Title

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NRG Oncology RTOG 0915 (NCCTG N0927): A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer

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Abstract

Purpose—To compare 2 stereotactic body radiotherapy (SBRT) schedules for medically inoperable early-stage lung cancer to determine which produces the lowest rate of grade ≥ 3 protocol-specified adverse events (psAEs) at 1 year.

Methods—Patients with biopsy-proven peripheral (greater than 2 cm from the central bronchial tree) T1/T2, N0 (clinically node negative by positron emission tomography), M0 tumors were eligible. Patients were randomized to receive either 34 Gy in one fraction (Arm 1) or 48 Gy in 4 consecutive daily fractions (Arm 2). Rigorous central accreditation and quality assurance

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confirmed treatment per protocol guidelines. This study was designed to detect a psAEs rate > 17% at a 10% significance level (1-sided) and 90% power. Secondary endpoints included rates of primary tumor control (PC), overall survival (OS) and disease-free survival (DFS) at 1 year. Designating the better of the two regimens was based on pre-specified rules of psAEs and PC for each Arm.

Results—Ninety four patients were accrued between September 2009 and March 2011. Median follow up time was 30.2 months. Of 84 analyzable patients, 39 were in Arm 1 and 45 in Arm 2. Patient and tumor characteristics were balanced between Arms. Four (10.3%) patients on Arm 1 (95% confidence interval (CI): 2.9%-24.2%) and six (13.3%) patients on Arm 2 (95% CI: 5.1%-26.8%) experienced psAEs. The 2-year OS rate was 61.3% (95% CI: 44.2%-74.6%) for Arm 1 patients and 77.7% (95% CI: 62.5%-87.3%) for Arm 2. The 2-year DFS was 56.4% (95% 39.6%-70.2%) for Arm 1 and 71.1% (95% CI: 55.5%-82.1%) for Arm 2. The 1-year PC rate was 97.0% (95% CI: 84.2%-99.9%) for Arm 1 and 92.7% (80.1%-98.5%) for Arm 2.

Conclusions—34 Gy in 1 fraction met pre-specified criteria and of the two schedules, warrants further clinical research.

Keywords

stereotactic body radiotherapy; early stage lung cancer; medically inoperable; fractionation

Introduction

Stereotactic Body Radiotherapy (SBRT) is routinely employed to treat medically inoperable patients with early stage non-small cell lung cancer (NSCLC). Many retrospective and single-institution reports have established the safety and efficacy of this modality in this vulnerable population.[1-20] A range of dose/fractionation schedules is described in these studies such that to date no single regimen has been established as standard. The Radiation Therapy Oncology Group (RTOG) conducted the first multicenter, cooperative group prospective study of lung SBRT for early stage NSCLC, RTOG 0236, reported in 2010.[21] This was a phase II trial in which treatment consisted of 54 Gy in 3 fractions delivered over 8-14 days. Eligible patients had “peripheral” lesions (i.e., ≤ 2cm from tracheo-bronchial tree[5]), were unable to undergo surgical resection due to concurrent medical co-morbidities and had biopsy-proven NSCLC tumors ≤ 5 cm in maximum diameter. Fifty nine patients were accrued to that study and fifty five were evaluable. The median follow-up time was 34.4 months. At 3 years, the primary tumor control (PC) rate was 97.6% and the overall survival (OS) rate was 55.8%. This high rate of PC was felt to be the contributing factor to the study's high OS rate when compared to historic reports of patients treated with conventional radiotherapy (RT). However, the rate of ≥ grade 3 protocol-specified toxicity in the trial was 16.3% (although without grade 5 toxicity) and an additional 6 patients experienced non-protocol specified high grade toxicity, related to complications of the skin or the ribs, giving an overall toxicity rate of approximately 25%. This overall toxicity rate is notable given the medically frail population treated. The potential for lung SBRT to generate serious and life-threatening toxicities has been previously shown in the prospective Indiana University trials for what are now termed “central” tumors.[12]

With this background, NRG Oncology RTOG 0915 (North Central Cancer Trials Group N0927) [ClinicalTrials.gov Identifier: NCT00960999] was developed to study the interplay between potential morbidity and mortality caused by treatment-related toxicity and from tumor progression by two SBRT schedules different than RTOG 0236's. In selecting regimens for this randomized phase II trial, single-fraction and a multi-fraction Japanese and US schedules were considered, mindful of the diverse practices in total dose, fractionation and dose-prescribing. The selection was informed by Park et al.'s radiobiological modeling which uses the concepts of biological equivalent dose (BED) and single fraction equivalent dose (SFED) to make predictions with respect to toxicity and tumor control for different schedules.[22] NRG Oncology RTOG 0915 selected 34 Gy in 1 fraction to a 48 Gy in 4 fractions to identify which had the least toxicity while maintaining a pre-specified level of tumor control.

