RTOG FOUNDATION

RTOG 3502

(ClinicalTrials.gov NCT #: 01753414)

POSTILV: A RANDOMIZED PHASE II TRIAL IN PATIENTS WITH OPERABLE STAGE I NON-SMALL CELL LUNG CANCER: RADICAL RESECTION VERSUS ABLATIVE STEREOTACTIC RADIOTHERAPY

Amendment 2: August 6, 2018

RTOG Foundation Collaboration with Varian

RTOG 3502
A Limited Participation Study

POSTILV: A RANDOMIZED PHASE II TRIAL IN PATIENTS WITH OPERABLE STAGE I NON-SMALL CELL LUNG CANCER: RADICAL RESECTION VERSUS ABLATIVE STEREOTACTIC RADIOTHERAPY

Protocol Version Date: August 6, 2018
Sponsor: RTOG Foundation

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Protocol Acceptance
On behalf of the RTOG Foundation, Inc.

August 6, 2018

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Date

RTOG FOUNDATION STUDY 3502

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RTOG FOUNDATION STUDY 3502

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POSTILV: A Randomized Phase II Trial in Patients with Operable Stage I Non-Small Cell Lung Cancer: Radical Resection versus Ablative Stereotactic Radiotherapy

SCHEMA

	R		**R**		**Follow up for**
	E		**A**	**Arm 1**: R0 resection with	**Arms 1 and 2**
Patients with	**G**	FDG-PET/CT	**N**	nodal dissection/sampling	
pathologically	**I**	staging	**D**	(RODS)	If recurrence then
proven, medically	**S**	to confirm	**O**		salvage treatment:
operable CT-staged	**T**	T1N0 disease*	**M**	**Arm 2**: SBRT given every other day	surgery, radiation,
T1N0 NSCLC	**E**		**I**	11 Gy in 5 fractions to a total dose	or systemic therapy
	R		**Z**	of 55 Gy in 10-15 days with an	
			E	inter-fraction interval of 2-3 days	

*Patients with T > 3 cm or N+ disease will be treated off study per standard of care and will not be followed.

Note: All participating institutions must be credentialed for participating surgeons, a dry-run case, phantom irradiation, IGRT, and 3DCRT (or IMRT, if used) prior to registering patients to the study; see Section 5.1.

Patient Population: (See Section 3.0 for Eligibility)
Patients must have histologically proven CT and PET/CT confirmed Stage I, T1N0M0 non-small cell lung cancer (NSCLC); patients must be medically operable

Required Sample Size: 76

ELIGIBILITY CHECKLIST – STEP 1 (10/22/14)
(page 1 of 4)

PRE-REGISTRATION CREDENTIALING for participating surgeons, a dry-run case, phantom irradiation, IGRT, AND 3DCRT (or IMRT, if used) IS REQUIRED.

_____(Y) 1. Was stage I non-small cell lung cancer (NSCLC) confirmed by biopsy (strongly recommended) or is the mass suspicious for NSCLC based on 2 or more criteria listed in Section 3.1.1?

_____(Y) Is the cancer one of the types eligible for the study as specified in Section 3.1.1?

_____(N) Any histologic evidence of pure bronchioloalveolar cell carcinoma subtype?

_____(N) 2. Is the primary tumor > 3 cm?

_____(Y) 3. Is patient nodal status N0 per definition in Section 3.1.2. ?

____(Y/N) Are there hilar or mediastinal lymph nodes > 1 cm on computed tomography (CT) or any size lymph nodes demonstrating suspicious uptake on positron emission tomography (PET) scan?

_____(Y) If yes, are all lymph nodes > 1 cm on CT or demonstrating suspicious uptake on PET scan negative for NSCLC on biopsy?

_____(N) 4. Does the patient have metastatic disease (M1)?

_____ (Y) 5. Is the primary tumor predicted to be technically resectable with high likelihood of negative surgical margins by a thoracic surgeon?

_____(Y) 6. Is the patient medically operable as defined in Section 3.1.3?

_____(Y) 7. Do the patient's PFTs meet the criteria specified in Section 3.1.3?

_____(Y/N) 8. Is pleural effusion present?

_____(Y) If yes, is the effusion too small to tap under CT guidance and not evident on chest x-ray? (Pleural effusion that appears on chest x-ray and only after thoracotomy or other invasive thoracic procedure will be permitted.)

_____(Y) 9. Is the patient's Zubrod Performance Score 0-1?

_____(Y) 10. Is patient ≥ 18 years of age?

____(Y/NA) 11. If a female of childbearing potential or an sexually active male, has the patient agreed to use an effective method of contraception?

_____(Y) 12. Have the required pretreatment evaluations and staging studies been obtained as specified in Section 3.0 and are results compatible with required parameters for registration to this study?

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

Continued on next page

_____(N) 14. Any prior radiotherapy for any other cancer which would overlap the planned SBRT fields?

_____(N) 15. Any previous chemotherapy or thoracic surgery involving lobectomy or pneumonectomy?

_____(N) 16. Is there evidence of active systemic, pulmonary, or pericardial infection?

____(N/NA) 17. If a female of childbearing potential, is the patient pregnant?

The following questions will be asked at Study Registration:
CREDENTIALING for participating surgeons, a dry-run case, phantom irradiation, IGRT, AND 3DCRT (or IMRT, if used IS REQUIRED BEFORE REGISTRATION.

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Method of Payment

_____ 14. Calendar Base Date

_____ 15. Randomization date

_____ 16. Thoracic Surgeon

Continued on next page.

_____(Y/N) 17. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 18. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 21. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____ (Y/N) 22. Specify use of IMRT.

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional RTOG audit.

Completed by _____ Date _____

Institution #
3502
Case #

ELIGIBILITY CHECKLIST –STEP 2 (2/14/13)
(page 4 of 4)

_____ 1. Institutional person randomizing case

_____(Y/N) 2. Is the patient able to continue protocol treatment?

_____ 3. If no, specify the reason the patient cannot continue to Step 2:
1) FDG-PET/CT not done;
2) T > 3 cm;
3) N+;
4) T > 3 and N+;
5) Patient refusal;
6) Other*

_____ *Specify the reason the patient cannot continue to Step 2.

_____ 4. Patient's Initials

_____ 5. Verifying Physician

_____ 6. Patient ID

_____ 7. Calendar Base Date (for Step 2)

_____ 8. Randomization date: (for Step 2)

1.0 INTRODUCTION

Lung cancer remains the leading cause of cancer death in both men and women in the U.S. [1], Asian countries [2], and the world [3]. Based on WHO report, there were 1.4 million lung cancer-related deaths in the world in 2008. The incidence is expected to increase with an expected doubling of the incidence of all cancers by 2030.

Approximately 85% of lung cancers are non-small cell lung cancer (NSCLC), and 16% of these present with localized disease (stage I and node-negative stage II are generally considered as local disease). For patients with local disease, radical resection, i.e. R0 resection with nodal dissection or sampling (RODS) has been the standard care for decades, with a 5-year survival rate of 70-80% [4]. Based on SEER data from 1973-2007, approximately 70% of early stage patients underwent surgical resection. The remaining patients were either medically inoperable or declined surgical intervention. Among this group, conventional fractionated radiation therapy (RT) was the mainstay of treatment with a 10-30% 5-year survival rate. In the 1990s, advances in technology allowed for the implementation of 3D conformal RT (3DCRT) with associated dose escalation and improved local control and long-term survival. Further advances in target motion definition, image-guidance, and stereotactic localization, have allowed for the development of stereotactic radiotherapy (SBRT). This modality has a reported 90% 3-year local control rate and 60-80% long-term survival rate. These rates are comparable to those obtained from surgery. The primary aim of this trial is to determine if the efficacy of SBRT is comparable to that of standard surgical interventions for patients with T1N0 NSCLC.

1.1 Treatment Outcome of Surgery

1.1.1 Efficacy

Currently, RODS remains the standard of care for stage I (T1-2a N0) NSCLC with 5-year survival rates of 60-70%. [5-13]. The preferred surgical procedure is a lobectomy with or without hilar/mediastinal lymph node dissection [14-21]. A less extensive operation such as a wedge resection or a segmentectomy with or without postoperative brachytherapy often is performed when a patient is unable to tolerate a lobectomy either because of inadequate respiratory reserve, cardiac dysfunction, vascular disease, general poor performance status, or other co-morbidities. In general, wedge resection is not considered to be a radical resection. Table 1a summarizes the tumor control rates after surgical resection in this patient population. According to the International Association for the Study of Lung Cancer staging project [4], the 5-year survival rates were 77% and 71% after radical excision of pT1N0 tumors <2 cm (n=1,816 patients) and pT1bN0 tumors (2–3 cm), (n=1,653 patients), respectively. For patients clinically staged N0, 5-year survival was 53% for cT1a and for cT1b, 43%. After RODS, there is a 10-35% rate of local recurrence [22-27]. Salvage options after resection are available but tend to have poor outcomes.

Table 1a: Survival Outcomes in T1-2N0M0 NSCLC Patients Treated with Surgery

Reference	N	Patient Category	Treatment	Local control (%)	Overall survival (%)	Postoperative complications
Errett, et al. (1985)[28]	97 100	Poor risk	Lobectomy Wedge resection	NR	74 (2yr), 75 (6yr) 72 (2yr), 69 (6yr)	2.1%,3% (30 day operative mortality)
Ginsberg, et al. (1995)[11]	125 122	Standard risk	Lobectomy Limited resection	~80 (5yr) ~55 (5yr)	~65% (5yr) ~45% (5yr)	2 postoperative deaths 1 postoperative death
Kodama, et al. (1997)[29]	46/77	Standard risk	Segmentectomy or Lobectomy	91.3 (5yr)	93 (5yr)	NR
Koike, et al. (2003)[30]	159 74	Standard risk	Lobectomy Limited resection	~150/159 (5yr) ~69/74 (5yr)	97.0 (3yr), 90.1 (5yr) 94.0 (3yr), 89.1 (5yr) (tumor <=2cm)	no severe cardiovascular or comorbid factors in either groups

Landreneau, et al. (1997)[31]	42 60 117	Stage I Poor risk	Open wedge resection Video-assisted wedge resection Lobectomy	76 (5yr) 84 (5yr) 91 (5yr)	58 (5yr) 65 (5yr) 70 (5yr)	0 operative death in wedge resection 3% operative mortality in lobectomy group
Martini, et al. (1995)[32]	511 25 62	T1-2	Lobectomy Pneumonectomy Wedge resection or segmentectomy	 50 (5yr)	77 (5yr), 70 (10yr) 59 (5yr), 35 (10yr)	14 postoperative death in lobectomy group
Miller, et al. (2002)[33]	75 25	T<1cm	Lobectomy or bilobectomy Limited resection	85.3 (5yr) 72 (5yr)	71 (5yr) 33 (5yr)	4 postoperative death
Okada, et al. (2006)[34]	262 305	Standard risk (≤2cm)	Segmentectomy or Lobectomy	82 (5yr) 85 (5yr)	89.1 (5yr) 89.6 (5yr)	6.6% 7.3%
Pastorino, et al. (1991)[35]	411 61	Stage I Standard risk	Lobar resection Sublobar resection	64 (5yr) 62 (5yr)	T1:55 (5yr) T2:46(5yr) T1:73 (5yr) T2: 35 (5yr)	3% peri-operative death lobar resection
Warren, et al. (1994)[36]	105 68	Standard risk T1-2	Lobectomy Segmentectomy	95.1 (5yr) 77.1 (5yr)	NR	NR
Birdas, et al. (2006)[37]	126 41	IB High risk	Lobectomy Sublobar + I-125 brachytherapy	96.8 95.2	51.8 (4yr) 54.9 (4yr)	NR
Fernando, et al. (2005)[38]	167 124	IA High risk	Lobectomy Sublobar resection (60+ brachytherapy)	90 (<2cm), 96.5 (>2cm) 82.5 (T2cm) 95.6 (T2cm) 96.7 with brachytherapy	85 m(<2cm),68.7m(>2cm) 55.8m(<2cm),50.6m(>2cm	NR
Santos, et al. (2003)[39]	102 101	T1-2 High risk	Sublobar resection Resection + brachytherapy	81.4 98	NR	NR
d'Amato, et al. (1998)[40]	14	T1 High risk	VATS wedge resection + brachytherapy	100 at 7m fu	NR	NR
Lee, et al. (2003)[41]	33	T1-2 High risk	Limited resection + brachytherapy	2 local recurrence	47(5yr)	NR
McKenna, et al. (2008)[42]	48	I-III High risk	Wedge resection + brachytherapy	3 local recurrence	NR	2 death in 30 day postoperatively

Attempts to minimize the extent of resection have demonstrated worse outcomes in general [10, 11, 31, 43, 44]. The only randomized trial comparing lobectomy with sublobar resection reported a significantly higher recurrence rate for sublobar resection (p=0.02). There also was a trend toward worse survival in the sublobar resection group, but this did not reach statistical significance (p=0.08) [11]. One meta-analysis and several non-randomized comparisons have confirmed these results. Local recurrence after wedge resection is higher than after segmentectomy. However, for tumors ≤ 2 cm, segmentectomy is equivalent to lobectomy. Survival after segmentectomy is worse for larger tumors [45, 46]. For patients aged > 71 years, lobectomy and wedge resection may be associated with similar survival.

1.1.2 Toxicity

Surgical treatment is invasive and associated with significant mortality and morbidity [47-52]. The reported mortality rates are 7.2% in China (for T4 tumors) [53], 2.4~4.9% in Europe [49, 54], and 4.5% in the U.S. within 30 days post-lobectomy. In 128 patients with screen-detected peripheral lung nodules who underwent a video-assisted thoracic surgical (VATS) lobectomy, grade 3 or greater complications were seen in 7.4% (out of 95 patients) and the 30-day perioperative mortality was 2.7% [55]. Similarly, operative complications occurred in 27% of patients with screen-detected lung nodules who underwent a thoracotomy, and the corresponding operative mortality was 1.7%. [56]. While morbidities may vary from report to report [48, 57-59], most of the studies reported mortality rates of 1-7% associated with surgical intervention (Table 1a).

