original report

Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non–Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial

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abstract

PURPOSE Patients with centrally located early-stage non–small-cell lung cancer (NSCLC) are at a higher risk of toxicity from high-dose ablative radiotherapy. NRG Oncology/RTOG 0813 was a phase I/II study designed to determine the maximum tolerated dose (MTD), efficacy, and toxicity of stereotactic body radiotherapy (SBRT) for centrally located NSCLC.

MATERIALS AND METHODS Medically inoperable patients with biopsy-proven, positron emission tomography–staged T1 to 2 (≤ 5 cm) N0M0 centrally located NSCLC were accrued into a dose-escalating, five-fraction SBRT schedule that ranged from 10 to 12 Gy/fraction (fx) delivered over 1.5 to 2 weeks. Dose-limiting toxicity (DLT) was defined as any treatment-related grade 3 or worse predefined toxicity that occurred within the first year. MTD was defined as the SBRT dose at which the probability of DLT was closest to 20% without exceeding it.

RESULTS One hundred twenty patients were accrued between February 2009 and September 2013. Patients were elderly, there were slightly more females, and the majority had a performance status of 0 to 1. Most cancers were T1 (65%) and squamous cell (45%). Organs closest to planning target volume/most at risk were the main bronchus and large vessels. Median follow-up was 37.9 months. Five patients experienced DLTs; MTD was 12.0 Gy/fx, which had a probability of a DLT of 7.2% (95% CI, 2.8% to 14.5%). Two-year rates for the 71 evaluable patients in the 11.5 and 12.0 Gy/fx cohorts were local control, 89.4% (90% CI, 81.6% to 97.4%) and 87.9% (90% CI, 78.8% to 97.0%); overall survival, 67.9% (95% CI, 50.4% to 80.3%) and 72.7% (95% CI, 54.1% to 84.8%); and progression-free survival, 52.2% (95% CI, 35.3% to 66.6%) and 54.5% (95% CI, 36.3% to 69.6%), respectively.

CONCLUSION The MTD for this study was 12.0 Gy/fx; it was associated with 7.2% DLTs and high rates of tumor control. Outcomes in this medically inoperable group of mostly elderly patients with comorbidities were comparable with that of patients with peripheral early-stage tumors.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Stereotactic body radiotherapy (SBRT), that is, a few, high-dose, very conformal, precisely delivered radiation treatments, has become the standard of care for medically inoperable patients with node-negative non–small-cell lung cancer (NSCLC).[1,2] It is well tolerated and provides high rates of local control,[3] and its introduction has been associated with improved survival at a population level.[4]

However, patients with centrally located tumors demonstrated higher rates of toxicity if treated to highly ablative doses,[5,6] which lead to the exclusion of tumors within a 2-cm radius of large airways from most SBRT protocols. A phase I study of a five-fraction SBRT regimen was commenced (ClinicalTrials.gov identifier: NCT00591838). This multi-institutional, seamless phase I/II study was designed with the primary objectives to determine the maximum tolerated dose (MTD) of SBRT for centrally located NSCLC in medically inoperable patients and to estimate the 2-year tumor control rate at the MTD. This article reports the primary and the following secondary objectives: rates of grade 3 or higher adverse events (AEs) other than a dose-limiting toxicity (DLT), late AEs (beyond the first year), and progression-free survival (PFS) and overall survival (OS) rates.

MATERIALS AND METHODS

Patients

Eligible patients required pathologic proof of NSCLC, a Zubrod performance status of 0 to 2, and stage T1 to T2 N0M0 (American Joint Committee on Cancer Staging Manual, Sixth Edition) tumors no larger than 5 cm and within or touching the zone 2 cm around the proximal bronchial tree (PBT) or immediately adjacent to the mediastinal or pericardial pleura. Computed tomography (CT) and positron emission tomography (PET) scans were required within 8 weeks before registration. Any enlarged or PET-positive nodes had to be sampled to confirm N0 status. All patients were evaluated by an experienced thoracic cancer surgeon to determine medical inoperability. There were no limits in terms of pulmonary function tests. All patients had to provide informed consent.

Radiation Treatment

Patients were planned and treated on various technological platforms; all had to be credentialed for lung SBRT by the Advanced Technology Consortium. Planning CT had to consider respiratory motion, which could not exceed 1 cm. Heterogeneity corrections were required for planning. The gross tumor volume was outlined on lung windows with no expansion for potential microscopic disease. If four-dimensional CT (ie, CT that sorts images into respiratory phases) was used to evaluate tumor motion, then an internal target volume had to be created to account for respiratory motion followed by a 5-mm circumferential planning target volume (PTV) expansion. If four-dimensional CT was not used, then the PTV expansion was 10 mm superior-inferiorly and 5 mm in other planes. Other details are available in the protocol (Data Supplement). Three-dimensional conformal planning and/or intensity-modulated radiotherapy (IMRT) were allowed.