Methods and Materials

Patient Eligibility

Patients had to be at least 18 years of age or older with a Zubrod performance status score of 0-2. Cytologic or histologic proof of NSCLC was required and early stage tumors were defined as American Joint Committee on Cancer 6th edition[23] T1-T2 (≤ 5 cm) N0M0 cancer based on both mandatory computed tomography (CT) and positron emission tomography (PET) staging. Tumors were required to be greater than 2 cm in all directions from the proximal bronchial tree, which was defined as the distal 2 cm of the trachea, carina, and named major lobar bronchi up to their first bifurcation. Ineligibility criteria included a synchronous malignancy within 2 years of entry and prior radiotherapy to the thorax. Planned use of concomitant (whether induction, concurrent or adjuvant) antineoplastic therapy while on protocol made patients ineligible. All patients were required to sign informed consent before being registered on the study.

Prior to enrollment, a specialist in thoracic oncology (thoracic surgeon, medical oncologist, radiation oncologist, or pulmonologist) had to judge a patient to be medically inoperable. Protocol specified indicators of “medically inoperability” included: baseline forced expiratory volume in the first second of expiration (FEV1) ≤ 40% predicted, postoperative FEV1 ≤ 30% predicted, carbon monoxide diffusing capacity (DLCO) ≤ 40% predicted, baseline hypoxemia or hypercapnia, severe pulmonary hypertension; diabetes mellitus with end-organ damage; severe cerebral, cardiovascular, or peripheral vascular disease; or severe chronic heart disease. If a patient had technically resectable disease but declined surgery after consulting with a thoracic surgeon, that patient was considered eligible.

Treatment planning and delivery

Patients were immobilized in a stable position using a device that permitted accurate reproducibility of the target position from treatment to treatment. A variety of rigid immobilization systems were allowed as long as they could be referenced to a pre-specified stereotactic coordinate system. All positioning systems were validated and accredited by the RTOG's Advanced Technology Consortium (ATC) before patients were enrolled on this trial. To account for the effect of internal organ motion (e.g., from breathing) on target

positioning and reproducibility, maneuvers including reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques were allowed. All systems used to account for internal organ motion were also validated and accredited by the ATC. The full extent of tumor motion was to be quantified using fluoroscopy or 4-dimensional (4D) CT scanning. Image guidance capable of confirming the position of the target at the time of treatment delivery was required: permitted imaging approaches included planar kV imaging devices, in-room helical CT, tomotherapy helical CT, and cone-beam CT equipment, in association with standard electronic portal imaging device verification.

The target lesion was outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target was generally drawn using CT pulmonary windows; however, soft tissue windows with contrast could be used to avoid including adjacent vessels, atelectasis, or chest wall structures within the GTV. No additional margin was added for possible microscopic extension and thus the clinical target volume (CTV) was considered equivalent to the GTV. Two acceptable methods were used to define the planning target volume (PTV) depending on the method of CT simulation:

1. Conventional (helical) CT-simulation (i.e., non-4DCT): The PTV included the GTV plus an additional 0.5 cm margin in the axial plane and 1.0 cm margin in the longitudinal plane (cranio-caudal); or
2. 4DCT-simulation: An internal target volume (ITV) around the GTV, accounting for tumor motion was defined from the 4D CT dataset. The PTV included the ITV plus an additional 0.5 cm margin uniformly applied to the ITV.