1.2 Treatment Outcome of Stereotactic Body Radiation Therapy (SBRT)

SBRT is an emerging radiation (RT) technique that targets very high-dose RT precisely to a tumor while minimizing dose to adjacent normal tissue. SBRT derived from stereotactic radiosurgery, which was first developed in the late 1950's for the treatment of intracranial lesions. Stereotactic radiosurgery, normally with high-dose RT delivered in 1 fraction under stereotactic targeting, provides equivalent treatment results as a craniotomy with surgical resection. Recent advances in RT planning, such as 3DCRT and intensity modulated radiation therapy (IMRT), motion control, and on board image (OBI), and image guided radiation therapy (IGRT) during treatment delivery in the last decade have led to the application of this technique to extracranial sites. While stereotactic RT refers to high-dose RT in a fractionated fashion to any organ sites (intra- or extracranial sites), SBRT has been adopted for stereotactic RT to extracranial body sites including lung. The U.S. National Cancer Institute defines SBRT as "a type of external radiation therapy that uses special equipment to position a patient and precisely deliver radiation to tumors in the body (except the brain). The total dose of radiation is divided into smaller doses given over several days. This type of radiation therapy helps spare normal tissue."

SBRT techniques were initially developed at Karolinska University Hospital in Sweden in the early 1990s for the treatment of tumors in the liver using a body stereotactic frame method [116]. Investigators there reported that the reproducibility of localization in the stereotactic system for tumors in the liver and the lung was within 5-8 mm for 90% of the patient set-ups. Diaphragmatic movements were reduced to 5-10 mm, by applying pressure on the abdomen. A non-coplanar treatment technique of 8 individually shaped beams was proposed [116]. The first clinical report also was from the same group in 31 patients with solitary tumors in the liver, lung, or retroperitoneal space with clinical target volumes ranging from 2 to 622 cm^3 (mean 78 cm^3). With a total mean PTV dose of 41 Gy (8-66 Gy), fraction dose of 14.2 Gy (7.7-30 Gy), and minimum PTV dose of 30.2 Gy (7.7-45 Gy) with treatment delivered in 1-4 fractions, the authors reported that 50% of patients had tumor reduction or complete resolution [117]. Later, a Japanese group developed an SBRT unit consisting of a linear accelerator, X-ray simulator, computed tomography scanner, and table [118]. A dose of 30-75 Gy was delivered in 5-15 fractions at the 80% isodose line over 1-3 weeks, with or without conventional radiation therapy. The gantry axes of the 3 machines were coaxial and could be matched by rotating the table. Patients were instructed to perform shallow respiration with oxygen. The motion of the tumor was monitored with the x-ray simulator. Between 1994 and 1997, 45 patients with 23 primary tumors and 43 metastatic lung tumors were treated. During a median follow-up of 11 months, local progression occurred in only 2 of 66 lesions with no or minimal toxicity.

The first prospective dose escalation SBRT trial performed in the U.S. was from the University of Indiana, led by Timmerman [119]. This study of 37 patients with stage I NSCLC demonstrated that a very high dose (60 Gy in 3 fractions BED 180 Gy) could be delivered safely to peripheral tumors, and that a dose less than 18 Gy per fraction was associated with more frequent local failure.

Modern SBRT is the result of multiple advanced RT techniques, including IMRT, 4DCT/ABC, OBI, high accurate image fusion capability, and precise treatment delivery. Specifically, SBRT is a form of high-precision radiotherapy delivery characterized by (a) highly reproducible immobilization to avoid patient movement during treatment sessions; (b) highly conformal radiation dose tightly covering the tumor, with rapid dose falloff in surrounding normal tissues in order to reduce toxicity; c) measures to individually account for tumor motion during imaging, treatment planning, and radiation delivery; d) use of OBI and 3D IGRT to secure precise radiation delivery; and e) the use of extremely high biological doses of RT usually delivered in 3 to 8 treatment fractions within a 2-week period [120]. The tumor control and overall survival (OS) rates for SBRT (Table 1b) are remarkably better than that of 3DCRT. In patients with medically inoperable stage I NSCLC, SBRT generated 3-year local control and OS rates of 66-90% and 43-90%, respectively. Results from RTOG 0236, a multicenter trial in medically inoperable NSCLC, have just been published [121]. Of 55 evaluable patients with stage I NSCLC (44 stage IA, 11 IB), the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0%-96.5%). The local-regional control rate was 87.2% (95% CI, 71.0%-94.7%). The 3-year rate of OS was 55.8% (95% CI, 41.6%-67.9%), and the median OS was 48.1 months (95% CI, 29.6 months to not reached).

The survival outcome of SBRT in stage I NSCLC is associated with multiple factors including comorbidities, tumor size, RT dose, and patient fitness. One of the most common causes of death in this group of patients was intercurrent diseases [122]. This is in marked contrast to the experience reported in 3DCRT series, in which the major cause of death was progression from lung cancer [85, 123, 124].

Patients with operable disease had overall survival (OS) rates of over 80% in most series after SBRT. However, the data on SBRT in operable stage I NSCLC is relatively limited [125-130]. In a retrospective study, Hiraoka, et al. reported that for tumors that received a BED of more than 100 Gy, OS at 3 years was 91% for operable patients [130]. This included 98 patients who refused surgery [129], and whose 5-year OS rate of 70.8% after a BED of 100 Gy was at least equivalent to that reported historically after surgery [131]. A recent study from Washington University retrospectively compared treatment results in patients with clinical stage I disease treated with SBRT and RODS [132]. The 3-year local tumor control rates were 89% with SBRT and 96% with surgery ($p = .04$) for stage IA. There was no difference in local tumor control in stage IB disease ($p = .89$). No disease-specific survival differences were found in patients with stage 1A ($p = .33$) or IB disease ($p = .69$). Results from a propensity score matched analysis in 57 high-risk surgical patients to 57 patients undergoing SBRT reported no difference in freedom from local recurrence (88% vs. 90%), disease-free survival (77% vs. 86%), and OS (54% vs. 38%) at 3 years. A study from William Beaumont Hospital compared outcomes between SBRT (n=58) and wedge resection (n=69) for patients with stage I NSCLC. At 30 months, no significant differences were identified in regional recurrence, locoregional recurrence, distant metastasis, or freedom from any failure between the 2 groups ($p > .16$). SBRT reduced the risk of local recurrence by 4% versus 20% for wedge resection ($p = .07$). OS was higher with wedge resection, but cause-specific survival (CSS) was identical. Results from a phase II randomized study reported at ASTRO 2010 showed that OS is comparable between SBRT and RODS in patients with operable stage I NSCLC. In patients with operable NSCLC, a retrospective study of 87 patients stage I NSCLC reported 5-year tumor control of 92%, OS 72% from 14 Japanese centers [265]. Results from a phase II single arm study from Japan reported at ASTRO 2010 showed that OS of SBRT is comparable to RODS in patients with operable stage I NSCLC [266].

Table 1b: Results of SBRT in the Treatment of Stage I Non-Small Cell Lung Cancer

Reference	# Pts	Stage	Dose & Fraction (Gy)	Treatment Duration (Days)	Median follow-up(months)	% local tumor control	% overall survival	Toxicity
Uematsu, et al. 2001[125]	50 (29 operable)	I	50-60 in 5-10fx	<12		94 (3yr)	66 (all cases, 3 yr) 86 (operable cases, 3 yr)	2 minor bone fracture, 6 temporary pleural pain
Koto, et al. 2007[133]	31	I	45/3fx, 68/8fx		32	77.9 (T1,3yr) 40.0 (T2,3yr)	71.7 (3yr)	5 grade 2 lung toxicity
Timmerman, et al. 2006[134]	70	I	24-60 in 3fx	<12	17.5	95 (2yr)	54.7 (2yr)	14 grade 3-5 toxicity for both central and peripheral disease
Lagerwaard, et al. 2008[135]	206	I	60/3fx,60/5fx, 60/8fx	5-14	34	91 (2yr)	64 (2yr)	3% ≥ grade 3 pneumonitis, 4 rib fracture
Hiraoka, et al. 2004[136]	254	IA,IB	48 in 4 fx	5-12		80 (BED<100) 93.5 (BED>100)	46 (BED>100, 3 yr) 42 (BED<100, 3 yr)	NR
Zimmermann, et al. 2005[137]	30	I	24.0-2737.5 in 3-5 fx	<12	18	93 (1.5 yr)	70 (1.5yr)	1 grade 3 acute pneumonitis, 1 rib fracture
Wulf, et al. 2004[138]	20	I, II	30-37.5 in 3fx or 26 Gy in 1 fx	<12	11	92 (1yr)	32 (2yr)	2 grade 2 pneumonitis
Nagata, et al. 2005[139]	45	IA, IB<4cm	48 in 4 fx	5-12 13	30	72 (3 yr dfs) 71 (3 yr dfs)98	83 (IA, 3yr) 72 (IB, 3yr)	2 grade 2 pneumonitis
Onishi, et al. 2004[140]	235	IA, IB	60 in 10 fx	5-8	13	NR, 94	83 (2yr)	5 grade 2 lung toxicity
Zimmermann, et al. 2006 [141]	68	I	24-40 in 3-5 fx	3-10	17	88 (3 yr)	53 (3yr)	3% grade 3 acute pneumonitis, 1% grade 3 late pneumonitis, 3% rib fractures, 2 benign pleural effusion
Takeda, et al. 2009[142]	121	IA/IB	50 in 5fx	<12	31	93 (IA)/96 (IB) (3yr)	90 (IA)/63 (IB) (3 yr)	3 >2 grade pneumonitis, 1 fatal bacterial pneumonia
Guckenberger & Wulf, et al. 2009[143]	124 (118 met)	I/II (Met)	26-326 in 1-68fx	<12	14	62 (BED<100) 89 ((BED>100) (3yr)	37 (primary) 16 (mets) 3yr	1 grade 3 pneumonitis 1 grade 3 esophageal ulceration
Chang, et al. 2008[144]	27	I & recurrent	40-50 in 4 fx	4	17	100 (17mo) (50Gy) 47 (40Gy)	NA	3 grade 2-3 dermatitis and chest wall pain.

Baumann, et al. 2008 & 2009[126, 145]	60 (2008) /57 (2009)	IA/ IB	45 in 3 fx	<12	36	92(3yr)	50/60 (3yr)	21% grade 3 toxicity 0%grade 4-5 toxicity
Salazar, et al. 2008[146]	60	IA/IB	40-53 Gy in 4 fx (73%) or EBRT45 Gy +3SBRTx3 fx (27%) BED=120 Gy	6+ weeks	NR	70/74 (CSS) 82	5yr CSS 74 (IA) 5yr CSS 64 (IB)NA	7% grade 2 toxicity
Le, et al. 2006[147]	32	I	15-30 Gy/1fx	1	12	91 (>20 Gy,1yr) 54 (<20 Gy, 1yr)	NR	12.5% grade 3-5, 3/4 central lesions, all >20Gy
Fakiris, et al. 2009[148]	70	IA/IB	60-66/3fx	<12	50.2	88.1 (3yr)	42.7 (3yr)	Grade 3-5:10.4%(peripheral); 27.3% (central)
Gomi, et al. 2007 [149]	56	IA	62.5/5fx	5<12	32	95 (3yr)	81.3 (3yr)	1 grade 4 pneumonitis, 1 grade 4 dermatitis, 1 grade 3 esophagitis and 1 rib fracture
Gril, et al.2010[150]	58	IA/IB	48/4fx, 60/5fx	<12	30	96	72 (3yr)	11% > grade 2 pneumonitis
Timmerman, et al. [121]	55	IA/IB	60 in 3fx	10-14	24.8	93.7 (2yr)	72 (2yr)	24% grade 3, 4% grade 4
Onishi, et al. 2007 [129]	257	IA/IB	18-75/1-22fx		38	86	70.8 (BED>100 Gy, 5yr), 30.2 (BED<100 Gy, 5yr)	5.4% >grade 2 lung toxicity

1.2.1 Dose Fractionations in SBRT

Similar to 3DCRT, adequate biologic equivalent dose (BED) is essential for optimal tumor control with SBRT [129, 130, 140, 143, 151-154]. SBRT normally delivers much higher BED than conventionally fractionated 3DCRT (typically BED of 70-85 Gy). Studies from Japan, Germany, and China all reported that SBRT with BED ≥ 100 Gy was associated with significantly better local control and long-term survival. For patients who received a BED ≥ 100 Gy, local tumor control was over 90%. The largest series [129] retrospectively reviewed 257 patients treated at 14 institutions in Japan using a number of different treatment doses and delivery approaches. At a median follow up of 38 months, the local recurrence rate was 8.4% in patients who were treated to a BED ≥ 100 Gy. A recent Germany study also reported that a BED > 100 Gy is critical for achieving good local control [143]. A Chinese study applied daily fractionated SBRT with a total BED up to 115 Gy and reported 3- and 5-year OS rates for T1-3 patients of 57.3% and 35.1%, respectively, and for stage T1-2 patients of 60.2 and 36.5%, respectively [151]. Studies from the U.S. also suggested that patients who received 16 Gy x 3 (BED=124 Gy) had significantly better local control than those who received lower doses. Dose response analysis showed that the outcome plateaued around 120 Gy BED.

The effect of fractionation is complicated for SBRT, and fractionation regimens vary from center to center. A number of fractionation schedules are undergoing evaluation [155]. In the U.S., a frequently used schedule for peripheral lung tumors is 60 Gy in 3 fractions with a total BED of 180 Gy. In Europe, Japan, and China, however, a BED >100 Gy is more commonly delivered in 4-10 fractions. Particularly in China, regimens with fraction size less than 12 Gy have been preferred. Selection of fractionation should maximize the therapeutic ratio of tumor control versus normal tissue toxicity by taking the tumor size and location into consideration for an optimized therapeutic gain [156] [157]. Overall, for tumors less than 3 cm, there is no significant difference in tumor control rates between various fractionation regimens as long as more than 100 Gy BED is given [150, 158]. For tumors larger than 3 cm, higher doses (BED of 120 Gy or above) may be needed. Similar to RODS, distant failure is the main cause of death [159]. Fractionation regimens with tumor BED around 120 Gy in 3-5 fractions include 16 Gy x 3, 13 Gy x 4, and 11 Gy x 5. The available data are compelling enough for SBRT to be considered an established treatment option in patients who are medically inoperable or for those patients who have refused surgical resection [132, 150, 160].

1.2.2 Toxicity of SBRT

Toxicity following SBRT has been limited. Reported long-term toxicity exceeding grade 2 Common Toxicity Criteria (CTC v. 3.0) is seen in less than 10% of patients and was mainly observed in patients with large or centrally located tumors [121, 135, 161, 162] when doses to the proximal bronchial tree were not strictly limited. In the series by Onishi [129], pulmonary complications exceeding grade 2 were observed in 14 patients (5.4%). Timmerman, et al. reported the need for caution when a BED of 180–210 Gy was administered for centrally located tumors adjacent to the mediastinum [134]. In the patients treated by Lagerwaard, et al., using a 'risk-adapted' approach with the BED limited to 105 Gy for central tumors, early toxicity was mild with fatigue (32%), nausea (10%), and chest pain (8%) as the most frequently encountered acute side effects [135]. Late toxicity was uncommon with radiation pneumonitis exceeding grade 2 in 6 patients (3%). Rib fractures and chronic pain syndromes located at the chest wall were observed in 4 and 3 patients, respectively.