The SBRT fractionation schedule was five fractions every second to third day over 1.5 to 2 weeks. Nine dose levels that ranged from 8 to 12 Gy/fraction (fx) in 0.5 Gy/fx increments were planned. The initial dose level chosen was 10 Gy/fx (total dose, 50 Gy/5 fx; biologically effective dose [BED_{10}], 100); the maximum dose level that was planned for this study was 12 Gy/fx (ie, 60 Gy/5 fx; BED_{10}, 132).

Principles of SBRT planning were followed, including conformality, prescription isodose (typically 60% to 90% of the dose at the center of the target) selected such that 99% of PTV received a minimum 90% of the prescription dose, and avoidance of hot spots in organs at risk (OARs). Guidelines on conformality indices and recommended maximum limits to OARs are listed in Appendix Tables A1 and A2 (online only). Quality assurance consisted of a real-time review of the treatment planning images and dosimetry for the first patient enrolled per institution and then retrospective review of contouring of the target, OARs, and doses to both for all other patients.

Assessments

Patients were assessed before each SBRT fraction, at 6 weeks, every 3 months for 2 years, every 6 months for the next 2 years, and annually thereafter. History, physical examination, toxicity, pulmonary function tests, and radiology were followed. CT scans for tumor response assessment were scheduled at 6, 12, 18, and 24 months. A fluorodeoxyglucose PET scan was recommended if there was suspicion of tumor recurrence. AEs were evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0). All serious AEs that were potentially a DLT were independently reviewed by a thoracic oncology expert. A data safety monitoring committee reviewed all grade 5 AEs and tabular toxicity data.

Statistics

The seamless phase I/II study design used the time-to-event continual reassessment method (TITE-CRM)[7] to allocate each patient to a dose level. A one-parameter sigmoid dose-toxicity model was assumed, with the parameter re-estimated as the toxicity accrued. TITE-CRM weights DLT-free patients by the proportion of the 1-year observation period they have completed, so the trial could remain open without closing between dose cohorts. The early part of the 1-year observation period was conservatively downweighted; the first half of the 1-year observation period only received 30% of the weighting. Dose could be continually modified over the entire sample of 100 trial participants, and analysis of efficacy objectives was based on all participants. This is both a phase I and a phase II trial (although there are no separate phase I and II cohorts) where the first primary objective is the determination of the MTD and the second primary end point is estimation of the probability of 2-year primary tumor control at the MTD. The initial targeted sample size was 94 patients selected for a given precision of estimation of the MTD, but accrual to the study was expanded, and ultimately, the targeted sample size was amended to 110 patients. Because the distribution of doses that would be tested was not known with certainty at the initiation of the trial, it was not possible to power the trial for the phase II end point, but it was believed that the number of participants assigned to the MTD would allow estimation of the tumor control rate at that dose.

DLT was defined as any grade 3 or worse toxicity that occurred within 1 year from the start of SBRT and reported as possibly, probably, or definitely related to protocol treatment from a list of prespecified symptoms (Table A3). Estimates and 95% CIs of the 1-year DLT rate were obtained from the dose-toxicity model (Figure A1). Local control was defined as the absence of local failure, which was any of the following: local enlargement (per Response Evaluation Criteria in Solid Tumors [RECIST]) confirmed by PET or biopsy, marginal failure, or involved lobe failure. Death without local failure was considered a competing risk (Table A4). Regional failure referred to nodes, and distant

failure included lesions in the uninvolved lobe of the lung. A failure for PFS was the first of local, regional, or distant failure, development of a second primary, or death as a result of any cause. Patients who were alive without failure were censored at the date of last follow-up. All outcomes were measured from the date of study registration until the date of failure or censoring/competing risk. Estimates for local control were calculated using the cumulative incidence method; estimates for PFS and OS were calculated using the Kaplan-Meier method. For local control, bootstrapping was used to calculate 90% CIs; 95% confidence intervals were calculated for all other end points. A one-sided *z* test that compared 2-year local control with the control rate of 70% was performed.

RESULTS

Patients and Treatment

The trial opened to accrual on February 2, 2009, and closed to accrual on September 5, 2013, after accruing 120 patients from 43 centers in the United States and Canada. This report includes all data received as of May 29, 2017. Figure 1 shows the number of patients accrued for each dose level and the number excluded from the analysis and reasons why. One hundred patients were eligible for analysis; 71 of them were accrued into the two highest dose levels.