Patients enrolled on NRG Oncology RTOG 0915 were randomized to one of two dose/fractionation schemes (Arms 1 or 2). Patients on Arm 1 received 34 Gy in 1 fraction to the prescription line at the edge of the PTV whereas patients on Arm 2 received 4 fractions at 12 Gy per fraction, for a total dose of 48 Gy to the prescription line at the edge of the PTV, with treatments given over 4 consecutive days. This protocol required use of validated tissue density heterogeneity corrections for dose planning. With respect to maximum dose, all treatment plans had to be created so that 100% corresponded to the maximum dose delivered and this point existed within the PTV. The prescription isodose surface had to be ≥ 60% and < 90% of the maximum dose. Adequate target coverage was achieved when 95% of the PTV was covered by the assigned total dose and when 99% of the PTV received ≥ 90% of the prescription dose. High-dose conformality was controlled such that the volume of tissue outside of the PTV receiving a dose >105% of the prescription dose had to be ≤ 15% of the PTV and the target conformality index (ratio of the volume receiving total prescription dose to the planning target volume) was ≤ 1.2. Dose conformality and gradient quality were controlled by parameters provided in Supplementary Table S1 (see Appendix). Treatment plans had to meet contoured organ dose constraints as specified per treatment Arm (see Supplementary Table S2).

Institutional review and accreditation

Prior to starting patient enrollment, the Institutional Review Board for a treatment center was required to review the trial and provide approval to conducting the study. For the

purposes of lung SBRT planning and delivery, central credentialing standards for protocol participation were defined by the ATC. This credentialing included irradiation of a standard chest phantom (supplied by the Radiologic Physics Center, Houston, Texas). All sites were also required to obtain central approval of their methods of immobilization, motion assessment and control, and target verification if IMRT was to be used. When a center enrolled its first patient on the trial, central review of the target, normal structure contouring, and dosimetry by the primary investigator or other radiation oncology co-chair was required before treatment delivery and was facilitated by the Image Guided Therapy QA Center at Washington University (St Louis, Missouri) to ensure that protocol planning criteria had been met.

Follow up and endpoints

Patients were seen at 6 and 12 weeks after SBRT, then every 3 months for 2 years, every 6 months for next 2 years and annually thereafter. Comprehensive interval history and physical examination were required at each follow up visit. Imaging of the chest by CT scan was required at each visit starting at the 12 week follow up visit to assess response and toxicity. Follow-up PET scans were recommended for all patients at 1 year after SBRT to assess response. Pulmonary function tests (FEV1, DLCO) were conducted at the 12 week visit and then every 6 months for the next 5 years after treatment. Tumors were measured at each follow-up visit using the Response Evaluation Criteria in Solid Tumors (RECIST) and response was graded according to the international criteria proposed in the RECIST Guideline version 1.1.[24] Because local treatment effects in the vicinity of the tumor target are recognized to make determination of tumor dimensions difficult, response criteria were not limited to CT assessment but were augmented by PET and/or biopsy when scoring primary tumor failures or marginal failures. The primary endpoint of the study was the rate of grade 3 or higher adverse events at 1 year that were pre-specified in the protocol and these included cardiac, gastrointestinal, fracture, skin, thoracic, and neurologic disorders. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used for grading adverse events. Pulmonary function disorders however were scored per the RTOG 0236 schema.[21] The time-point for toxicity was selected based on data suggesting that most acute events would be noted within the first year after SBRT.[25] Secondary endpoints included assessment of primary tumor control, DFS and overall survival (OS) at 1 year; assessment of changes in fluorodeoxyglucose (FDG) standardized uptake values (SUV) on PET as a measure of treatment response and outcomes; pulmonary function changes by treatment Arm and response; and associations between biomarkers and PC and/or ≥ grade 2 radiation pneumonitis.

Statistical methods

The primary endpoint was the rate of ≥ grade 3 protocol-specified adverse events (psAEs) at 1 year. Based on historical data, any regimen was considered promising for further study if the rate of non-psAEs by 1 year exceeded 95% (i.e., the rate of psAEs < 5%), and any regimen with a rate of non-psAEs < 83% (rate of psAE > 17%) was deemed unsafe. A sample size of 38 analyzable patients with Fleming two-stage design[26] in each Arm yielded a 1-sided type I error of 0.1 and an actual power of 88%. Among the first 21 analyzable patients, if ≥4 psAEs were reported, that Arm would be terminated and deemed unsafe; if no