1.2.3 Quality of Life After SBRT

Data on quality of life (QOL) is limited after SBRT for NSCLC. For stage I NSCLC, QOL was assessed in 39 patients treated with SBRT by using The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 and the QLQ LC13 lung cancer-specific questionnaire. Assessments were done before treatment, at 3 weeks, and at 2, 4, 6, 9, and 12 months after treatment, and until death or progressive disease. Toxicity was evaluated using CTCAE, v. 3.0. Emotional functioning improved significantly after treatment. Other functional scores, QLQ C30, and QLQ LC13 lung symptoms (such as dyspnea and cough) showed no significant changes. [164]. These results may be better than those reported for 3DCRT, RFA, and surgical resection. Using Markov model analysis, a recent cost effectiveness study report indicates that SBRT may offer comparable OS and quality-adjusted life expectancy as compared with surgical resection [266]. Randomized prospective studies comparing surgery vs. SBRT in early-stage lung cancer are warranted to further investigate the relative survival, quality of life, and cost characteristics of both treatment paradigms [266].

In this trial, quality of life endpoints will not be evaluated; however, provided that the primary hypothesis and performance metrics are satisfied, the subsequent phase III trial will incorporate detailed QOL measures in order to definitively and comprehensively evaluate SBRT for larger scale clinical utility.

1.3 Translational Research

1.3.1 Background/Hypothesis

Severe pulmonary complications occur in about 10-20% patients after lobectomy [192-198]. After SBRT, 10% of patients experience grade ≥ 3 radiation-induced lung toxicity (RILT) [199-201]. Currently, there are no well-established methods to predict which patients will experience lung toxicity. In general, the risk of pulmonary toxicity increases with decreasing pulmonary reserve, larger radiation treatment volumes, and the use of concurrent chemotherapy. Many dosimetric factors, such as mean lung dose, V20, and D30 [202-209], have been associated with the risk of lung toxicity after radiation. However, these associations have not enabled prediction of which patients will experience lung toxicity. The mechanisms of RILT are not well understood; however, several reports have suggested a possible role of pro-fibrogenic and pro-

inflammatory cytokines such as Interleukin-1 (IL-1), IL-6, IL-8, IL-10, TNF-α, platelet-derived growth factor and transforming growth factor beta 1 (TGFβ1) [210-218]. Among these factors, TGFβ1 has been the most extensively studied. TGFβ1 stimulates connective tissue formation and decreases collagen degradation resulting in fibrosis. It also plays an important role in the inhibition of epithelial cell proliferation. Researchers from Duke University have reported that the plasma TGFβ1 at the end of radiation correlates with symptomatic lung toxicity in patients treated with definitive radiation therapy [219, 220]. Kong, et al. further demonstrated that the loss of mannose 6-phosphate insulin-like growth factor-2 receptor contributes to increased TGFβ1 levels and subsequent radiation-induced pneumonitis [221]. In patients treated with an escalated dose of radiation, Anscher, et al. found a significant correlation between TGFβ1 levels and late grade ≥ 3 non-pulmonary radiation toxicity [222]. Additional reports have shown that elevated plasma levels of TGFβ1 4 weeks into the course of conventionally fractionated conformal radiation therapy are highly correlated with the occurrence of grade ≥ 2 RILT [210, 223]. A combined analysis of University Michigan and Peking Union of Medical College data further confirmed this finding [224].

Data also has been published demonstrating an association between RILT and levels of IL-1, IL-6, and IL-8 [215, 216, 225-228]. IL-1 (IL-1ra and IL-1β) is produced by macrophages, monocytes, fibroblasts, and dendritic cells and is an important mediator of the inflammatory response of many tissues [229-232]. IL-1β promotes inflammation in injured lung tissue, and has been reported to be significantly associated with RILT [216, 233]. IL-6 also is a major mediator of the acute-phase inflammatory response and is synthesized by a variety of cells in the lung parenchyma. Researchers have demonstrated a trend toward increased plasma concentrations of IL-6 after thoracic RT [212, 216]. Animal models also have confirmed these trends [228, 237, 238]. In addition, IL-8, a member of the CXC chemokine family, is believed to serve as a chemical signal that attracts neutrophils to the site of inflammation [239-241]. Significant differences in the median values of IL-8 were observed between patients with and without symptomatic RILT [225]. Overall, plasma IL1, IL-6, and IL-8 levels may serve as a predictor for RILT after conventionally fractionated radiation therapy [212, 216]. Most recently, it was reported that the plasma level of IL-8 prior to and during conventionally fractionated radiation therapy is significantly associated with grade ≥ 2 RILT [242].

Genomic markers also have shown promise in helping to elucidate the mechanism of RILT. The single nucleotide polymorphisms (SNP) of several specific genes found in white blood cells have been shown to be elevated in the setting of radiation-induced injury in several organs [243-245]. CT/CC genotypes of TGFβ1 rs1982073:T869C genes are associated with a lower risk of RILT in patients with NSCLC treated with definitive chemoradiation [246]. It also recently was demonstrated that the frequency of the 7351C allele of Tissue Plasminogen Activator, which is associated with TGF β1 activation is increased in patients with grade ≥ 2 RILT when compared to historical controls (0.73 vs. 0.68, p = 0.01)[247].

Protein elevations also may hold cues as to the mechanism of RILT. It has been demonstrated that there are differential changes in protein-associated pathways between animals sensitive to and resistant to radiation lung damage [248]. Using a multiplexed quantitative proteomics approach involving ExacTag labeling, RP-HPLC, and LC-ESI-MS/MS, over 100 proteins have been identified and quantified in platelet-poor plasma. C4b-binding protein alpha chain, complement C3, and vitronectin have significantly higher expression levels in patients with grade ≥ 2 RILT. Interestingly, all of these proteins are associated with inflammatory pathways that interact with IL-1 ß, TNF, and TGF-ß1 [249].

Given these previous studies, we hypothesize that blood-based biomarkers, including plasma TGFβ1, will be able to predict which patients will develop grade ≥3 pulmonary complications after treatment with either SBRT or surgery, and specimens will be banked for future translational research. Translational research endpoints will not be evaluated in this trial. If the primary hypothesis and performance metrics are satisfied, the subsequent phase III trial will incorporate translational research endpoints.

1.4 Study Rationale/Hypothesis

Standard therapy for stage I NSCLC has been R0 resection, consisting primarily of lobectomy with lymph node dissection/sampling (RODS), generating 3-5 year OS rates of 50-80%, local control rates of 70-90%, grade 3 complication rates of 10-30%, and hospital stays of 1-3 weeks. A significant number of patients are either medically inoperable or refuse surgical intervention. Historically, conventional fractionated 2DRT or 3DCRT (60-70 Gy over 5-7 weeks) has been reserved for medically inoperable patients with a 5-year cause-specific survival rate of ~30%, local control rate of 15-50%, grade 3 toxicity rate of 5%, radiation therapy cost of $20,000 to $30,000, and outpatient treatment duration of 6-7 weeks. With advancement of radiation technology, SBRT has become available at most of the large centers and generates local tumor control rates of 85% to 95% in both medically inoperable and operable patients [127] with relative rare adverse events, such as pneumonitis and rib fracture. The role of SBRT in patients who are operable candidates is being evaluated in a phase II clinical trial, RTOG 0618, which was initiated in 2008 and completed accrual as of March 1, 2010.

The central hypothesis of this study is that SBRT, although potentially yielding a lower local-regional tumor control rate will provide equivalent OS and significantly better QOL than RODS in patients with stage I NSCLC. The study population includes medically operable patients with PET/CT staged T1N0 (Stage IA) NSCLC. Eligible patients will be randomized to 2 arms. Patients enrolled to Arm 1 will be treated with surgical resection. Patients enrolled to Arm 2 will be treated with SBRT of 55 Gy in 5 fractions (BED 118 Gy) for both peripheral and central tumors. We selected this fractionation as it is also a safe regimen [280, 281]. Three-year OS, 3-year local progression-free survival, disease-specific survival, treatment cost, duration of hospital stay, and time to local progression will be compared between the 2 arms. By completing this trial, we hope to be able to provide necessary preliminary information to continue to a definitive trial to determine whether high-dose SBRT will generate outcomes comparable to those of surgical resection in patients with stage I NSCLC.

1.5 Study Significance

The outcome of this study will be clinically significant for several reasons: If SBRT is proven to be at least equivalent to RODS, patients with stage I NSCLC (approximately 20,000 new cases annually worldwide) would have a non-invasive treatment option that may offer significant advantages. With respect to advancing the SBRT approach:

1. This trial will provide important data regarding potential differences in local-regional tumor control and patterns of failure between SBRT and RODS. These endpoints are critical to establishing equivalence of the 2 approaches with respect to survival.
2. A key secondary objective of this trial is to qualitatively and quantitatively assess the logistical feasibility of joint clinical trial conduct between the RTOG and institutions in China. Parameters measuring feasibility include pre-registration requirements, patient accrual rate, eligibility rate, randomization conduct, baseline forms completion, follow-up forms completion/delinquency, and loss to follow-up rate. This study will serve to motivate the building and evaluation of logistics for international collaboration in the cooperative group setting, and serve to develop a critical means of expanding participation and conducting trials more rapidly, as well as delivering an advantageous therapy to populations of great need.
3. The banking of biological specimens will provide for future identification of molecular prognostic factors for response to these very different therapeutic modalities.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 The primary aim of this study is to determine whether SBRT provides local-regional tumor control that is not more than 15% lower than RODS. This difference is considered a threshold deficit at which overall survival (OS) will not be compromised.

2.2 Secondary Objectives

2.2.1 To qualitatively and quantitatively assess feasibility of this joint RTOG-China clinical trial. Parameters to be assessed include satisfaction of pre-registration requirements (e.g. surgical and RTQA credentialing), patient accrual rate, patient eligibility rate, randomization conduct baseline forms completion and timeliness, follow-up forms completion/delinquency, and loss to follow-up rate;

2.2.2 To compare overall survival and disease-free survival between study arms;

2.2.3 To estimate and compare time to local-regional failure, time to distant metastases, and patterns of failure between study arms;

2.2.4 To compare treatment toxicities using the Common Terminology Criteria for Adverse Events (CTCAE, v. 4) between study arms; specific comparisons will include adverse events at 1, 3, 12, 24, and 36 months post-therapy;

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (10/22/14)

3.1.1 Stage I NSCLC (AJCC, 7th ed.), T1N0M0; **note**: T1N0 disease must be confirmed by FDG-PET/CT (see Section 3.1.5).

Biopsy confirmation of diagnosis is strongly recommended but not required. If the biopsy is attempted and non-diagnostic, if the patient refuses biopsy, or if the risk of biopsy is considered too high, patients may be enrolled if the mass is suspicious for NSCLC based on 2 or more of the following criteria:

- Positive smoking history;
- Absence of benign calcifications within suspicious nodule;
- Activity on PET greater than normal tissue;
- Evidence of growth compared to previous imaging;
- Presence of spiculation.

The following primary cancer types are eligible: squamous cell carcinoma; adenocarcinoma; large cell carcinoma/ large cell neuroendocrine carcinoma; non-small cell carcinoma not otherwise specified.

3.1.2 Patients with hilar or mediastinal lymph nodes $\leq$ 1 cm and no abnormal hilar or mediastinal uptake on PET and CT will be considered N0. Mediastinal lymph node biopsy is required for patients with visible nodes: patients with > 1 cm hilar or mediastinal lymph nodes on CT or with nodes appearing as abnormal on PET (including suspicious but nondiagnostic uptake). Such patients will not be eligible unless directed biopsies of all abnormal lymph nodes are negative for cancer or these nodes demonstrate a lack of change during the prior 6 months and thus are considered to be non-malignant.

3.1.3 The patient must be considered a reasonable candidate for surgical resection using a lobectomy or pneumonectomy of the primary tumor within 6 weeks prior to registration, according to the following criteria based on the American College of Chest Physicians guidelines [165]:

- A qualified thoracic surgeon should make the determination that there would be a high likelihood of negative surgical margins;
- Baseline FEV1 >60% predicted, postoperative predicted FEV1 >40% predicted;
- Diffusion capacity of the lung for carbon monoxide (DLCO) >60% predicted, postoperative predicted DLCO > 40 % predicted;
- No baseline hypoxemia and/or hypercapnia;
- If the estimated postoperative FEV1 or DLCO <40% predicted indicates an increased risk for perioperative complications, including death, from a standard lung cancer resection (lobectomy or greater removal of lung tissue), then cardiopulmonary exercise testing to measure maximal oxygen consumption (VO2max) must be >60%;
- No severe pulmonary hypertension;
- No severe cerebral, acute or chronic cardiac, or peripheral vascular disease;

3.1.4 Pleural effusion, if present, must be deemed too small to tap under CT guidance and must not be evident on chest x-ray. Pleural effusion that appears on chest x-ray will be permitted only if there is no evidence of malignancy after invasive cytologic assessment.

3.1.5 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:

- History/physical examination, including documentation of weight within 6 weeks prior to registration;
- Evaluation by an experienced thoracic surgeon within 6 weeks prior to registration;
- FDG-PET/CT scan for staging and RT plan within 4 weeks prior to registration;
- CT scan (preferably with intravenous contrast, unless medically contraindicated) within 4 weeks prior to registration to include the entirety of both lungs, the mediastinum, liver, and adrenal glands; primary tumor dimension will be measured on CT scan.

3.1.6 Zubrod Performance Status 0-1 within 6 weeks prior to registration;

3.1.7 Age ≥ 18;

3.1.8 For women of childbearing potential, a serum or urine pregnancy test must be negative within 72 hours prior to registration;

3.1.9 Women of childbearing potential and male participants who are sexually active must practice adequate contraception during treatment if assigned to treatment with SBRT.