Pretreatment characteristics across the five dose cohorts of patients are listed in Table 1. The median age was 72 years, and the majority (84%) had a performance status of 0 to 1. The histology, T stage, and gross tumor volume/PTV differed somewhat across the dose cohorts (Table 1). Use of three-dimensional conformal radiotherapy and IMRT was approximately evenly divided for the study as a whole, except that more patients (60.6%) in the 12.0 Gy/fx arm were treated using IMRT. Isodose coverage of the PTV was near protocol requirements for most patients, as was dose spillage and adherence to protocol-recommended limits for OAR doses. Overall, SBRT review demonstrated that 62% were per protocol, 35% had acceptable variation, and 2% had unacceptable variation (one patient in the lowest dose cohort and one in the 11.5 Gy/fx cohort). Median follow-up for all patients was 37.1 months (range, 1.7 to 75.0 months) and for surviving patients was 54.7 months (13.3 to 75 months).

Toxicity

Of the 100 patients eligible for efficacy analyses, 11 were not evaluable for DLT analyses (10 as a result of death within the first year of observation without the report of a DLT and one who did not complete SBRT). Five patients experienced a DLT within the first year (Table 2). The only grade 5 DLT (death not otherwise specified) occurred in a

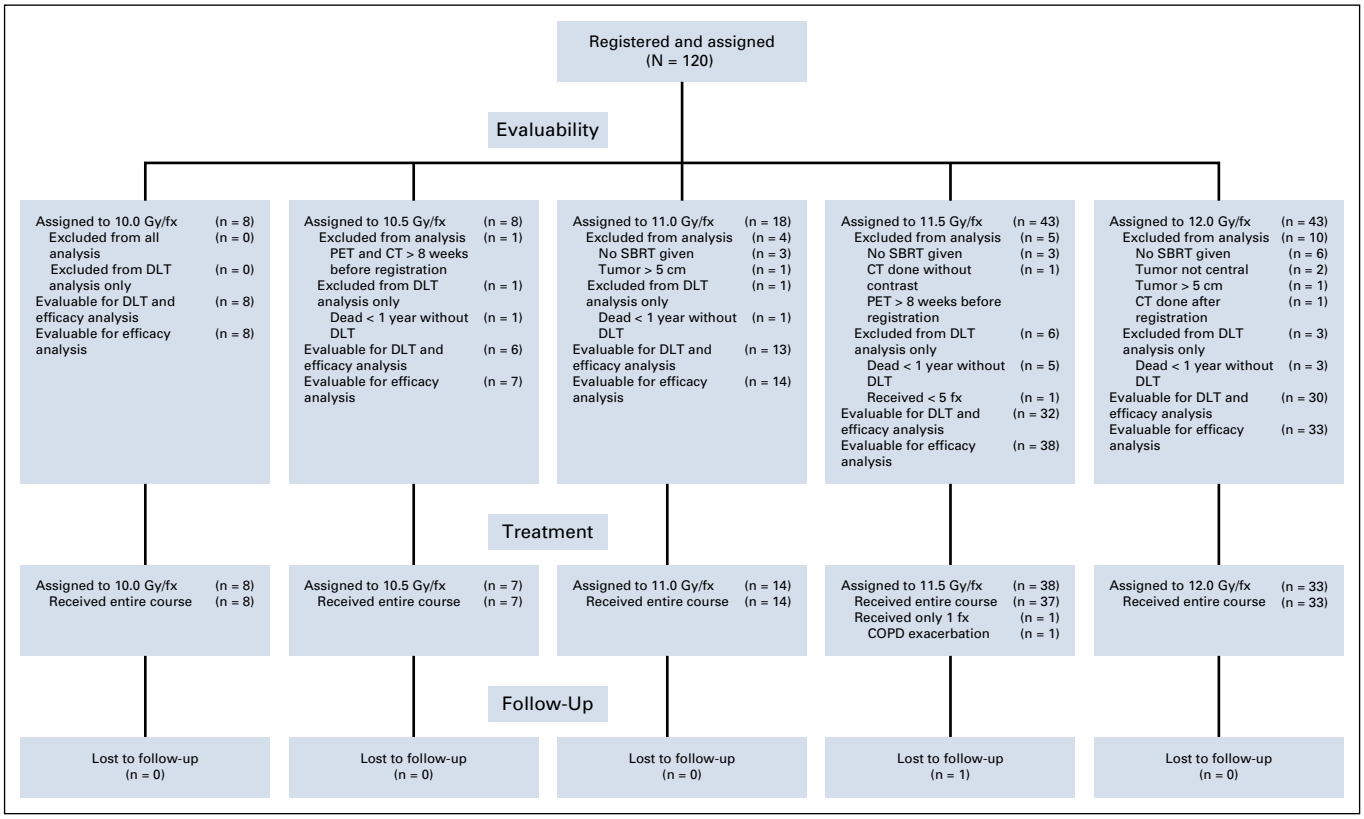

FIG 1. CONSORT diagram. COPD, chronic obstructive pulmonary disease; CT, computed tomography; DLT, dose-limiting toxicity; fx, fraction; PET, positron emission tomography; SBRT, stereotactic body radiotherapy.