psAEs were reported, that Arm would be also terminated and deemed safe; if 1 to 3 psAE were reported, the accrual would continue, and a regimen would be considered safe if a total of ≤ 4 psAEs out of 38 analyzable patients were observed. Primary tumor control (PC) at one year was considered the key efficacy endpoint and was defined per RTOG 0236 as the absence of primary tumor failure (PF).[21] Briefly, PF was defined by post-SBRT tumor enlargement by a pre-specified percentage with proof of viability by PET and/or biopsy. PF also included "marginal" failures (defined as within 1 cm of the PTV). The term "local failure" referred to PF combined with a separate focus of failure in the involved lobe, with "local control" being the absence of "local failure". Primary tumor control (PC) was calculated as the proportion of analyzable patients at 1 year (excluding those who died without primary failure) who did not have primary tumor failure (local or marginal). Each experimental regimen was evaluated independently, and a regimen was considered for further evaluation only if both the rate of psAEs < 5% (based on the aforementioned two-stage design) and 1-year PC was ≥ 90%. If both regimens met both criteria, then the regimen with lower rate of psAEs would be selected. The study criteria by which the most favorable Arm is selected are summarized in Table 1. Analyzable patients are eligible patients who received any protocol treatment and potentially followed for at least 1 year. The Clopper-Pearson method[27] was used to calculate the 95% confidence interval (CI) of binomial rates. Overall survival (OS) was defined as the time from registration to date of death (from any cause). Disease-free survival (DFS) was the time from registration to death from any cause, primary failure, involved node failure, regional failure, distant metastasis, or second primary, whichever occurred first. Overall survival (OS) and DFS were estimated using the Kaplan-Meier method. A two-sided significance level of 0.05 was used throughout.

Results

The study opened in September 2009, closed in March 2011 and accrued a total of 94 patients. Median follow up time was 30.2 months. Of 94 medically inoperable patients accrued, 10 patients (8 in Arm 1and 2 in Arm 2) were excluded for the following reasons by 34 Gy and 48 Gy Arms, respectively: no protocol treatment in 2 (25%) and 0(0%); withdrawal of consent prior to SBRT in 1 (12.5%) and 0(0%); baseline DLCO not evaluated in 2 (25%) and 1 (12.5%); baseline PET not per protocol in 1 (12.5%) and 0 (0%); baseline PFTs not per protocol in 0 (0%) and tumor location not per protocol in 1 (12.5%); and 2 (25%) and 0 (%) patients. Of 84 analyzable patients, 100% and 95.6% of targets and 89.5% and 82.2% of normal tissue structures were outlined per protocol or minor deviations (as pre-specified in the protocol), for Arms 1 and 2, respectively. Thirty nine patients were randomized to Arm 1 (34 Gy) and 45 to Arm 2 (48 Gy). Patient and treatment characteristics were well balanced between Arms (Table 2). There were no reports of using non-protocol therapy in combination with SBRT.

Regarding the primary toxicity endpoint, 4 patients in Arm 1 met these criteria. (10.3%, 95% CI: 2.9-24.2%). For Arm 2, 6 patients met these criteria (13.3%, 95% CI: 5.1-26.8%). For Arm 1, 4 grade 3 psAEs were reported, all involving changes in DLCO. For Arm 2, psAEs were: 2 as grade 3 DCLO; 2 as grade 3 pneumonitis, 1 as grade 3 FVC % predicted. One grade 5 psAE event was noted for each study Arm. On the 34 Gy Arm, the patient died 15 days after completion of treatment and this death was reported as a "general disorder" felt

to be unrelated to SBRT. On the 48 Gy Arm, the patient died 319 days after treatment of respiratory failure judged possibly related to SBRT. Because 3 psAEs (7.9%) in Arm 1 and 6 psAEs (15.8%) in Arm 2 were experienced in the first 38 analyzable patients, Arm 1 was determined to be safe as the null hypothesis was rejected. Of clinical interest, the majority of reported toxicities were < grade 2. Table 3 presents selected categories for these lower grades of toxicity by Arm.

At analysis, 17 patients had died in each Arm. Causes of death reported for the 34 Gy and the 48 Gy Arms were due to: disease (local, regional, or distant) in 6 (35.3%) and 3 (17.6%) patients; second primary or other malignancy in 0 (0%) and 3 (17.6%) patients; other causes in 8 (47.1%) and 6 (35.3%) patients; and unknown causes in 3 (17.6%) and 4 (23.8%) patients, respectively. Primary control at 1 year was 97.0% and 92.7% % for the 34 Gy and 48 Gy Arms, respectively. The cumulative incidences of primary failure at 2 year were 2.6% and 2.2% for each Arm (death without primary failure was the competing event). Rates of OS and DFS for each Arm are shown in Figures 1 and 2 and outcomes are summarized in Table 4. As noted in Table 1, four scenarios were provided to determine which of the two Arms in this trial would be considered suitable for further study based on the combination of primary toxicity and secondary survival endpoints. On that basis, 34 Gy in one fraction met the pre-specified criteria with respect to adverse events and primary control with the lower rate of psAEs rate at 1 year and was judged the better of the two treatment schedules.