3.1.10 Patients must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Direct evidence of regional or distant metastases after PET and surgical staging studies, or synchronous primary malignancy or prior invasive malignancy in the past 3 years, with the following exceptions:

- carcinoma in situ;
- early stage skin cancer that has been definitively treated;
- when an invasive malignancy has been treated definitively and the patient has remained disease free for ≥ 3 years;

3.2.2 Primary tumors >3 cm;

3.2.3 Prior systemic chemotherapy or thoracic surgery involving lobectomy or pneumonectomy;

3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.5 Pure bronchioloalveolar carcinoma subtype of non-small cell lung cancer;

3.2.6 Active systemic, pulmonary, or pleural pericardial infection;

3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

4.1.1 EBUS is required within 4 weeks prior to treatment if there are suspicious nodes on the CT or PET/CT scan and/or if there was no prior mediastinoscopy. Patients who already have had mediastinoscopy, chamberlain procedure, or VATS are eligible for this trial if they meet the eligibility criteria.

5.0 REGISTRATION PROCEDURES

Note: This is a limited institution study.

5.1 Regulatory Pre-Registration Requirements (6/6/2013)

5.1.1 Prior to the recruitment of a patient for this study, investigators at participating institutions must obtain IRB/REC approval for this protocol, and submit IRB/REC approval and supporting documentation to the RTOG Headquarters (FAX 267-940-9409) or e-mail them to RTOG3502Regulatory@acr.org.

The following documents also are required:

- Site contract;
- RT Credentialing (see Section 5.2 for details)
- Surgeon credentialing (see Section 5.3 for details)
- FDA 1572 (Investigator's agreement to follow FDA regulations and comply with the protocol)
- Investigator's current CV
- Investigator's completion of the American College of Radiology's Conflict of Interest form. This document can be found on the RTOG website: http://www.rtog.org/Researchers/PoliciesManuals/ConflictofInterestPolicy.aspx
- Documentation of investigator's completion of Human Subject Protection Training (information about the National Institutes of Health (NCI) training can be accessed at http://grants.nih.gov/grants/policy/hs/training.htm; comparable training is acceptable);
- IRB/REC initial approval letter, annual continuing review approvals, and approvals of each amendment of the protocol;
- IRB/REC approved consent (English and native language versions*); *Note: Institutions must provide certification/verification of IRB/REB consent translation to RTOG Headquarters (described below);
- All Regulatory submissions must also include a completed IRB certification Form as a cover sheet, with the following information documented on the form:
  - Site NCI code;
  - Investigator's CTEP ID, if available;
  - IRB/REC registration number;
  - FWA number.

5.1.1.1 Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REC approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual REC approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.2 Pre-Registration Requirement: RT Credentialing (6-AUG-2018)

5.2.1 For participating institutions from China, a specific credentialing process will be arranged by a Medical Physics Co-Chair, Fang Fang Yin, PhD, or Ying Xiao, PhD, prior to registration of patients.

Since the participating Chinese institutions have not completed the RTOG membership application process, a special credentialing document has been created that combines requirements from the RTOG membership application, American College of Radiology (ACR) practice guidelines, and specific benchmark credentialing for special procedures, such as downloadable tests from the American Association of Physics in Medicine (AAPM) Task Group 119 (www.aapm.org). This credentialing document is available to participating sites on the RTOG web site, www.rtog.org, under RTOG Foundation Study 3502.

The credentialing process for this study is distinctively different from the standard RTOG procedure in that a comprehensive review similar to that of ACR accreditation is performed by the Medical Physics Co-Chairs or their designees at each participating institution. The institution is required to prepare the documents specified in the credentialing document (summarized in Section 5.2.5 below) and have them ready for an onsite visit. More than one visit and/or follow-up submission of documentation may be needed for the completion of the credentialing. A phantom study with the MD Anderson Dosimetry Lab (MDADL) must be successfully completed. Close interactions between the Medical Physics Co-Chairs and participating institutions are necessary for this pioneering trial.

A summary of the credentialing requirements is provided below in Table 5.2 and in Sections 5.2.2 to 5.2.5. It is mandatory for institutions to complete the credentialing document (on the RTOG web site under RTOG Foundation Study 3502) to confirm that the institution has fulfilled all requirements. Institutions must have the completed questionnaire and requested data on site for review by the visiting Medical Physics Co-Chair, Fang Fang Yin, PhD, or Ying Xiao, PhD, who will initial each page, sign the document, and deliver it to RTOG Headquarters for filing/storage.

Table 5.2

Summary of Radiation Therapy Quality Assurance Credentialing Requirements		
Components	**Document & Data for Onsite Visit**	**Document & Data Submission**
Facility Information	√	
Delivery System(s) and QA	√	
Planning System(s) and QA	√	
Policy and Procedure(s)	√	
Treatment & Other Records	√	
IGRT (including 4D imaging)	√	
Motion Management	√	
IMRT	√	
3D-CRT	√	
Dry-Run Case		√
Phantom irradiation		√

5.2.2 The delivery system for participating institutions includes a linear accelerator which can produce 6MV photon beams. An in-room IGRT system should be available using 3D (kV or MV Cone-beam CT or CT on-rail system) images, for localization and verification purposes. CyberKnife and Tomotherapy units, or equivalent, also are allowed if proper motion management is implemented and credentialed by Medical Physics Co-Chair. The quality assurance program should be implemented following TG 142 or equivalent, including the supplemental information in TG 142, as judged by visiting Medical Physics Co-chair.

5.2.3 The treatment planning system should have a 3D inhomogeneity dose calculation method. Convolution/superposition algorithms are required for this protocol. Monte Carlo calculation algorithms are also allowed. Acceptance testing and commissioning reports/documents should be available for the visiting Medical Physics Co-chair. Proper QA for the planning system should be done as outlined in Section 5.2.5.

5.2.4 Dry-Run Case

Participating institutions in China are required to download a dry-run case. Directions are accessible on the RTOG web site:
http://www.rtog.org/ClinicalTrials/RTOGFoundationStudies/RTOGFoundationStudy3502.aspx

Sites are to submit the completed case to the RTOG RTQA Center for review by the Principal Investigators. The dry-run case is a mock case provided by RTOG and should be planned exactly following the guidelines of the protocol.

5.2.5 Evaluation Criteria

A summary of the evaluation criteria and required documentation from the credentialing document (on the RTOG web site under RTOG Foundation Study 3502) is included below. The participating site needs to prepare these documents and have them ready for onsite review.

- The most recent calibration reports (less than 2 years) for primary standard ion chamber and electrometer should be submitted to visiting Medical Physics Co-Chair to review. TLDs or equivalent dosimeters comparison reports for the last 3 years (if the machine is less than 3 years old, the commissioning report and the latest calibration report will serve the purpose) for each energy in all linear accelerators used for SBRT protocol should be available for the visiting medical physics co-chair. A *Pass should be indicated* (or onsite

measurements ≤ *5%).*

- *Criteria for Delivery System(s) QA*
  Follow the AAPM *TG 142 Standards for SBRT/IMRT.*
- Criteria for *Treatment Planning QA*
  Each site should present all treatment planning system commissioning/acceptance/upgrade report(s) for superposition/convolution algorithm or better as described in TG 53.

  All QA recommendations and acceptance criteria in TG 53 (or equivalent as judged by the visiting Medical Physics Co-Chair) should be used as the standard, including CT Houndsfield number to electronic density table. The site should also have error log books.
- *Documents for Policy and Procedure/Treatment Records*
  Each site should have a Policy and Procedures manual, treatment record and/or chart (either in electronic or paper version), and consent form, equivalent to those developed by the American College of Radiology (ACR).
- *Documents for IMRT commissioning*
  Each site should present acceptance testing and commissioning report as described by TG 119 or equivalent. The acceptance testing criteria for IMRT dose delivery equipment and QA protocol should follow standards as described in TG 142 or equivalent. When tracking or gating strategies are used for motion management, a moving phantom must be used for the benchmark cases described by TG 119.
- *Documents for 4D and IGRT*
  A respiratory management procedure/sample chart should be developed to reflect that breathing motion is appropriately managed or appropriately accounted for target motion larger than 15 mm in one direction and presented to the visiting Medical Physics Co-Chair. The simulation CT system should have a QA program following AAPM TG-66 or equivalent. 4D imaging protocols and/or 3-phase 3D CT plus fluoroscopic imaging protocols should be available for inspection. The acceptable deviation from the review also should be less than 5 mm.

5.2.6 Digital RT Data Submission to RTOG Using TRIAD (6-AUG-2018)
TRIAD is the image exchange application used by the RTOG Foundation. All required digital RT planning data will be uploaded using this application. See the study-specific webpage on the RTOG website at **www.rtog.org** for details regarding TRIAD account and installation.

5.3 Pre-Registration Requirement: Surgeon Credentialing

Only teaching hospitals performing over 100 lung cancer surgeries each year are eligible to participate in this study.

Participating surgeons must complete and sign the credentialing form, Appendix V, prior to the institution entering any patients onto this study. The institution will e-mail the completed form to Andrew Chang, MD, Thoracic Surgery Co-Chair, at andrwchg@umich.edu for review and approval. Dr. Chang will then e-mail the reviewed form to RTOG. Institutions should allow adequate processing time (7-10 days) before registering the first patient.

5.4 Registration

5.4.1 Summary of Procedures

This study incorporates a two-step registration process.

All patients can be registered after completing the Eligibility Checklist, STEP 1 via online registration; see the text below for online registration instructions.

All patients must be staged by FDG-PET/CT to confirm T1N0 disease. At this point, patients with confirmed T1N0 disease may be randomized.

Note: Sites must complete the Eligibility Checklist, STEP 2 via online registration for ALL patients, even for patients found not to have T1N0 disease, to indicate whether or not patients are able to continue protocol treatment and if not, to specify the reason.

Patients found not to have T1N0 disease on PET/CT will be treated off study per standard of care and will not be followed.

5.4.2 Online Registration

Patients can be registered only after eligibility criteria are met.

Special assistance for institutions from China can be obtained from the following web site: http://www.rtog.org/ClinicalTrials/RTOGFoundationStudies/RTOGFoundationStudy3502.aspx

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form (http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219) and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

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

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

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

Institutions can contact RTOG web support for assistance with web registration: websupport@acr.org.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., confirmation of registration and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Note: All participating institutions will be credentialed for a dry-run case, phantom irradiation, IGRT, and 3DCRT (or IMRT, if used) as described in Section 5.1 prior to registering patients to the study. Centers not credentialed for IMRT are not permitted to enroll and treat patients with this approach.

Protocol treatment must begin within 14 calendar days after randomization.

The protocol procedures associated with SBRT will respect updated guidelines set by ACR/ASTRO [182].

6.1 Simulation/Immobilization

6.1.1 Positioning/Immobilization

The patient will be scanned in the supine position with both arms raised above the head to allow beams from multiple directions. Securing a comfortable position is critical as it allows accurate reproducibility of the target localization from treatment to treatment. Uncomfortable positions should be avoided as they will most likely cause uncontrolled movement during scanning or treatment. A variety of immobilization systems may be used, including vac-bag, alpha cradle, and stereotactic frames. While frames are intended to index the patient to a stereotactic coordinate, their use alone (i.e. without image guided positioning) is insufficient for this trial.

Immobilization should be sufficient to maintain the intra-fraction patient position (tumor and adjacent skeletal) to within 3 mm. A post-treatment verification image should be taken to document the intra-fraction error for set up. The comparison between these images with reference images should be quantitatively analyzed and must not be > 5 mm. The institution should store these datasets on site for possible review/audit by the Principal Investigators.

6.1.2 CT Simulation and Motion Management

Target motion will be managed appropriately to ensure target localization and reproducibility. Tumor motion will be assessed by using fluoroscopy, 3-phase CT scanning or optimally 4D-CT scanning of 10 breathing phases. For CT scanning, intravenous contrast is not mandatory. If IV contrast is used, CT images without IV contrast should also be acquired and used for dose calculations. The slice spacing between reconstructed CT images should be ≤3 mm encompassing the entire lung volume.

An internal target volume (ITV) approach can be used up to a limit of 1.5 cm movement in one direction.

When the tumor motion is more than 1.5 cm in any one direction, as demonstrated using one of the techniques described above, special measures should be applied to reduce internal organ motion. Acceptable maneuvers for motion control include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking using fiducial markers, and active breath-holding techniques. Regardless of the tumor motion management method applied, image guidance for target localization is required for initial positioning at the start of each treatment fraction.

6.1.3 Localization/Verification

Localization images or Cone Beam CT (CBCT) should be obtained at each treatment on the treatment unit. ITV from 3D CBCT should be compared to the ITV from the planning CT. 4DCBCT also can be used for target verification, if available, but it is not required. These images should be taken immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. Verification images (3D) should be taken if more than 3 mm shifts are performed before treatment, as indicated by image guidance and after treatment to document the patient positioning accuracy.

6.1.4 SBRT Dose Fractionations

SBRT is given every other day. A total dose of 55 Gy will be given in 5 fractions within 10-15 days with an inter fraction interval of 2-3 days. The dose for all patients will be prescribed to the isodose line that covers 95% of the PTV. Treatment duration up to 20 days is permitted to allow for circumstances such as holidays or unanticipated medical conditions. Tissue heterogeneity corrections must be applied for dose calculation using convolution/superposition calculation techniques or a Monte Carlo algorithm. Planes should be normalized to provide 95% coverage of the planning target volume with the prescription dose. Dose constraints are provided in Tables 6a and 6b.

6.1.5 SBRT Target Delineation

The gross tumor volume (GTV) will be delineated by an appropriately trained physician using CT pulmonary windows for tumor surrounded by lung parenchyma. Soft tissue windows should be used for tumors adjacent to chest wall, or centrally located IV contrast may be used to avoid inclusion of adjacent vessels or chest wall structures within the GTV. The correctness of the GTV delineation should be checked in axial, sagittal and coronal views. **This target will not be enlarged whatsoever for prophylactic treatment (including no "margin" for presumed**

microscopic extension); rather, include only an abnormal CT signal consistent with gross tumor (i.e. the GTV and the clinical target volume [CTV] are identical). An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (craniocaudal) will be added to the GTV to constitute the PTV.

As an alternative, sites equipped with 4D CT scanning equipment may generate an Internal Target Volume (ITV) using the inspiration and expiration images or maximum intensity projections (MIP) as appropriate. Sites should be aware that the MIP reconstruction may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g. the diaphragm, great vessels). The 4D scan acquired for planning, however, should be obtained after initial assessment of tumor motion confirming that the tumor motion will be no greater than 0.5 cm in the axial plane and 1.0 cm in the craniocaudal plane. If 4D CT is not available, the composite GTV should be based on either the CT data covering the whole tumor trajectory taken over multiple breathing cycles or the summation of GTVs drawn on multiple rapid planning scans. Regardless of the method of ITV generation, if a PET scan is also acquired, the PET target should be compared to the ITV to ensure sufficient target size for coverage of the moving tumor. In general, an ITV should NOT be defined by the merger of a deep inspiration CT scan and a deep expiration CT scan, as such would typically overestimate tumor motion. The ITV, then, is generated using a CT dataset where motion control maneuvers are already successfully employed. This ITV can be expanded by the institution's geometric set-up uncertainty (e.g. 4-5 mm) to generate the PTV.