TABLE 1. Baseline Characteristics of Patients by Dose Level

Characteristic	Dose Level, No. (%)					
	Level 5: 10.0 Gy/fx	Level 6: 10.5 Gy/fx	Level 7: 11.0 Gy/fx	Level 8: 11.5 Gy/fx	Level 9: 12.0 Gy/fx	Total
No. of patients	8	7	14	38	33	100
Age, years						
Median	74	75	72	71	72	72
Minimum-maximum	59-81	53-89	59-81	52-87	55-89	52-89
Q1-Q3	67-79	59-85	64-75	67-80	63-78	64-78.5
Sex						
Male	6 (75.0)	3 (42.9)	6 (42.9)	15 (39.5)	13 (39.4)	43 (43.0)
Female	2 (25.0)	4 (57.1)	8 (57.1)	23 (60.5)	20 (60.6)	57 (57.0)
Race						
Black	1 (12.5)	0 (0.0)	0 (0.0)	2 (5.3)	1 (3.0)	4 (4.0)
White	7 (87.5)	7 (100.0)	14 (100.0)	36 (94.7)	32 (97.0)	96 (96.0)
Ethnicity						
Hispanic or Latino	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (3.0)	2 (2.0)
Not Hispanic or Latino	8 (100.0)	7 (100.0)	12 (85.7)	37 (97.4)	31 (93.9)	95 (95.0)
Unknown	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.6)	1 (3.0)	3 (3.0)
Zubrod performance status						
0	0 (0.0)	1 (14.3)	3 (21.4)	9 (23.7)	7 (21.2)	20 (20.0)
1	7 (87.5)	6 (85.7)	8 (57.1)	21 (55.3)	22 (66.7)	64 (64.0)
2	1 (12.5)	0 (0.0)	3 (21.4)	8 (21.1)	4 (12.1)	16 (16.0)
Smoking history						
Never smoked	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (3.0)	2 (2.0)
Former smoker	6 (75.0)	4 (57.1)	11 (78.6)	25 (65.8)	20 (60.6)	66 (66.0)
Current smoker	1 (12.5)	1 (14.3)	3 (21.4)	7 (18.4)	6 (18.2)	18 (18.0)
Unknown	1 (12.5)	2 (28.6)	0 (0.0)	5 (13.2)	6 (18.2)	14 (14.0)
Pack-years*						
No. of patients	5	5	12	33	26	81
Median	62	80	52	42	34.625	45
Minimum-maximum	20-138	28-90	15-88	0-104	0-112.5	0-138
Q1-Q3	22-100	75-82.5	31.35-72.5	21-60	15.6-53	22.25-65
T stage						
T1	7 (87.5)	4 (57.1)	9 (64.3)	22 (57.9)	23 (69.7)	65 (65.0)
T2	1 (12.5)	3 (42.9)	5 (35.7)	16 (42.1)	10 (30.3)	35 (35.0)
Histology						
Squamous cell carcinoma	2 (25.0)	2 (28.6)	7 (50.0)	17 (44.7)	17 (51.5)	45 (45.0)
Adenocarcinoma	6 (75.0)	4 (57.1)	5 (35.7)	16 (42.1)	8 (24.2)	39 (39.0)
Bronchoalveolar carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	1 (1.0)
NSCLC NOS	0 (0.0)	1 (14.3)	2 (14.3)	5 (13.2)	7 (21.2)	15 (15.0)
Ultracentral						
No	8 (100.0)	6 (85.7)	11 (78.6)	27 (71.1)	30 (90.9)	82 (82.0)
Yes	0 (0.0)	1 (14.3)	3 (21.4)	10 (26.3)	3 (9.1)	17 (17.0)
Not able to be determined	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	1 (1.0)

(continued on following page)

TABLE 1. Baseline Characteristics of Patients by Dose Level (continued)