Discussion

NRG Oncology RTOG 0915/NCCTG N0927 was a phase II randomized study that prospectively evaluated two dose/fractionation schedules to determine whether one of them might result in less toxicity while maintaining excellent primary tumor control. Given the medical vulnerability of the target population, avoidance of treatment-related toxicity was felt to be an appropriate endpoint for comparing regimens. Having achieved its primary endpoint, NRG Oncology RTOG 0915 showed that 34 Gy had lower ≥ grade 3 toxicity for a similar short-term PC compared to 48 Gy Arm and was therefore judged the more favorable of the two randomized Arms. Although the focus of this study was on grade 3 or higher psAEs, we included Table 3 providing ≤ grade 2 toxicities, for informational purposes. Mindful that this study was not designed for formal comparisons of individual toxicities or any associations with patient or tumor factors, no ≥ grade 3 psAEs presented as chest wall-related symptoms in either arm. This is of interest because published single-fraction studies have not specifically documented rates of this toxicity. OS data beyond 1 year suggest a trend favoring the 48 Gy Arm but in a non-significant fashion with overlapping CIs. Comparisons of survival data in this randomized phase II setting need caution as it was not powered to address this question. Whether this observation represents a statistical anomaly or a real difference is unknown but encourages further characterization of patient outcomes with time.

Results from NRG Oncology RTOG 0915 appear comparable with those studies from which its doses were referenced. Hara et al's[20] 2006 retrospective analysis of 59 patients with malignant lung tumors < 4cm treated with 1 fraction only included 11 patients with primary lung tumors. Patients were treated over a range of doses from 26 Gy to 34 Gy. The median

follow up was 12 months. Fifty tumors received ≥ 30 Gy (range, 30–34 Gy). The overall survival rate was 76.5% at 1 year and 41% at 2 years. The 2-year local progression-free rate (LPFR) for tumors that were irradiated at doses ≥ 30 Gy was 83% and 52% for tumors treated with < 30 Gy. Overall, grade 3 respiratory toxicity was seen in one patient, with no higher grade toxicities reported. Although a dose-response effect was proposed for single-fraction therapy, the authors did not stratify their outcomes by tumor type (primary vs. metastatic), toxicity or doses delivered.

Published clinical experience for 48 Gy in 4 fractions is more extensive. In 2005, Nagata et al.[2] reported on a phase I/II study of 45 early stage NSCLC patients treated with 48 Gy in 4 fractions. At a median follow up of 30 months, no grade 3 pulmonary toxicities were noted. For stage IA lung cancers at 1 year, LPFR, DFS and OS rates were 100%, 80%, 93%, respectively, and for IB cancers, 100%, 92%, 82%, respectively. Recently preliminary data for JCOG 0403 for its cohort of medically inoperable T1 patients treated with 48 Gy in 4 fractions have been presented in abstract form.[28] One hundred and four patients were enrolled with a median follow-up of 46.8 months. Of 100 patients analyzed, at 3 years OS was 59.9%, DFS was 49.8% and local progression free survival was 53%. Grade 3 AEs were observed in 27 (25%) patients and grade 4 AE in 2 patients. No grade 5 AE was observed.

Comparing the results of NRG Oncology RTOG 0915 to RTOG 0236's is understandable given that the radiobiologic potency of the regimens for tumor control is clearly different. While NRG Oncology RTOG 0915 data mature, its 2-year results appear comparable to 0236's with respect to primary tumor control, OS and DFS and with possibly lesser toxicity rates.[21] However, the appropriate means for testing one schedule against the other would be a phase III trial that uses OS as the primary endpoint. OS is a rational endpoint since it should reveal the interplay between the cancer control achieved and the toxicities generated by each regimen and how these interact in a population whose survival is already compromised by existing and progressive comorbidities.