6.2 Delineating Organs at Risk and Dosimetric Limits (6-AUG-2018)

Please see the atlas on the RTOG web site, www.rtog.org, on the page for RTOG 1106. All required structures must be named according to naming convention provided on RTOG website. See list available at http://www.rtog.org/ClinicalTrials/RTOGFoundationStudies/RTOGFoundationStudy3502.aspx

6.2.1 Lung

Lung contours should be limited to active alveolar regions without inclusion of fluid and atelectasis. Automated contouring tools may be used but appropriate thresholds, specific to each CT scan, should be chosen. Editing of autotracked contours is always required. The proximal bronchial tree should be excluded, and small sized vessels (less than 1cm, or vessels beyond the hilar region) should be included. The right and left lungs should be contoured as separate structures, and the DVH of whole lung should be generated by inclusion of both lungs. Normally the lung dose limits are based on the DVHs of both lungs with exclusion of composite GTV. Special attention should be paid that only the GTV overlapping normal lungs is subtracted (i.e., only the component of the GTV existing within the lung); the GTVs outside of lung such as the mediastinal nodal GTVs should not be subtracted. All inflated and collapsed lung should be contoured; trachea/ bronchus as defined below should not be included in this structure. When there is collapsed lung, the use of IV contrast and/or PET scanning may be very helpful at distinguishing collapsed lung from tumor extension.

6.2.2 Proximal Tracheal Bronchial Tree

The proximal bronchial tree should be contoured using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. The proximal tracheal bronchial tree should be contoured as one structure, should include the most inferior 2 cm of distal trachea and the proximal airways on both sides. The following airways should be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi should end immediately at the site of a segmental bifurcation, as recommended by RTOG 0618.

6.2.3 Esophagus

The esophagus should be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at the level of cricoid and continuing on every CT slice to the gastroesophageal junction.

6.2.4 Spinal Cord

For specifically treating lung tumors, the spinal cord should be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at the same cranial level as esophagus to L2, when the cord ends. RTOG studies recommend at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV, as such definition may go beyond the true cord ends for inferior tumors.

6.2.5 Ribs and Chest Wall

Delineation of ribs and chest wall will be contoured by using corrected lung contours with a 2 cm expansion at lateral, anterior and posterior directions. Intercostal muscles are to be included, while other muscles and skin are excluded. This is a result of combined consideration of previous methods of including ribs alone or comprehensive inclusion of the chest wall [185, 186]. One can also confine the rib contours to the relevant tissue that exists within a 3 cm range from the PTV.

6.2.6 Brachial Plexus

The brachial plexus originates from the spinal nerves exiting the spinal canal through the neural foramina from the C4/5 (C5 nerve roots) to the T1/2 (T1 nerve roots) level. Using high quality CT scanning with IV contrast, it is possible to identify the actual roots and trunks of the brachial plexus directly with no need of a surrogate. We recommend outlining this structure starting from C5 root (within the C4/5 neural foramen) and ending at the subclavian neurovascular bundle without including the vessels. To contour the brachial plexus correctly, it is critical to first identify the anterior and middle scalene muscles, the subclavian and axillary arteries and veins, and relevant cervical and thoracic vertebrae on axial CT.

6.2.7 Heart/Pericardium

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at one slice below the level of the inferior aspect of the pulmonary artery trunk crossing the midline and extend inferiorly to the apex of the heart.

6.2.8 Skin OAR

The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

6.2.9 Great Vessels

The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

6.2.10 Structures are to be labeled exactly according to the "Standard DICOM Name" in the left column of the table below. Additional structures will be deleted and if any missing structures are noted, the case will be requested for resubmission.

STANDARD DICOM NAME	Description
GTV	Gross Tumor Volume
ITV	Internal Target Volume
PTV	Planning Target Volume
PTV_20	PTV + 2cm
Lung_R	Right Lung
Lung_L	Left Lung
Lungs	(Right + Left Lung) minus GTV
BronchialTree	Proximal Bronchial Tree
BroncTree_20	Proximal Bronchial Tree + 2cm
Esophagus	Esophagus
SpinalCord	Spinal Cord
Rib	Ribs & Chest Wall
BrachialPlexus	Brachial Plexus
GreatVessels	Great Vessels
Heart	Heart & Pericardium
SkinOAR	Skin (outer .5cm rind)

SkinOAR-PTV	Skin (outer 0.5 cm rind) minus PTV
SkinOAR-PTV_20	Skin (outer 0.5 cm rind) minus PTV_20
External	Entire Body/External Contour
External-PTV	External Contour minus PTV
External-PTV_20	External Contour minus PTV_20
Trachea	Trachea

6.3 Radiation Planning/Dose Conformality Requirements (9/12/13)

6.3.1 General Guidelines

The dose to the target should be maximized while the dose to the adjacent OARs minimized. Both co-planar and non-coplanar beam arrangements are allowed. All dose calculations and Monitor Unit calculations should include tissue heterogeneity corrections as available in the planning system based on the CT data. A superposition/convolution algorithm or better is required. Photons of 6 MV to 10 MV will be allowed to optimize the dose plan. 10 MV photons only will be used when there is adequate soft tissue before the tumor at the beam entrance direction.

Dose calculations should be performed on the 3D CT scan reconstruction generated without breathing phase binning (i.e. an average scan or untagged scan reconstruction).

A hot spot is allowed within the ITV. The prescription isodose line shouldn't be below 60% as specified in Section 6.3.4.

Successful treatment planning will require accomplishment of all of the following criteria:

6.3.2 Normalization

An initial treatment plan used to select the isodose line for PTV coverage should be normalized such that 100% corresponds to the center of mass of the PTV. This point will typically also correspond (but is not required to correspond) to the isocenter of the treatment beams.

6.3.3 Prescription Isodose Surface Coverage

The dose prescription will be chosen such that 95% of the target volume (PTV) receives the prescribed dose of 55 Gy, and 99% of the target volume (PTV) receives a dose that does not fall below a minimum dose that is defined as 90% of this dose, 99% of ITV and 100% of composite GTV should receive the prescribed dose.

6.3.4 Target Dose Heterogeneity

The prescription isodose surface selected using the initial plan must be ≥ 70%. It is preferred to keep the max dose to a 30% maximum increase of the dose at the center of mass (COM) of the PTV and ≤ 90% of the dose at the center of mass of the PTV. The COM_{PTV} corresponds to the normalization point (100%) of the plan.

6.3.5 Hot Spot Consideration

a) *Location:* Any dose > 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside the PTV.

b) *Volume:* Conformality of PTV coverage will be judged to meet criteria in Sections 6.3.2 to 6.3.5, with ratio of the volume of the prescription dose to the volume of the PTV is ideally < 1.2 (see table below). These criteria will not be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3.5 cm results in the inability to meet a conformality ratio of 1.2.

6.3.6 Conformality and Dose Fall Off Gradient

The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:

a) *Location*: The maximum total dose over all treatment in Gy to any point 2 cm or greater away from the PTV in any direction must be no greater than D2cm where D2cm is given by the table below.

b) *Volume*: The ratio of the volume of the 50% of prescription dose in this trial as the volume of 27.5 Gy to the volume of the PTV must be no greater than R50% given by the table below, modified from RTOG 0618.

Table 6a: Dosimetric Guidelines for SBRT Plan Evaluation

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (Gy)		Percent of Lung Receiving 20 Gy Total or More, V_{20} (%)	
	Deviation		Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0	<10	<15

Note 1: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.
Note 2: Protocol deviations greater than listed here as “minor” (Variation Acceptable) will be classified as “major” (Deviation Unacceptable) for protocol compliance.

6.3.7 Dose Limits of Organs at Risk

This trial will follow the dose constraints of National Comprehensive Cancer Network (NCCN) 2010 guidelines for treatment of non-small cell lung cancer, under 5 fractions. These are simplified limits found in recent RTOG trials

Table 6b: Dose Volume Constraints for Organs at Risk

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)**	**Avoidance Endpoint**
Spinal Cord	<0.25 cc <0.5 cc	22.5 Gy (4.5 Gy/fx) 13.5 Gy (2.7 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Ipsilateral Brachial Plexus	<3 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	neuropathy
Skin	<10 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration
Parallel Tissue	**Critical Volume**	**Critical Volume Dose Max (Gy)**		**Avoidance Endpoint**
Lung (Right & Left)	1500 cc	12.5 Gy (2.5 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy (2.7 Gy/fx)		Pneumonitis

Serial Tissue*	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)**	**Avoidance Endpoint**
Esophagus, non-adjacent wall	<5 cc	27.5 Gy (5.5 Gy/fx)	105% of PTV prescription	stenosis/fistula
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	105% of PTV prescription	pericarditis
Great vessels, non-adjacent wall	<10 cc	47 Gy (9.4 Gy/fx)	105% of PTV prescription	aneurysm

Proximal tracheal bronchial tree, non-adjacent wall	<4 cc	18 Gy (3.6 Gy/fx)	105% of PTV prescription	stenosis/fistula

Note: The volume maximum column shows suggested limits for these structures for planning purposes. Exceeding these limits is not a protocol violation.

6.4 3D-CRT, IMRT, IGRT Treatment Delivery Verifications

6.4.1 3D-CRT/Intensity Modulated Radiation Therapy (IMRT)

3D-CRT should be the first choice of treatment technique. However, IMRT is allowed if necessary as long as the participating institution has passed the dry run case using IMRT planning.

3D-CRT fields should not be smaller than 3.5 cm except for the use of IMRT where a 2x2 mm limit is used. If multiple segments per beam are given, this minimum requirement holds for all segments separately.

6.4.2 Image Guided Radiation Therapy (IGRT) for Treatment Delivery Verifications

Image guidance should be used to guide precise treatment delivery. ACR/ASTRO guidelines for IGRT should be followed [187]. Pre-registration IGRT credentialing requirements are specified in the credentialing document (on the RTOG web site under RTOG Foundation Study 3502). After any set-up correction is performed, the appropriateness of the correction should be verified by imaging. This can be performed directly after the set-up correction is made, but this may also be performed after the treatment itself. The procedure is described in Section 6.1.3. There are small enough dose contributions with only one imaging study done per treatment session, and this is not expected to have any clinical relevance to the patient. However, the imaging dose to the patient may become significant if repeated studies are done. Caution is advised with excessive localization imaging.

6.5 SBRT QA Procedures (6-AUG-2018)

6.5.1 Submission of Treatment Plan

In order to be able to document the actual delivered dose on an individual basis, the treatment plans, images, and delineated structures used for treatment planning will be submitted to the RTOG via a TRIAD (see Section 12.2) (exported using the Dicom RT protocol) as well as centrally stored securely on site. This will also allow a retrospective derivation of dose-effect relations. See Section 12.0 for data submission details.

6.6 R.T. Quality Assurance Reviews

The Principal Investigators, Jinming Yu, MD, PhD, and Feng-Ming (Spring) Kong, MD, PhD, and Physics Co-Chairs Ying Xiao, PhD, and Fang-Fang Yin, PhD will oversee quality assurance reviews. These reviews will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by RTOG RTQA.

6.7 Radiation Therapy Adverse Events

Note: All adverse events will be scored according to CTCAE, v. 4, which can be accessed on the RTOG web site: http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx (scroll to the bottom of the page).

6.7.1 Potential Adverse Events Associated with SBRT

Potential adverse events associated with SBRT include pneumonitis, fibrosis, atelectasis, bronchial obstruction, bronchial stricture, bronchopleural fistula, chest wall pain, fracture, changes in pulmonary function tests (e.g. reductions in FEV1, DLCO or FVC) pulmonary fibrosis, burn, dermatitis radiation, alopecia, cough (may be productive), dyspnea, fever, fatigue, pericarditis, pericardial effusion, chest pain – cardiac, palpitations, heart failure, myocardial infarction, paresthesias, generalized muscle weakness, esophagitis, dysphagia, aortic or arterial injury, hemoptysis, pain of skin.

Radiation pneumonitis is a subacute inflammation of the end bronchioles and alveoli, which can occur weeks to months after completion of treatment. For radiation pneumonitis, it is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray

should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

It is unlikely that symptomatic pneumonitis will occur during the weeks radiation is actually delivered to the patients. However, if a patient experiences pneumonitis before completing therapy, therapy will be put on hold until symptoms resolve. At that point, a clinical decision whether to finish therapy will be made in conjunction with the treating physician in conjunction with the study Principal Investigator. When symptomatic pneumonitis resolves to grade 0, CTCAE, v. 4 , the treating physician will contact a Co-Principal Investigator (Dr. Yu or Dr. Kong) for a decision to continue or terminate protocol therapy.

6.7.2 Bronchial Injury

The vast majority of patients have radiographic changes during follow-up scan, such as experienced some degree of atelectasis (collapse) of lung downstream from the area of treatment. This was felt to be related to bronchial injury of bronchi or bronchioles within or near the treated tumor. By unknown mechanisms over a period of 3-6 months, pulmonary parenchyma distal to the site of bronchial injury results in this focal lung collapse. The majority of patients are asymptomatic. In others, the injury apparently correlated to a drop in diffusing capacity and arterial oxygen tension on pulmonary function tests. This process of collapse may not be reversible, is mostly likely associated with large fraction sizes, as reported from Indiana University. This is the justification of using smaller fraction sizes in this study.

Bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. The consequences of bronchial toxicity, e.g. cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), will be graded and reported on adverse event forms based on CTCAE, 4.

Bronchial injury also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking. A PET scan can be very useful to minimize and avoid such mischaracterization. As indicated, endoscopic exam can be applied for further assessment.

6.7.3 Changes in Pulmonary Function Tests

Patients enrolled to this study should have pulmonary function tests (PFTs), including Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), and Diffusing Capacity for Carbon Monoxide (DLCO). The CTCAE, v. 4 includes specified criteria for grading adverse events related to PFT parameters. The grading criteria for PFT changes use the "percent predicted" values from 0-100% which are recorded on the patient's PFT report. A percent predicted of 90% conveys that the patient is able to perform the PFT test to a result that is 90% of what would be expected for the normal general population of the same height, age, and sex. The CTCAE, v. 4 grading criteria for PFTs assumes that all patients have normal baseline pulmonary function, which is often not true for lung cancer patients. In this study we will use RTOG protocol specific toxicity classification for PFTs that adjusts for baseline abnormalities. Changes that occur after therapy will be referenced to the baseline for a given patient, which will be abnormal for most patients. This scale defines a proportional decline from the baseline. Grade 1 toxicity will be a decline from baseline to a level 0.90 times the baseline, grade 2 will be a decline to a level 0.75 x baseline, grade 3 will be a decline to a level 0.5 of baseline, grade 4 will be a decline to a level 0.25 x baseline, and grade 5 will be death. This scheme is depicted in the table below.

