected in two standard blood collection tubes (one purple top and one red top). Blood samples can be drawn in the clinic or blood lab, and temporarily placed vertically at 4°C until plasma/serum are prepared within 2 hours of collection.

Collection of Plasma and Buffy Coat Samples

a. Collect one 10 ml tube of blood using one EDTA (purple top) tube, and invert gently one to two times to mix with anticoagulant.
b. Store the blood at 4° C or ice as soon as possibl

co Cntlrifge undr

Blood Collection Instructions (Continued)

Serum Sample Preparation

a. Collect one 5-10 ml tube of blood without coagulants (Red-topped tube).
b. Sit at room temperature for 30 min to allow clot formation.
c. Centrifuge in a standard clinical centrifuge ~ 2500xG at 4^{o} for 30 minutes.