Characteristic	Dose Level, No. (%)					
	Level 5: 10.0 Gy/fx	Level 6: 10.5 Gy/fx	Level 7: 11.0 Gy/fx	Level 8: 11.5 Gy/fx	Level 9: 12.0 Gy/fx	Total
GTV (mL)†						
No. of patients	5	4	13	25	21	81
Median	11.23	6.91	9.48	14.76	14.86	11.2
Minimum-maximum	3.74-77.98	5.08-23.92	2.40-40.18	3.39-60.19	0.54-58.16	0.54-77.98
Q1-Q3	7.14-15.42	5.44-15.96	5.87-18.07	8.55-26.97	4.88-20.35	6.11-23.69
PTV (mL)						
Median	34.33	46.18	39.05	43.03	32.14	41.57
Minimum-maximum	17.82-160.32	19.26-89.05	12.30-114.56	14.85-155.05	7.48-117.25	7.48-160.32
Q1-Q3	23.03-43.98	26.20-69.49	31.01-65.39	28.03-77.02	18.94-58.67	25.76-66.32
Main organs at risk‡						
Brachial plexus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.1)	2 (2.0)
Esophagus	0 (0.0)	1 (14.3)	4 (28.6)	5 (13.2)	3 (9.1)	13 (13.0)
Heart	1 (12.5)	1 (14.3)	2 (14.3)	5 (13.2)	6 (18.2)	15 (15.0)
Main bronchus	1 (12.5)	0 (0.0)	5 (35.7)	17 (44.7)	13 (39.4)	36 (36.0)
Rib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	1 (1.0)
Small bronchi	4 (50.0)	1 (14.3)	3 (21.4)	5 (13.2)	6 (18.2)	19 (19.0)
Trachea	0 (0.0)	0 (0.0)	2 (14.3)	0 (0.0)	2 (6.1)	4 (4.0)
Vessel	2 (25.0)	5 (71.4)	5 (35.7)	20 (52.6)	7 (21.2)	39 (39.0)

Abbreviations: fx, fraction; GTV, gross tumor volume; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PTV, planning target volume; Q, quartile.

*Smoking history was solicited from the patient. Some patients did not report years smoked and/or number of cigarettes smoked per day.

†Not all patients had GTV data because sites were permitted to submit internal target volume instead.

‡Patients may have more than one organ at risk; percentages will not sum to 100.

patient in the 10.5 Gy/fx cohort 157 days after the start of SBRT; the patient was found unresponsive at home. The MTD (defined in the protocol as the dose at which the probability of DLT is closest to 20% without exceeding it) was the highest dose level tested at 12.0 Gy/fx. The probability of DLT in this arm was 7.25% (95% CI, 2.8% to 14.5%; Appendix Fig A1, online only).

Maximum toxicity (grade 3 or higher) reported at any time is listed in Table 3. No patients in the 10, 10.5, or 11 Gy/fx had a grade 3 AE during the first year, whereas four patients (12.1%) each in the 11.5 and 12 Gy/fx arms did. There was a minimal impact on patients' pulmonary function tests, with only two patients showing a grade 2 reduction in forced expiratory volume in 1 second and one patient showing a grade 2 reduction in diffusion lung capacity for carbon monoxide.

In terms of toxicity beyond the first year, four patients had grade 5 events, three in the 11.5 Gy/fx arm (one death not otherwise specified that occurred 439 days after the start of SBRT [possibly an esophageal ulcer that progressed and eroded into a major vessel, but no autopsy was performed] and two bronchopulmonary hemorrhages that occurred 462 and 1,972 days after the start of SBRT) and one in the 12 Gy/fx arm (bronchopulmonary hemorrhage that occurred 374 days after the start of SBRT).

Efficacy

Table 4 lists the relapses observed as well as number of patients with events observed. The 2-year local control rate (defined as absence of infield, marginal, or involved lobe failure) in the 11.5 Gy/fx cohort was 89.4% (90% CI, 81.6% to 97.4%) and in the 12.0 Gy/fx cohort, 87.9% (90% CI, 78.8% to 97.0%). These rates were statistically significantly higher than the prespecified control rate of 70% ($P < .001$ for both). Two-year PFS in the 11.5 Gy/fx cohort was 52.2% (95% CI, 35.3% to 66.6%) and in the 12 Gy/fx cohort, 54.5% (95% CI, 36.3% to 69.6%). Two-year OS was 67.9% (95% CI, 50.4% to 80.3%) and 72.7% (95% CI, 54.1% to 84.8%), respectively (Fig 2). Most deaths were a result of causes other than lung cancer (Table A4). Three-year outcomes are listed in Table 4 and shown in Figure 2.