As an example, a patient who enters the study with a percent predicted DLCO of 55% who experiences a post treatment decline to a percent predicted DLCO of 40% would have a grade 4 event in the original CTCAE, v. 4 criteria; however, under the modified PFT toxicity classification for patients with abnormal baseline, his decline would constitute a decrease to 0.72 of the baseline value which is between 0.75 and 0.5 or a grade 2 event.

RTOG Pulmonary Function Test Toxicity Scale					
	Grade				
Adverse Event	1	2	3	4	5
FEV-1 Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death
FVC Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death
DLCO Decline	0.90-0.75 times the patient's baseline value	<0.75-0.50 times the patient's baseline value	<0.50-0.25 times the patient's baseline value	<0.25 times the patient's baseline value	Death

6.7.4 Radiation-Induced Lung Toxicity (RILT)

RILT includes pneumonitis and fibrosis. Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Radiation fibrosis is a late (months to years) complication due to fibroblast proliferation and scar formation in the lung parenchyma. It can be difficult to distinguish fibrosis from pneumonitis on CT scans, though clinically fibrosis often present with shortness of breath from pulmonary function reduction without significant cough, fever or other signs of inflammation. Table 6c below described the diagnosis and grading system of pneumonitis and fibrosis.

Table 6c: Diagnosis and Grading System for Radiation Pneumonitis and Clinical Fibrosis

	Radiation Pneumonitis	**Clinical Fibrosis**
Grade 1	Minimal or mild symptoms of dry cough and/or dyspnea on exertion, without evidence of tumor progression or other etiology, with radiographic evidence of acute pneumonitis	Radiographic evidence of radiation fibrosis without or with minimal dyspnea
Grade 2	Persistent dry cough requiring narcotic antitussive agents or steroid, and/or dyspnea with minimal effort but not at rest, without evidence of tumor progression or other etiology, with radiographic evidence of acute pneumonitis, and requiring steroid for treatment	Radiographic evidence of radiation fibrosis causing dyspnea with minimal effort but not at rest, not interfering with activities of daily living
Grade 3	Severe cough, unresponsive to narcotic antitussive agent and /or dyspnea at rest, with radiographic evidence of acute pneumonitis, and requiring oxygen (intermittent or continuous) for treatment	Radiographic evidence of radiation fibrosis causing dyspnea at rest, interfering with activities of daily living, and home oxygen indicated

Grade 4	Radiation pneumonitis causes respiratory insufficiency, requiring assisted ventilation	Radiation fibrosis causes respiratory insufficiency, requiring assisted ventilation
Grade 5	Radiation pneumonitis directly contributes to the cause of the death	Radiation fibrosis directly contributes to the cause of the death

6.7.5 Chest Wall Pain and/or Rib Fracture

Chest wall pain presents either as a result of intercostal neuropathy, inflammation, or rib fracture (focal radiation induced osteoporosis can result in both occult and obvious rib fractures generally propagated by severe coughing/sneezing episodes or chest wall trauma). The pain typically occurs several months after treatment and may last several more months. The chest pain will be scored per CTCAE, v. 4.

6.7.6 Radiation-Induced Toxicity of Heart and Esophagus

Radiation-induced toxicity of heart and esophagus will be scored per CTCAE, v. 4.

6.8 Radiation Therapy Adverse Event Reporting

All AE reporting on the study case report forms (CRFs) should follow grading criteria instructions on the specific CRF. Note: All adverse events will be scored according to CTCAE, v. 4, which can be accessed on the RTOG web site: http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx (scroll to the bottom of the page).

6.8.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1).

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

6.8.2 Serious Adverse Events (SAEs)

Definition of an SAE: Any serious adverse experience occurring during any part of protocol treatment and 30 days after whether or not related to the study drug that results in any of the following outcomes:

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section.

6.9 Serious Adverse Event (SAE) Reporting Requirements

It is the responsibility of the investigator to document all adverse events which occur during the study.

In addition to standard practice of recording AEs and SAEs on the case report form, this study will utilize an RTOG SAE Report Form for reporting of SAEs. The SAE Report Form, SAE Reporting Guidelines, and SAE Report Form Instructions are available on the RTOG web site, www.RTOG.org.

6.9.1 Reporting SAEs

Any SAE that occurs during any part of protocol treatment and 30 days after whether or not related to the study treatment must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions also must be reported.

The SAE report should comprise a full written summary, detailing relevant aspects of the SAEs in question. The SAE summary also must include the investigator's assessment of expectedness and relatedness to specific protocol treatment (e.g. radiation or surgery). When applicable, information from relevant hospital case records and autopsy reports should be included. Initial and follow-up information, when it becomes available, should be faxed to the RTOG SAE Fax Line 215-940-8918 or e-mailed to RTOG3502AE@acr.org. Each participating site must report the SAE to their regulatory authority. RTOG will report the SAE to the FDA.

SAEs brought to the attention of the investigator at any time after cessation of treatment and considered by the investigator to be related or possibly related to treatment also must be reported.

All SAEs must be reported to RTOG by facsimile to the RTOG SAE Fax Line 215-940-8918 or e-mailed to RTOG3502AE@acr.org within 24 hours. RTOG will complete a preliminary review of the SAE details and may contact the site with suggested revisions.

6.9.2 Assessment of Causality and Expectedness

Every effort should be made by the investigator to explain each SAE and assess its expectedness and relationship, if any, to study treatment. Causality should be assessed using the following categories: no (not related), or yes (reasonable possibility).

The investigator may change his/her opinion of expectedness and/or causality in light of follow-up information, by amending the SAE Report Form.

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY (10/22/14)

8.1 Surgical Resection Guidelines

8.1.1 Resection Procedures

Anatomic resection, i.e.lobectomy, bilobectomy, or pneumonectomy, will be performed at the discretion of the responsible thoracic surgeon. The final goal of surgery is complete resection, i.e., removal of the primary tumor with at least a 2 cm margin together with mediastinal and hilar nodal dissection or systematic mediastinal and hilar nodal sampling.

A radical resection is defined as a **complete resection** if all of the following apply:

- Free resection margins proven microscopically: resection margins should be considered to be the bronchial, venous and arterial stumps, peribronchial soft tissue, any peripheral margin near the tumor or any additionally resected tissue;
- There should be no extracapsular extension of tumor in lymph nodes removed separately or those at the margin of the main lung specimen;
- The highest mediastinal lymph node that has been removed must be negative.

The resection is considered an **incomplete resection** if any of the following apply:

- Tumor involvement of resection margins;
- Extracapsular extension of tumor in lymph nodes removed separately, or those at the margin of the main lung specimen;
- Lymph nodes known to be positive but not removed (this would be an R2 resection if recognized by the surgeon);
- Positive cytology of pleural or pericardial effusions.

The lung resection is considered an **uncertain resection** if the resection margins are proved to be free of disease microscopically, but one of the following applies:

- The intraoperative lymph node evaluation has been less rigorous than systematic nodal dissection or lobe-specific systematic nodal dissection as described below;
- The highest mediastinal lymph node removed is positive;
- The bronchial margin shows carcinoma in situ;
- Pleural lavage cytology is positive.

8.1.2 Intra-Operative Nodal Staging

According to the guidelines of the American and European Societies of Thoracic Surgeons, a systematic nodal dissection is recommended in all cases [167]. All the nodal stations are excised and put in different vials with separate labeling. The highest removed mediastinal node should be identified. After pathological examination of the lymphatic tissue specimens, the number of involved lymph nodes and nodal stations, and the status of the nodal capsule should be documented.

Systematic nodal sampling with a lobe-specific systematic nodal approach will only be acceptable for a peripheral squamous T1 tumor. A lobe-specific systematic nodal dissection implies dissection and histological examination of intrapulmonary (lobar-level 11, interlobar-level 12 and segmental-level 13-14) and hilar nodes (level-10) and, at least, three of the following mediastinal nodal stations depending on the lobar location of the primary tumor.

- The right upper and middle lobes: the subcarinal (level-7) and right superior/inferior pretracheal nodes (level-2 and -4)
- The right lower lobe: the subcarinal (level-7) and right inferior pretracheal nodes (level- -4) and either the paraesophageal (level-8) or pulmonary ligament (level-9) nodes.
- The left upper lobe: subcarinal (level-7), subaortic (level-5)/paraaortic (level-6), left inferior pretrachial (level-4) and anterior mediastinal nodes (level-3a).
- The left lower lobe, subcarinal, left inferior pretrachial (level-4), paraesophageal (level-8) and pulmonary ligament nodes (level-9).

8.1.3 Mediastinal Nodal Sampling

Mediastinal nodal sampling is allowed.[168]. When sampling is elected, hilar and 3 high risk nodal regions should be sampled based on the location of the primary tumor:

- The right upper and middle lobes: the subcarinal (level-7) and right superior/inferior pretracheal Nodes (level-2 and -4);
- The right lower lobe: the subcarinal (level-7) and right inferior pretracheal nodes (level- -4) and either the paraesophageal (level-8) or pulmonary ligament (level-9) nodes;
- The left upper lobe: subcarinal (level-7),subaortic (level-5)/paraaortic (level-6), left inferior pretrachial (level-4) and anterior mediastinal nodes (level-3a);
- The left lower lobe, subcarinal, left inferior pretrachial (level-4), paraesophageal (level-8) and pulmonary ligament nodes (level-9).

Both nodal dissection and sampling specimens should include, at least, 6 nodes, 3 removed from intrapulmonary and/or hilar stations and 3 removed from mediastinal stations, one of which must be the subcarinal station. Numbering and /or nomenclature outlined in the regional nodal stations / lymph node map definitions should follow nodal zones defined by IASLC/AJCC [169; 270] in Appendix VI.

8.1.4 Pathology Assessment Guidelines

The surgeon needs to report the time of excision out of the body on the Surgery/Pathology Study Form.

Primary tumor tissue and normal lung tissue will be submitted to trial Tissue Bank within 14 days after surgery for those patients who have consented to banking their tissues (Appendix I) .

The removed lymph nodes undergo histopathological evaluation as follows [167]:

1. As a first step, all resected intrapulmonary, hilar, and mediastinal nodes should be examined macroscopically. In the presence of gross tumor, one hematoxylin-eosin (HE) stained section should be performed at the most macroscopically suspicious site to demonstrate the metastasis and its possible extracapsular extension.

2. If the macroscopic evaluation does not show any suspicion of metastasis, a single section of a node should be avoided. The probability to detect a metastasis on center section is related to the size of the lymph node, the size of the lesion, and the location of the tumor within the node. To avoid this problem, it is recommended to perform several sections of the nodes, 2-mm slices in the longitudinal plane and to examine each block separately. Thin sections of 2 mm may increase the workload of the pathologist but increase the detection rate of metastases. Small nodes can be sliced and embedded in one block if possible.
3. There are different methods to detect additional metastatic deposits in lymph nodes like serial sectioning or immunohistochemistry (IHC). IHC using a cocktail of cytokeratins such as the anti-epithelial antibody mAb Ber-Ep4, AE1/AE3 is a sensitive and specific method for detecting isolated tumor cells or clusters of cells. Three levels of section are enough for this analysis.

8.1.5 Treatment for Unexpected N1 and N2 disease

If a patient has unexpected nodal positive disease, his/her further care should be discussed by a multidisciplinary team. Based on the results of phase III randomized trials and recent meta-analyses, cisplatin-based adjuvant chemotherapy improves survival in patients with stage II or III NSCLC [170-177] and such treatment should be offered if the patient is medically fit. Considering that the literature is evolving, the consideration of adjuvant chemotherapy should follow NCCN guidelines.

8.1.6 Post-Operative Care and Follow Up

The patient should undergo inpatient pulmonary rehabilitation [178] and receive prophylactic doses of low molecular weight heparin (LMWH) until discharge [179, 180]. The patient should be followed-up for complications related to surgery, and undergo surveillance at regular intervals with imaging and review of symptoms. Smoking cessation after curative intent therapy to prevent a second primary lung cancer is strongly supported by the available evidence [181].

8.2 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chair, Andrew Chang, MD, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Drs. Wu, Chang, Orringer, and D'Amico will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

8.3 Adverse Events Associated with RODS

Atelectasis, lung infection, pneumonitis, dyspnea, adult respiratory distress syndrome, pleural infection, thromboembolic event, myocardial infarction, ventricular arrhythmia, arterial injury, venous injury, wound infection, bronchopleural fistula, postoperative hemorrhage, sepsis, recurrent laryngeal nerve palsy, intraoperative respiratory injury, changes in pulmonary function tests (e.g. forced expiratory volume (FEV1) decreased; carbon monoxide diffusion capacity (DLCO) decreased; vital capacity abnormal).

8.4 Surgery Adverse Event Reporting Requirements

See Section 6.9 for details.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 Cytotoxic Therapy

Cytotoxic therapy is not recommended for patients with stage IA (T1N0) disease. Patients with unexpected pathologic stage II or III disease should be offered adjuvant cisplatin-based chemotherapy, although there will be no primary, chemotherapy-related endpoints for this trial. Adjuvant chemotherapy for patients with stage IB NSCLC is controversial [188-191] but is sometimes offered to patients with higher-risk T2 tumors (> 4 cm) in routine clinical practice. To be consistent for trial treatment, adjuvant therapy is not recommended for patients with

clinical stage T1N0 and pathologic stage T2N0 tumors. The adjuvant chemotherapy regimen and the timing of chemotherapy will be at the discretion of the treating oncologist. However, docetaxel and gemcitabine containing regimens should be avoided due to concerns of exacerbating radiation lung injury. Otherwise, any cisplatin/carboplatin-based 2-drug regimen is considered acceptable (e.g. cisplatin/etoposide, carboplatin/paclitaxel, cisplatin/paclitaxel, cisplatin/pemetrexed, carboplatin/pemetrexed, cisplatin/vinorelbine).

9.1.2 Salvage Therapy

If a patient has disease progression after trial treatment (either RODS or SBRT), salvage therapy should be implemented per standard of care. Salvage therapy could include multimodality care, such as surgical resection, radiation (including SBRT) and systemic therapy based on the stage of the disease, per NCCN guidelines.