Conclusion

NRG Oncology RTOG 0915/NCCTG N0927 was a randomized phase II lung SBRT study of 34 Gy in 1 fraction versus 48 Gy in 4 fractions to find the least toxic yet still efficacious regimen for medically inoperable patients. Both regimens appeared safe with low rates of toxicity and high rates of PC at 1 year. Given a primary endpoint of pre-specified toxicity rates and a secondary endpoint of PC at 1 year, our results suggest that 34 Gy is an appropriate schedule for further investigation, most appropriately in a phase III trial involving a comparison with the RTOG standard of 54 Gy in 3 fractions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Summary

NRG Oncology RTOG 0915 was a randomized phase II trial of stereotactic body radiotherapy for medically inoperable peripheral early stage non-small cell lung cancer patients that compared 34 Gy in 1 fraction to 48 Gy in 4 fractions using rates of pre-specified grade 3 or higher toxicities at 1 year as the primary endpoint. The single-fraction schedule yielded lower rate of toxicities for comparable primary tumor control and warrants further clinical investigation.

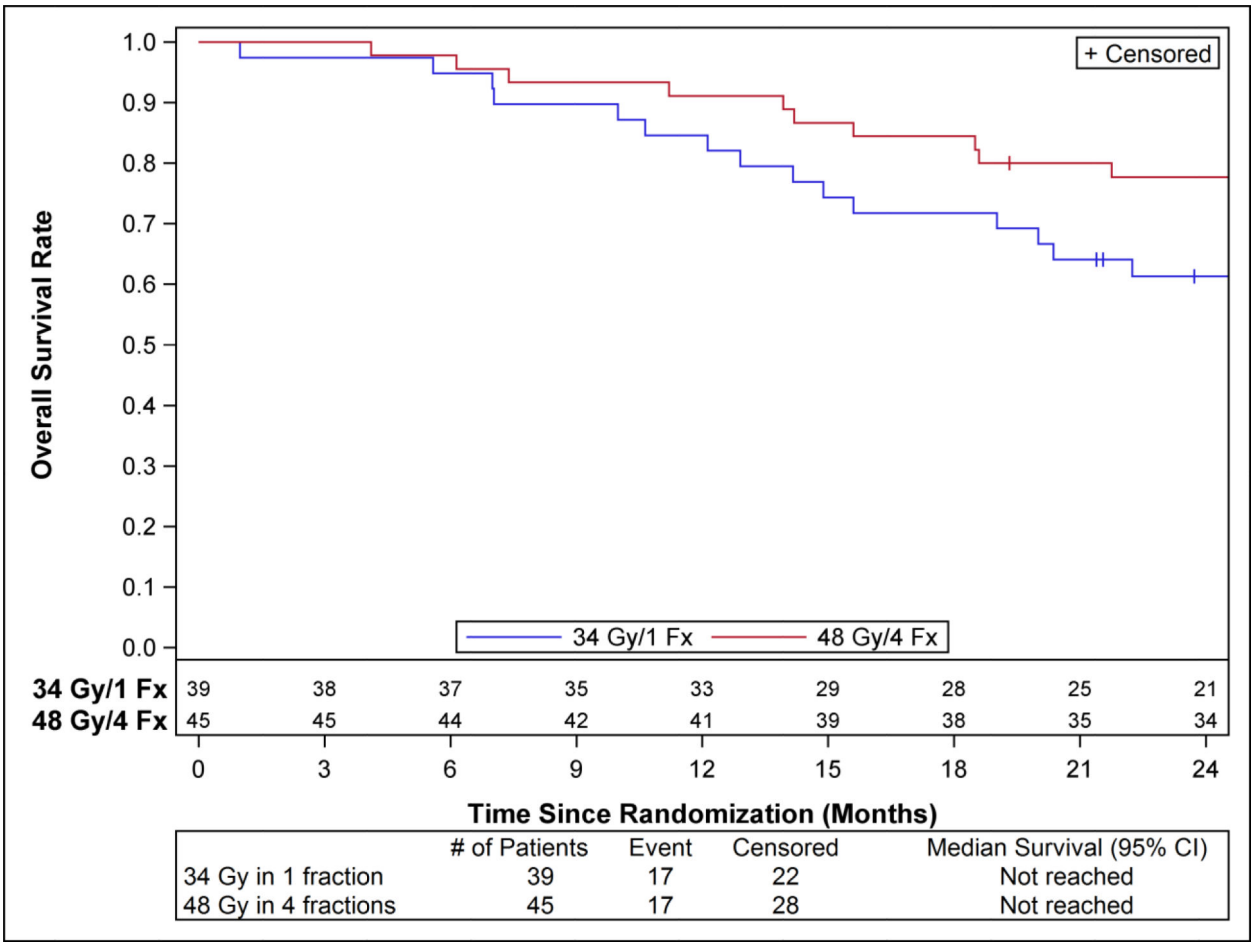

Figure 1.
Overall Survival for patients treated with 34 Gy and 48 Gy.

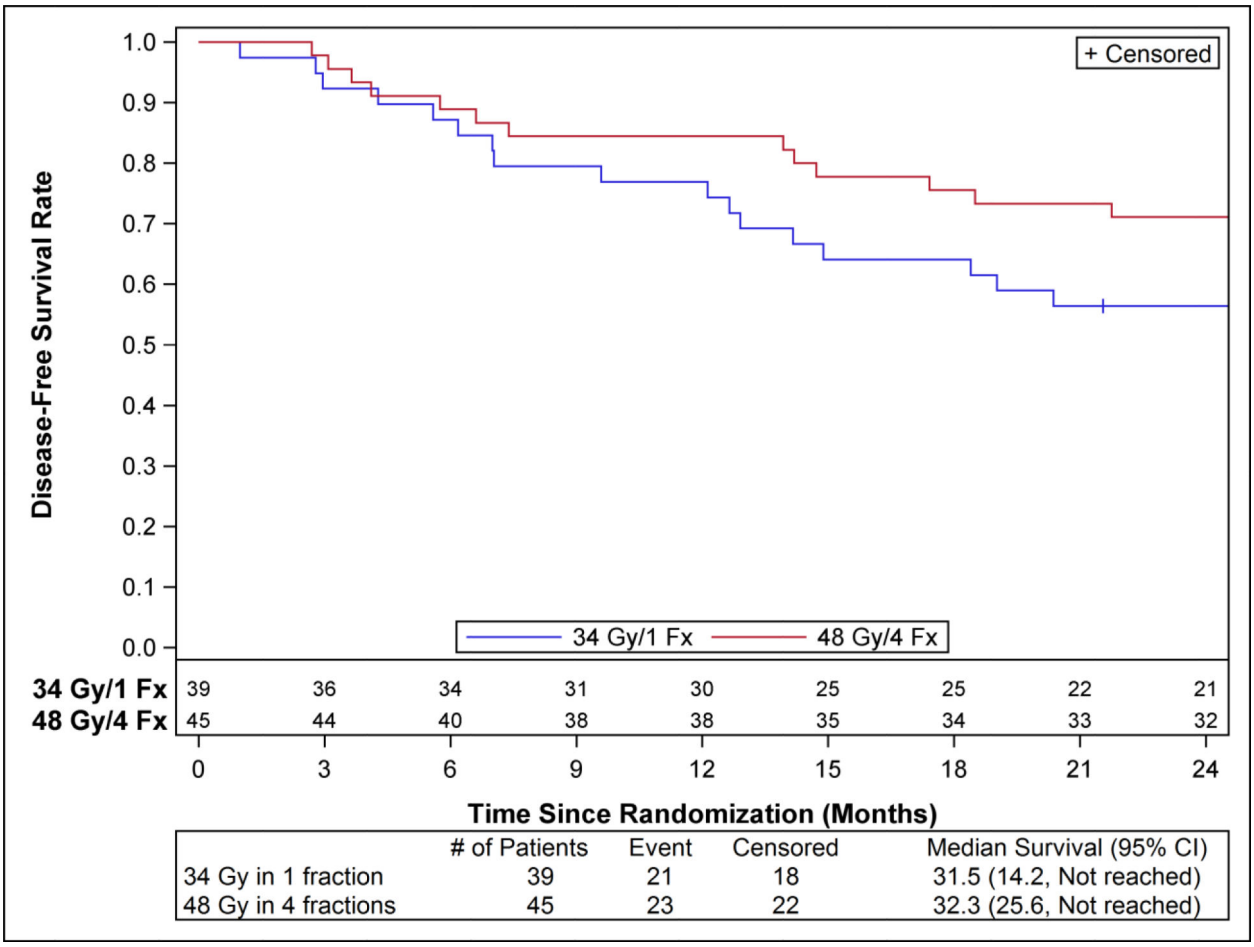

Figure 2.
Disease-Free Survival for patients treated with 34 Gy and 48 Gy.