DISCUSSION

NRG Oncology/RTOG 0813 was a unique phase I/II seamless multicenter study that used the TITE-CRM design

TABLE 2. DLTs by Dose Level (as Determined by Independent Review)

Treatment Arm	Evaluable Sample Size	No. of DLTs	Probability (95% CI)	DLTs	Grade	Days Since End of SBRT
Level 5: 10 Gy/fx	8	0	2.0 (0.6 to 5.1)			
Level 6: 10.5 Gy/fx	6	1	2.7 (0.8 to 6.5)	Death NOS	5	147
Level 7: 11 Gy/fx	13	1	4.3 (1.5 to 9.6)	Sinus bradycardia	5	130
Level 8: 11.5 Gy/fx	32	2	5.7 (2.1 to 12.0)	Hypoxia	3	88
				Hypoxia	3	166
Level 9: 12 Gy/fx	30	1	7.2 (2.8 to 14.5)	Pneumonitis	3	174
				Pleural effusion	3	264

Abbreviations: DLT, dose-limiting toxicity; fx, fraction; NOS, not otherwise specified; SBRT, stereotactic body radiotherapy.

to determine the MTD, toxicity, and outcomes of SBRT for centrally located early-stage lung cancer. The advantage of this design is that unlike the traditional 3 plus 3 phase I clinical trial design, there is no need to close the study to assess DLTs between dosing cohorts. This was of particular relevance for this study because the DLT time frame was 1-year post-SBRT, so the study would have been closed for extended periods before dose escalation. The study design allowed for immediate accrual at the MTD for assessment of phase II evidence of efficacy, and this led to a larger number of patients being treated at, or close to, the MTD. Thus, there is a more robust confidence in the toxicity profile at the two highest dose levels, although it should be emphasized that any toxicity beyond the first year did not influence the determination of MTD. This study design relies on prompt reporting of AEs because the dose assigned to a subsequent patient may need to be modified on the basis of toxicity observed. Study accrual was satisfactory, many centers participated, and data submission and quality of plans met the expectations.

In this study that assessed toxicity rates of a five-fraction SBRT schedule for centrally located NSCLC, we reached the highest dose level allowed by the protocol. Rates of high-grade toxicity prespecified as DLTs were relatively low; the highest dose level was associated with a 7.2% rate of DLTs on the basis of the Bayesian logistic model (95% CI, 2.8% to 14.4%), well below the protocol-specified target rate of 20%. Of note, serious toxicities beyond the first year were observed but not included in the definition of DLT per the study design. Observed 2-year local control (ie, absence of local progression) at the two highest dose levels achieved was high (89.4% and 87.7%, respectively). A 2-year OS of 70% in this medically inoperable group of mostly elderly patients with comorbidities compares favorably with an SBRT series for peripheral tumors.[2,5]

Several groups have reported on outcomes of SBRT for centrally located lung cancers. A systematic review in 2013 summarized 20 studies in 563 patients with centrally located NSCLC or metastases.[8] Local control rates were greater than 85% if a BED_{10} greater than 100 was used, treatment-related mortality was 2.7%, grade 3 to 4 toxicity was 9%, and OS was similar to that in patients with peripheral tumors. Given the heterogeneity of planning, SBRT delivery, toxicity recording, and variety of prescription doses used (48 to 60 Gy/4 fx; 35 to 60 Gy/5 fx; 48 to 60 Gy/8 fx), it was not possible to determine which schedule should be recommended.

Of note, there is no universally accepted definition of a centrally located cancer; in some series (including RTOG 0236[3]), it is a tumor within 2 cm of the PBT; in others,[9] it is a tumor within 2 cm of any mediastinal critical structure, including bronchi, esophagus, heart and major vessels, brachial plexus, spinal cord, phrenic nerve, and recurrent laryngeal nerve; and in still others (including our study), a tumor within 2 cm in all directions around the PBT and immediately adjacent to mediastinal or pericardial pleura (PTV touching the mediastinal pleura). The term ultracentral is relatively more recent[10,11] and also not uniformly applied.[9,12]

Several publications since the 2013 systematic review have reported single-center experiences with SBRT for central tumors. Some note no increase in toxicity[13,14] despite that patients with central tumors were treated with lower mean BED_{10} doses than those with peripheral tumors. Chang et al[15] treated 100 patients with central tumors with 50 Gy/4 fx (provided that dose volume constraints were met) with similar toxicities as peripheral lesions and high rates of local control. In contrast, Modh et al[16] reported higher toxicity rates in 125 patients with central tumors treated with three- to five-fraction schedules, especially for tumors less than 1 cm from the PBT.[9] Tekatli et al[17] reported on 80 patients with central (but not ultracentral) tumors treated with 60 Gy/8 fx with long median follow-up (47 months) and a 7.5% grade 5 toxicity. Their series of 47 patients with ultracentral tumors treated with 60 Gy/12 fx reported grade 3 or higher toxicity in 38% of patients; seven of 10 deaths were fatal lung hemorrhage (15% of the cohort).[12] The Stanford group[10] reported on 34 patients with central tumors,