9.2 Non-permitted Supportive Therapy

9.2.1 Molecularly Targeted Therapy

No molecularly targeted therapy is planned for the patients treated on this trial. The addition of molecularly targeted therapy is not permitted, except in the setting of another clinical trial or progression of disease. Patients may be entered on appropriate trials of adjuvant therapy with either cytotoxic or molecularly targeted therapy.

9.2.2 Other Cancer Therapy

Aside from the therapy outlined above for surgical resection, SBRT, and systemic therapy, patients must not receive other concomitant local or regional antineoplastic therapy (including standard fractionated radiotherapy, non-approved systemic therapy, and surgery except as described in this protocol) except at disease progression.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/blood submission. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Blood Submission

In this study, tissue and blood will be collected from consenting patients (see Appendix I) for banking at Qinhua University, Beijing. Collection and banking are highly recommended, but optional.

Tissue will be collected pre-treatment.

Patients enrolled to the surgical arm (Arm 1) will undergo a venous or arterial blood draw at the following time points:

- In the clinic prior to surgery OR pre-operatively OR prior to surgical removal of the tumor;
- Intra-operatively, after surgical removal of the tumor;
- Prior to discharge;
- 4-6 weeks post-op.

Patients enrolled to the SBRT arm (Arm 2) will undergo a venous blood draw at the following time points:

- Prior to the 1st fraction of SBRT;
- After the 3rd fraction of SBRT;
- After all SBRT (the last day);
- 4-6 weeks after the end of SBRT.

10.2 Specimen Collection for Banking (6-AUG-2018)

Specimens should be collected, documented, and submitted to Qinhua University, Beijing.

Nan Bi, MD, PhD /Jie He, MD
Chinese Academy of Medicine
Qinhua University
Beijing 100021, China
86-10-87788799

[Drs. Bi and He will specify the following for participating sites]:

- What specimens (e.g. H & E slides, block, serum) will be collected;
- At what time point (e.g. pretreatment, preoperatively, intraoperatively) will specimens be collected;
- How specimens will be stored (e.g. frozen, ambient);
- How specimens will be shipped (on dry ice, overnight).

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II.

11.1.1 Details of Follow-Up Evaluations

11.1.1.1 In follow up, PET and CT scans are required to document disease relapse/progression. Biopsy of the relapse/progression site is encouraged, but not required. Submission of the biopsy report (if applicable) and scan reports is required (see Schedule of Forms). Submission of imaging studies (scans with recurrent disease and the scans used for reference) is required for patients with recurrent disease.

Chest CT with IV contrast will be performed at least at 3, 6, 9, 12, 18, 24, and 36 months after completion of treatment (the date of surgery or at the last day of SBRT) per current standard of care. Response evaluation after SBRT can sometimes be difficult as fibrosis and subclinical radiographic changes are observed in a majority of patients. A solid pattern of fibrosis often may be misinterpreted as recurrent disease [267]. Regular radiological follow-up is required to establish local control. 18F-FDG PET can be helpful in distinguishing fibrosis from tumor recurrence, but treated volumes can show 18F-FDG uptake related to therapy for at least 12 months after treatment [162]. Careful radiological follow-up of patients is paramount in patients treated by RODS, as salvage surgery or definitive chemoradiotherapy might still be possible in case of local or regional recurrence [268-269].

11.1.1.2 In follow up, pulmonary function tests should be done per the treating physician's discretion.

11.1.1.3 After treatment is completed, patients will be seen in follow up every 3 months for years 1-2 years, every 6 months for year 3, then annually until publication of study results.

11.2 Measurement of Response

11.2.1 Guidelines for Assessing Treatment Response after SBRT

11.2.1.1 *CT Tumor Response*

Tumor response on CT will be assessed per RECIST 1.1, as described below; see http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf for additional details.

- Complete Response (CR): Disappearance of all target lesions. Any pathologic lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm)
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.2.1.2 *PET Tumor Response*

Guidelines for assessing post-SBRT changes on PET/CT will be per the table below, defined by Kong, et al. at the University of Michigan [257], using the blood pool in the aortic arch as a reference. This system is considered to be more reproducible than that of PERECIST [258] which uses the liver as a reference. The aortic arch is also less likely to be confounded by disease conditions in the liver which may increase FDG-activity. Metabolic tumor volumes will also be assessed and recorded.

PET Tumor Response of Irradiated Target Lesions

Complete Metabolic Response (CMR)	Tumor FDG-activity decreased to less than mean background of the aortic arch blood pool.
Partial Metabolic Response (PMR)	At least a 30% decrease in the maximum of relative tumor FDG-activity of target lesions
Progressive Metabolic Disease (PMD)	At least a 20% increase in the maximum of relative tumor FDG-activity of target lesions
Stable Metabolic Disease (SMD)	Neither sufficient reduction to qualify for MPR nor sufficient increase to qualify for MPD

The percentage of decrease or increase was globally estimated based on readings of (tumor activity-aorta activity)/aorta activity.

11.2.2 Local regional tumor control is defined as freedom from local-regional recurrence after RODS and freedom from progression of local primary tumor and disease occurrence at nodal regions after SBRT.

Local-regional recurrence after RODS includes recurrence, defined by CT, confirmed by PET/CT whenever possible, i.e., development of tumor masses at the site of resection, or hilum (N1 nodal region), mediastinum (N2-N3 nodes), or ipsilateral supraclavicular fossa for upper lobe tumors (N3 nodes), or within 3 cm of the staple line of RODS.

Local regional progression after SBRT includes tumor progression on CT per RECIST criteria, confirmed by PET/CT, within the same lobe, hilum (N1 nodes), mediastinum (N2-N3 nodes), or ipsilateral supraclavicular fossa for upper lobe tumors (N3 nodes), or within 3 cm of original PTV.

Local progression is defined as at least a 20% increase in the sum of diameters of the target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

11.2.3 Guidelines for Assessing Failure Patterns After SBRT and RODS

The definition of local failure is critical; recurrence rates may vary just due to varying definitions [259]. Participating physicians should be trained in the use of a standardized recording system. The distance between the center of recurrent tumor and the edge of the treated lesion will be measured as part of the following classification.

Type of Recurrence	**Modality**	**Description (after treatment effects have subsided)**
Local Failure		
Primary tumor failure (PLF)	SBRT	Appearance of residual tumor located within the extent of the primary targeted tumor.
Marginal failure (MF)	RODS/SBRT	RODS: Appearance of tumor ≤ 2 cm in any direction of the staple-line or the structures immediately adjacent to prior tumor site (chest wall/ mediastinum/ diaphragm/ spine). SBRT: Appearance of tumor ≤ 2 cm in any direction of the primary tumor PTV* or structures immediately adjacent to primary tumor (lung/ chest wall, mediastinum/ diaphragm/ spine).
Involved Lobe failure (ILF)	RODS/SBRT	RODS: Appearance of tumor > 2 cm in any direction of the staple-line or the structures

		immediately adjacent to prior tumor site (chest wall/ mediastinum/ diaphragm/ spine). SBRT: Appearance of tumor > 2 cm in any direction of the primary tumor or structures immediately adjacent to primary tumor (lung/ chest wall, mediastinum/ diaphragm/ spine).
Port site/wound failure (PWF)	RODS	Appearance of tumor at a port or incision site after VATS or open resection.
Regional Nodal Failure		
Hilar nodal failure (HNF)	RODS/SBRT	Appearance of tumor in ipsilateral hilar nodal regions
Ipsilateral mediastinal nodal failure (MNF)	RODS/SBRT	Appearance of tumor in ipsilateral mediastinal and/or subcarinal nodal regions.
Contra-lateral mediastinal nodal failure (CNF)	RODS/SBRT	Appearance of tumor in contralateral mediastinal nodal regions.
Contralateral hilar nodal failure (CNF)	RODS/SBRT	Appearance of tumor in contralateral hilar nodal regions
Supraclavicular nodal failure (SNF)*	RODS/SBRT	Appearance of tumor in ipsilateral and contralateral supraclavicular nodal regions
Distant Failure		
Non-primary lobe failure (NLF)#	RODS/SBRT	Appearance of tumor within another ipsilateral (non-primary) lobe, ≥ 2 cm from the original planning target volume
Distant metastatic failure (DMF)	RODS/SBRT	Appearance of tumor deposits characteristic of NSCLC metastasis (chest wall other than incision sites, mediastinal structures/diaphragm, malignant pleural/pericardial effusion), contralateral lung and/or other distant sites.

*This is classified as distant nodal failure in RTOG 1021/ACOSOG Z4099.
#This is classified as local-regional failure in RTOG 1021/ACOSOG Z4099.

11.3 Criteria for Discontinuation of Protocol Treatment

Protocol treatment will be discontinued if the patient

- has progression of disease so that SBRT is not a reasonable treatment;
- becomes inoperable for radical surgical resection;
- cannot tolerate SBRT treatment;
- wants to withdraw from the study

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION (6-AUG-2018)

Translation of data forms is critical. The institution is responsible for all translation costs. All data forms below must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved, RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual data form in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral

third party. The professional title and credentials of the neutral third party translator must be specified as well.

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1720
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (6-AUG-2018)

Item	Due
Initial Evaluation Form **(I1)** Pathology Report **(P1)**	Within 2 weeks of registration
Radiotherapy Form **(T1)**	Within 1 week of RT end
Surgical Form **(S1)** Surgical Procedure Report **(S2)** Surgical Pathology Report **(S5)** **NOTE: The S2 and S5 should be de-identified and emailed to jserianni@acr.org as PDF files**	Within 4 weeks after protocol surgery
Follow-up Form **(F1)**	Every 3 months for years 1-2 years, every 6 months for year 3, then annually until publication of study results

12.2 Summary of Dosimetry Digital Data Submission (Submit to RTOG Headquarters; see Section 12.2.1) (6-AUG-2018)

Item	Due
Preliminary Dosimetry Information (DD)	
Digital Data Submission – Treatment Plan submitted in DICOM format to RTOG via TRIAD, exported from treatment planning machine by Physicist Digital data submission includes the following: • **Planning CT** • RT Structure File including all required tumor volumes and critical normal structures • RT Plan File for final plan • RT Composite Dose File for treated beams • Digital DVH data including all required tumor volume and critical normal structures • Digital Data Submission Form **(DDSI)** [on the RTOG website, Foundation study 3502, under Forms]	Within 1 week of start of RT

Final Dosimetry Information Radiotherapy Form **(T1)** Daily Treatment Record **(T5)** [Copy of daily treatment chart submitted via email to RTOG-RTQA@acr.org.]	Within 1 week of end of RT
PET and/or CT progression scans **(MR)** PET and/or CT progression reports **(ME)** Digital Data Submission Form **(DDSI)** [on the RTOG web site, Foundation study 3502, under Forms]	At time of progression
NOTE: For all digital data submissions (preliminary, final Dosimetry or PET/CT scans for progression), sites must complete a Digital Data Submission Form (DDSI) via the RTOG web site. **Also, sites will notify RTOG via e-mail RTOG-RTQA@acr.org after any digital data is submitted. The e-mail must include study number, site name, and case numbers.**	
Modified digital patient data as required by RTOG will be submitted via TRIAD.	

12.2.1 Digital Data Submission to RTOG Headquarters
Digital data will be submitted to RTOG via TRIAD.

12.2.2 Method of Plan Submission
Sites will follow directions for establishing a TRIAD account for the purpose of submitting digital RT data. Refer to the RTOG website for instructions.
http://www.rtog.org/ClinicalTrials/RTOGFoundationStudies/RTOGFoundationStudy3502.aspx,

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

13.1.1 Two-year local-regional tumor control, which is defined as freedom from local-regional recurrence after RODS and freedom from progression of local primary tumor and disease occurrence at nodal regions after SBRT (see Section 11.2.2)

13.2 Secondary Endpoints

13.2.1 Overall survival;
13.2.2 Disease-free survival;
13.2.3 Frequency of site-specific failure (patterns of failure);
13.2.4 Time to local-regional tumor failure and distant metastases;
13.2.5 PET tumor response;
13.2.6 Frequency of adverse events, graded by CTCAE, v. 4;
13.2.7 Trial feasibility parameters.

13.3 Sample Size

This randomized phase II trial will compare SBRT and RODS among patients with T1N0M0 NSCLC.

The trial is designed to determine whether there is a 15% or smaller absolute decrement in local-regional tumor control at 2 years for SBRT relative to RODS. Specifically, we assume that patients treated with RODS will have 90% of 2 year local regional control, and aim to demonstrate that those with SBRT would have no greater than 15% lower local-regional control largely due to lack of nodal dissection, or 75% local-regional control. The rationale for permitting up to 15% lower 2-year local tumor control for the SBRT arm is that SBRT is expected to have equivalent survival as such local failure would be effectively salvaged by surgery, radiation, chemotherapy or combined trimodality therapy [252]. Additionally, we expect the patients treated with SBRT would

have a better quality of life and more favorable toxicity profiles (less severe treatment complications such as inter-operative death). The null hypothesis is that SBRT has a > 15% lower local-regional control rate, and the alternative is that the difference is 15% or less. To ensure probability of 0.80 for correctly concluding that the difference is 15% or less (that is, when this is the true state) and probability 0.20 of falsely concluding that the difference exceeds 15%, 36 patients per treatment arm is required, a total of 72 patients. To account for ineligible patients and attrition of the cohort during the 24-month follow up, a 5% inflation of the sample size is applied, leading to **a total of 76 patients.** With 24 months of accrual and a minimum follow-up of 24 months, the trial will be completed.

13.4 Accrual

Five institutions will participate in this trial. It is estimated that 100 patients in each participating center will undergo a complete resection for stage I NSCLC each year. Of these patients, 5-10% are expected to consent to enroll on this trial. Thus, we anticipate that enrollment will be completed in 24 months. We plan to report primary results at a maximum of 2 years after the last patient has been enrolled (i.e. when all patients have accumulated either 2 years of follow up or a primary endpoint failure event).

13.5 Analysis Methods

13.5.1 Primary Endpoint

A test of binomial proportions will be used to compare local-regional failure proportions between treatment arms. If despite randomization, there are imbalances in important patient and disease covariates, then logistic regression will be used to estimate the effect of treatment accounting for other covariates [253]. Survival analysis methods, specifically the Cox proportional hazards model and the cumulative incidence function, will be used to evaluate the time to local-regional failure hazard by treatment arm and the cumulative probability of local-regional failure events over time by treatment arm [254].