Table 1

Schema for determining the preferred Arm in NRG Oncology RTOG 0915.

Scenario	Primary Tumor Control Rate at 1 Year	psAE Rate at 1 Year	"Preferred" of the two Arms
1	Both Arms > 90%	Both Arms ≤ 17%	Arm with lower psAE rate
2	Both Arms < 90%	Both Arms ≤ 17%	Reassess validity of either fractionation as RTOG 0236 competitor
3	n/a	Both Arms > 17%	Neither; both are too toxic
4	One Arm > 90%	Both Arms ≤ 17%	Arm with PC rate > 90%

psAE=pre-specified adverse event; n/a=not applicable; PC=primary tumor control

Table 2

Selected pre-treatment patient and tumor characteristics.

	34 Gy in 1 fraction (n=39)	48 Gy in 4 fractions (n=45)
Age		
Median (min-max)	75 (57-89)	75 (52-87)
Gender		
Male	16 (41.0%)	22 (48.9%)
Female	23 (59.0%)	23 (51.1%)
Zubrod performance status		
0	8 (20.5%)	15 (33.3%)
1	22 (56.4%)	19 (42.2%)
2	9 (23.1%)	11 (24.4%)
Histology		
Squamous cell carcinoma	9 (23.1%)	16 (35.6%)
Adenocarcinoma	23 (59.0%)	26 (57.8%)
Non-small cell lung cancer NOS	7 (17.9%)	3 (6.7%)
Maximum tumor diameter in cm, median (range)	2.0 (1.0-4.98)	2.0 (0.8-4.3)
T stage		
T1	32 (82.0%)	40 (88.9%)
T2	7 (18.0%)	5 (11.1%)
Peak SUV		
Median (min-max)	6.5 (1.0-24.6)	6.3 (1.0-28.0)
FEV1 (l/sec)		
Median (min-max)	1.32 (0.49-2.67)	1.21 (0.37-3.59)
FEV1 (%)		
Median (min-max)	60.0 (17.0-118.0)	54.0 (0.7-121.0)
DLCO (%)		
Median (min-max)	49.5 (1.5-93.0)	45.0 (6.2-93.0)

Table 3

Selected grade 1 and grade 2 protocol-specified adverse events of clinical interest with 34 Gy and 48 Gy.

Type of Adverse Event	34 Gy in 1 fraction Number of events (%)			48 Gy in 4 fractions Number of events (%)		
	Any (Grade 1-5)	Grade 1	Grade 2	Any (Grade 1-5)	Grade 1	Grade 2
Fatigue/malaise	6 (15)	2 (5)	4 (10)	5 (11)	5 (11)	0 (0)
Musculoskeletal disorders (including pain)	8 (21)	5 (13)	3 (8)	3 (7)	3 (7)	0 (0)
Injury (including fracture)	7 (18)	4 (10)	3 (8)	1 (2)	0 (0)	1 (2)
Respiratory disorders	18 (46)	13 (33)	5 (13)	15 (33)	8 (18)	2 (4)

Note: Total number of patients reporting any event by dose: 34 Gy=39; 48 Gy=45.

Table 4

Outcomes for patients treated with 34 Gy and 48 Gy.

	Arm 1 (34 Gy in 1 fx) (95% CI)	Arm 2 (48 Gy in 4 fx) (95% CI)
Overall Survival		
Dead/Total	17/39	17/45
1 year	84.6% (68.9, 92.8)	91.1% (78.0, 96.6)
2 year	61.3% (44.2, 74.6)	77.7% (62.5, 87.3)
Disease-free Survival		
Fail/Total	21/39	23/45
1 year	76.9% (60.3, 87,3)	84.4% (70.1, 92.3)
2 year	56.4% (39.6, 70.2)	71.1% (55.5, 82.1)
Primary Tumor Control		
Fail/Total analyzable*	1/33	3/41
1 year	97.0% (84.2, 99.9)	92.7% (80.1, 98.5)

*Analyzable patients at 1 year after excluding those who died without primary failure.