TABLE 3. Maximum Toxicity (Grade 3 or Higher) Reported at Any Time

	Grade, No.											
	Level 6: 10.5 Gy/fx (n = 7)			Level 7: 11.0 Gy/fx (n = 14)			Level 8: 11.5 Gy/fx (n = 38)			Level 9: 12.0 Gy/fx (n = 33)		
System Organ Class Term	3	4	5	3	4	5	3	4	5	3	4	5
Worst overall	0	0	1	3	0	1	5	0	3	5	1	1
Cardiac disorders	0	0	0	0	0	0	0	0	0	2	0	0
Heart failure	0	0	0	0	0	0	0	0	0	1	0	0
Restrictive cardiomyopathy	0	0	0	0	0	0	0	0	0	1	0	0
Sinus bradycardia	0	0	0	0	0	1	0	0	0	0	0	0
GI disorders	0	0	0	0	0	0	1	0	0	1	1	0
Dysphagia	0	0	0	0	0	0	1	0	0	0	0	0
Esophageal pain	0	0	0	0	0	0	0	0	0	1	0	0
Esophageal perforation	0	0	0	0	0	0	0	0	0	0	1	0
Esophagitis	0	0	0	0	0	0	1	0	0	1	0	0
General disorders and administration site conditions	0	0	1	0	0	0	0	0	1	0	0	0
Death NOS	0	0	1	0	0	0	0	0	1	0	0	0
Investigations	0	0	0	0	0	0	2	0	0	0	0	0
Platelet count decreased	0	0	0	0	0	0	1	0	0	0	0	0
Weight loss	0	0	0	0	0	0	1	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	0	0	1	0	0	0	0	0
Anorexia	0	0	0	0	0	0	1	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	0	0	0	3	0	0	5	0	2	3	0	1
Atelectasis	0	0	0	1	0	0	1	0	0	0	0	0
Bronchopulmonary hemorrhage	0	0	0	0	0	0	0	0	2	0	0	1
Dyspnea	0	0	0	0	0	0	3	0	0	1	0	0
Hypoxia	0	0	0	1	0	0	2	0	0	1	0	0
Pleural effusion	0	0	0	0	0	0	0	0	0	1	0	0
Pneumonitis	0	0	0	1	0	0	0	0	0	1	0	0
Other	0	0	0	0	0	0	0	0	0	2	0	0
Vascular disorders	0	0	0	0	0	0	1	0	0	0	0	0
Hypertension	0	0	0	0	0	0	1	0	0	0	0	0

NOTE. All adverse events (AEs) were graded per Common Terminology Criteria for Adverse Events (version 4.0). No patients in level 5 experienced a grade 3 or higher AE. These toxicities are serious AEs (SAEs) reported as possibly, probably, or definitely a result of stereotactic body radiotherapy at any time after stereotactic body radiotherapy (ie, including dose-limiting toxicities, other SAEs within first year, and any SAEs after the first year).

Abbreviations: fx, fraction; NOS, not otherwise specified.

including seven with ultracentral tumors, treated with 50 Gy/4 to 5 fx. The grade 2 and higher toxicity rate was 22%, which is comparable to that for peripheral tumors; ultracentral tumors did not demonstrate higher toxicity or a significant difference in control rates, albeit with a short follow-up of 18.4 months. The Nordic multicenter phase II trial of 56 Gy/8 fx, reported in abstract form, observed 21 of 74 patients who experienced grade 3 or higher toxicity.[11]

The conclusion of most (although not all) of these series is that tumor location is an important predictor of toxicity. Heterogeneity of patients and their tumor locations as well as the various organs at risk and the differences in how SBRT is planned and delivered likely account for at least some of the observed differences in toxicities.

As would any study, this multicenter phase I/II study has its limitations. First, relatively few tumors were ultracentral; thus, other than bronchi and vessels, the other centrally located organs at risk (eg, esophagus) were overlapping the PTV in only a few patients. Thus, conclusions about what dose is tolerated by those organs have to be tempered by small numbers in whom those organs were truly at risk. Second, because limited numbers of patients were treated with the lower three dose levels, it is not possible to state