13.5.2 Other Time-to-Event Endpoints and Sites of Failure

The Kaplan-Meier estimator and logrank test will be used to estimate survival distributions and compare survival by treatment arm. The hazard rate ratio with 95% confidence interval will be estimated via the Cox proportional hazards model. If the proportionality assumption is not met, then other models will be considered as appropriate. Contingency table methods and logistic regression will be used for discrete endpoints such as site-specific failure proportions and PET response. Cumulative incidence of time to local-regional failure, other site-specific failure (i.e., distant metastases), and cause-specific survival will be estimated using appropriate competing risks methods. Models for cause-specific hazards and cumulative incidence of these events will used to estimate different aspects of the relative event-specific failure risk between groups [255] [256]. PET tumor response (Section 11.2.1.2) and an evaluation of assessment of failure patterns after SBRT and RODS (Section 11.2.3) will be investigated.

13.5.3 Adverse Events

Frequency distributions of specific adverse events of interest will be compared between treatment arms using Fisher's exact test. If there appear to be imbalances in patient or disease characteristics by treatment arm, then stratified methods or logistic regression modeling will be used to compute adjusted tests. Logistic regression modeling will be used to explore the relationship between treatment toxicities and other factors in addition to treatment.

13.5.4 Trial Feasibility Parameters

Trial feasibility parameters will be summarized using descriptive statistics. Formal hypothesis testing will not be conducted; rather, observed quantities will be compared to performance benchmarks based on typical RTOG trials. Some specific expectations are as follows:

- Credentialing: 100% credentialing completed and documented before patient enrollment;
- Eligibility: Among screened and enrolled patients, 95% retain eligibility status after central review by RTOG Headquarters staff;
- Baseline forms: Completed and provided within 30 days of registration;
- Follow-up forms and delinquency: Follow-up loss < 3% where follow-up loss is defined as the proportion of patients unavailable to be evaluated for the primary endpoint due to loss of contact, follow-up assessment provided within 60 days of evaluation time point.

13.6 Data Monitoring Committee, Interim Analyses, and Stopping Criteria

An independent Data Monitoring Committee will be constituted to oversee this trial. Accrual, other study conduct parameters, and adverse events will be reviewed at semi-annual meetings of this committee.

One formal analysis for futility with respect to demonstrating noninferiority will be performed after completion of enrollment and follow up to 1 year, including only those patients who have reached the 2-year follow-up time point. Early reporting will be considered if the estimated 2-year local-regional control rate in the SBRT arm (Arm 2) is less than 60% (in which case the exact upper one-sided 95% confidence bound would fall below 75%, the threshold noninferiority value for this trial), and if this rate is more than 15% lower than the observed rate in the RODS arm (Arm 1).

Results for dissemination will be developed, and a manuscript drafted for review, approval, and submission. After manuscript acceptance, patient follow up will be discontinued and the trial terminated. It is anticipated that termination will occur approximately 5.5 years from initiation of patient entry. This time-frame may be extended depending on factors such as the observed accrual and event rates, in which case a new trial termination date will be established.

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APPENDIX I (6-AUG-2018)

The consent form is a separate document from the protocol and has been reviewed by the new RTOG Foundation−contracted IRB vendor, Advarra.

APPENDIX II: STUDY PARAMETER TABLE: *See section 11.1 for details and exceptions

Assessments	Within 6 wks prior to registration, unless otherwise noted	Arm 1				Arm 2				Both Arms
		Prior to surgery in clinic OR Pre-Op OR prior to surg.removal of tumor	Intra-Op after surgical removal of tumor	Prior to dis-charge	4-6 wks Post-Op	Prior to 1st fraction of SBRT	After 3rd fraction of SBRT	After all SBRT (the last day)	4-6 weeks after end of SBRT	q 3 mos. for years 1-2, 6 mos. for year 3, then annually*
History & Physical	X				X				X	X
Thoracic Surgeon evaluation	X									
Document weight	X				X				X	X
Performance Score	X				X				X	X
PFTs (with DLCO)	X									X*
FDG-PET/CT scan	Within 4 wks				X					At 3, 12, 24 mos.
CT of chest/upper abdomen, with contrast	Within 4 wks				X					Chest CT with contrast at 3,6.9, 12, 18, 24, 36 mos.
EBUS	Within 4 wks prior to treatment									
Adverse event assessment					X			X	X	X
Pregnancy test, if applicable	Within 72 hrs.									
†Blood for research		X	X	X	X	X	X	X	X	
†Tissue for banking	For Both Arms: prior to treatment									

†For patients who consent to participate in the specimen banking component of the study; see Appendix I.

APPENDIX III

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 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 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 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX IV

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

LUNG

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)*

T1a Tumor 2 cm or less in greatest dimension

T1b Tumor more than 2 cm but 3 cm or less in greatest dimension

T2 Tumor more than 3 cm but 7 cm or less with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumor more than 3 cm but 5 cm or less in greatest dimension

T2b Tumor more than 5 but 7 cm or less in greatest dimension

T3 Tumor more than 7 cm or one that directly invades any of the following: parietal (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodules in a different ipsilateral lobe

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph nodes metastasis

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension

N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

M1a Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion*

M1b Distant metastasis

* Most pleural (and pericardial effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element, and the patient should be classified as M0.

STAGE GROUPING

Occult Carcinoma	TX, N0, M0
Stage 0	Tis, N0, M0
Stage IA	T1a-b, N0, M0
Stage IB	T2a, N0, M0
Stage IIA	T2b, N0, M0
	T1a-b, N1, M0
	T2a, N1, M0
Stage IIB	T2b, N1, M0
	T3, N0, M0
Stage IIIA	T1a-b, N2, M0
	T2a-b, N2, M0
	T3, N1-2, M0
	T4, N0-1, M0
Stage IIIB	T1a-b, N3, M0
	T2a-b, N3, M0
	T3, N3, M0
	T4, N2-3, M0
Stage IV	Any T, Any N, M1a-b

APPENDIX V (10/22/14)

THORACIC SURGEON'S CREDENTIALING FORM

Please complete this questionnaire following a careful review of the eligibility (Section 3.0) and surgical (Section 8.0) sections of RTOG Foundation 3502 and return this form to your Research Associate. **Surgeon credentialing is a pre-registration requirement** (Section 5.3).

1. This study recommends careful documentation of stage of disease. Systematic mediastinal sampling or mediastinal lymph node dissection is strongly recommended for all patients at the time of lung resection. Is this a procedure that you perform routinely and would you agree to do for this protocol?

   YES _____ NO_____
   Comments:

2. This protocol recommends systematic nodal sampling or dissection at thoracotomy at all levels of hilar and mediastinal nodes according to the American Thoracic Society Lymph Node Map.

   Are you familiar with this nodal mapping system?
   YES_____ NO_____
   Comments:

   Do you routinely perform systemic mediastinal nodal sampling or dissection at the time of pulmonary resection?
   YES_____ NO_____
   Comments:

   Do you agree to perform systematic nodal sampling or nodal dissection as specified in the protocol? Section 8.0 of the protocol specifies removal of lymph nodes from stations 2R, 4R, 7, 9R and 10R for right sided resections and from stations 5, 6, 7 9L, and 10L for left sided resections.
   YES_____ NO_____
   Comments:

3. This study requires anatomic pulmonary resection for all patients in surgery arm. Do you agree to attempt radical resection (lobectomy or pneumonectomy) of all patients if the patient is randomized to surgery?
   YES_____ NO_____
   Comments:

(Continued on the next page)

4. Please check the item that best describes the scope of your practice:

   _____ General Surgery plus Thoracic Surgery
   _____ Primarily Thoracic Surgery; some Cardiac Surgery
   _____ Primarily Cardiac Surgery; some Thoracic Surgery
   _____ Equal mix of Thoracic and Cardiac Surgery
   _____ Only Thoracic Surgery

5. Please estimate the number of lobectomies and/or pneumonectomies you perform per year. _

6. Please estimate the number of lobectomies and/or pneumonectomies you perform per year. _____

   NOTE: Surgeons must have performed a minimum of 10 lobectomies/pneumonectomies per year in order to participate in RTOG Foundation 3502.

7. If there are other surgeons at your institution who will be participating in this program, have they also completed one of these forms?

   YES_____ NO_____

If you have any specific questions about this form or other aspects of the trial, please contact:

Andrew Chang, MD
University of Michigan Cancer Center
Ann Arbor, MI 48109, USA
734-763-7418/FAX 734-615-2656
andrwchg@umich.edu

_____	_____
Signature of Surgeon completing this form	**Institution Name**
_____	_____
Printed Name of Surgeon	**Telephone number of Surgeon**
_____	_____/_____
Physician's Fax Number	**Site RTOG Institution Number**

(Continued on the next page)

Return this form to your Research Associate.

RTOG Research Associates: E-mail the completed form to Dr. Chang: andrwchg@umich.edu.

Dr. Chang will e-mail the reviewed form, indicating the decision (via the box below) to RTOG HQ, RTOG3502@acr.org

☐ Reviewed and approved

☐ Reviewed and not approved: Dr. Chang also will contact the site.

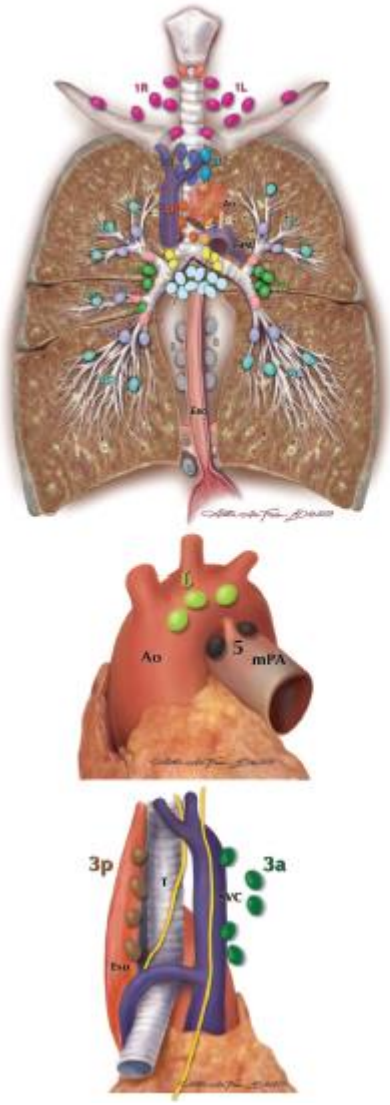
_____ _____

Andrew Chang, MD, Date

Thoracic Surgery Co-Chair

APPENDIX VI

AJCC NODAL ATLAS



Supraclavicular zone
- 1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone
- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Prevascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

AORTIC NODES

AP zone
- 5 Subaortic
- 6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone
- 7 Subcarinal

Lower zone
- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone
- 10 Hilar
- 11 Interlobar

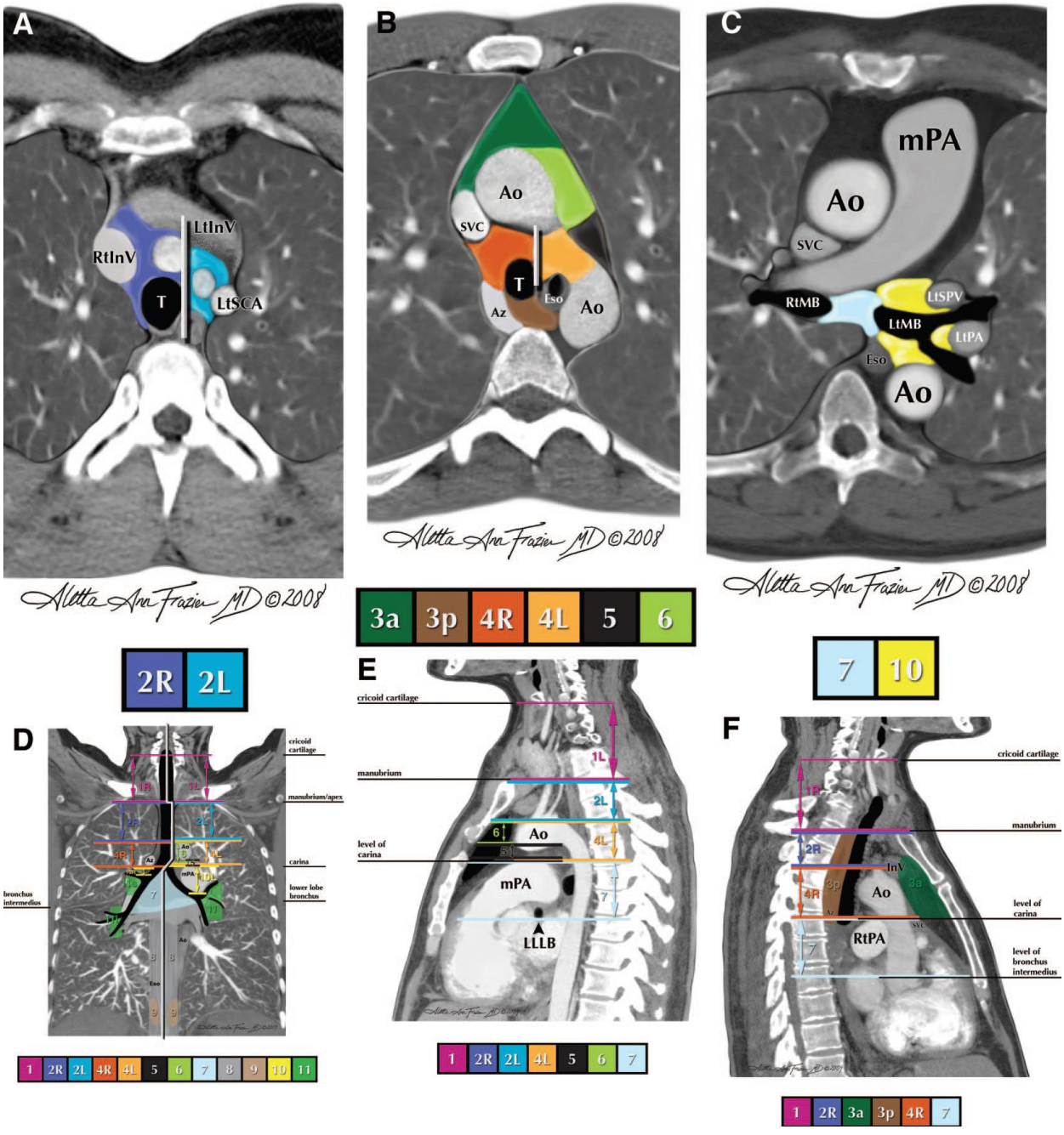
Peripheral zone
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

Continued on next page

169. Pisters 2007
270. Rusch VW 2009.

APPENDIX VI (Continued)

AJCC NODAL ATLAS



169. Pisters 2007
270. Rusch VW 2009.