TABLE 4. Relapse Pattern and Outcomes

Relapse Pattern	Outcomes, No. (%)				
	Level 5: 10.0 Gy/fx (n = 8)	Level 6: 10.5 Gy/fx (n = 7)	Level 7: 11.0 Gy/fx (n = 14)	Level 8: 11.5 Gy/fx (n = 38)	Level 9: 12.0 Gy/fx (n = 33)
Failure at any time					
Infield	1 (12.5)	0 (0.0)	3 (21.4)	3 (7.9)	2 (6.1)
Marginal	1 (12.5)	0 (0.0)	2 (14.3)	1 (2.6)	4 (12.1)
Involved lobe	2 (25.0)	0 (0.0)	2 (14.3)	2 (5.3)	2 (6.1)
Primary tumor*	2 (25.0)	0 (0.0)	3 (21.4)	4 (10.5)	6 (18.2)
Local†	2 (25.0)	0 (0.0)	4 (28.6)	5 (13.2)	6 (18.2)
Regional	2 (25.0)	0 (0.0)	2 (14.3)	3 (7.9)	4 (12.1)
Distant	2 (25.0)	2 (28.6)	3 (21.4)	8 (21.1)	5 (15.2)
Local control rate, % (90% CI)					
1 year	100 (NA)	100 (NA)	100 (NA)	92.1 (86.8 to 100)	97.0 (90.9 to 100)
2 year	87.5 (62.5 to 100)	100 (NA)	85.7 (64.3 to 100)	89.4 (81.6 to 97.4)	87.9 (78.8 to 97.0)
3 year	75.0 (37.5 to 87.5)	100 (NA)	85.7 (64.3 to 100.0)	86.7 (78.5 to 94.7)	84.7 (72.7 to 93.9)
OS rate, % (95% CI)					
No. of deaths	8	6	9	25	20
1 year	100 (NA)	71.4 (25.8 to 92.0)	85.7 (53.9 to 96.2)	84.2 (68.2 to 92.6)	93.9 (77.9 to 98.4)
2 year	75.0 (31.5 to 93.1)	57.1 (17.2 to 83.7)	71.4 (40.6 to 88.2)	67.9 (50.4 to 80.3)	72.7 (54.1 to 84.8)
3 year	75.0 (31.5 to 93.1)	42.9 (9.8 to 73.4)	64.3 (34.3 to 83.3)	51.6 (34.7 to 66.2)	54.0 (35.6 to 69.2)
Median, months (95% CI)	41.6 (21.3 to 67.9)	25.8 (1.7 to 61.1)	51.4 (16.5 to NR)	38.1 (24.8 to 65.0)	39.7 (28.4 to NR)
PFS rate, % (95% CI)					
No. of failures	8	6	11	30	24
1 year	87.5 (38.7 to 98.1)	57.1 (17.2 to 83.7)	78.6 (47.2 to 92.5)	68.4 (51.1 to 80.7)	78.8 (60.6 to 89.3)
2 year	50.0 (15.2 to 77.5)	57.1 (17.2 to 83.7)	57.1 (28.4 to 78.0)	52.2 (35.3 to 66.6)	54.5 (36.3 to 69.6)
3 year	37.5 (8.7 to 67.4)	42.9 (9.8 to 73.4)	50.0 (22.9 to 72.2)	35.7 (20.8 to 50.8)	32.5 (17.3 to 48.6)
Median, months (95% CI)	23.4 (3.4 to 60.1)	25.8 (1.7 to 48.5)	38.0 (10.6 to 60.0)	24.8 (12.2 to 38.1)	26.8 (13.8 to 34.0)

Abbreviations: fx, fraction; NA, not applicable; NR, not reached; OS, overall survival; PFS, progression-free survival.
*Primary tumor failure = infield failure plus marginal failure.
†Local failure = primary tumor failure plus involved lobe failure.

that 55 to 60 Gy/5 fx is needed to achieve the high levels of tumor control that we observed. Third, although contouring, planning, and doses to organs at risk generally met protocol expectations, there were variations in contouring that may have affected the doses received. Moreover, although all centers had their SBRT delivery accredited, the actual data on the daily setup, target coverage, or technique to account for respiratory motion were not collected. Thus, any geographic misses or increased doses delivered to OARs could have occurred, although the high local control rate suggests that geographic misses were not common. The correlation of dosimetry with toxicity and any effect of different technological platforms is beyond the scope of this report. In addition, RECIST criteria used to assess local control in this study have significant limitations in the postradiotherapy setting.[18]

Despite these limitations, NRG Oncology/RTOG 0813 is an important study with implications for practice because the ability to treat patients with centrally located node-negative tumors in multiple institutions across the United States and Canada while maintaining plan qualities and achieving good patient outcomes and relatively modest rates of toxicity is an important achievement. Given the increasing age of patients with lung cancer and the concomitant increase in comorbidities, these patients are often at higher risk for surgery. Indeed, all patients accrued in this study were seen by an experienced thoracic surgeon and deemed medically inoperable. Thus, this study provides robust data about the safety and efficacy of a five-fraction SBRT schedule that is well tolerated and associated with relatively low rates of serious treatment-related toxicity.

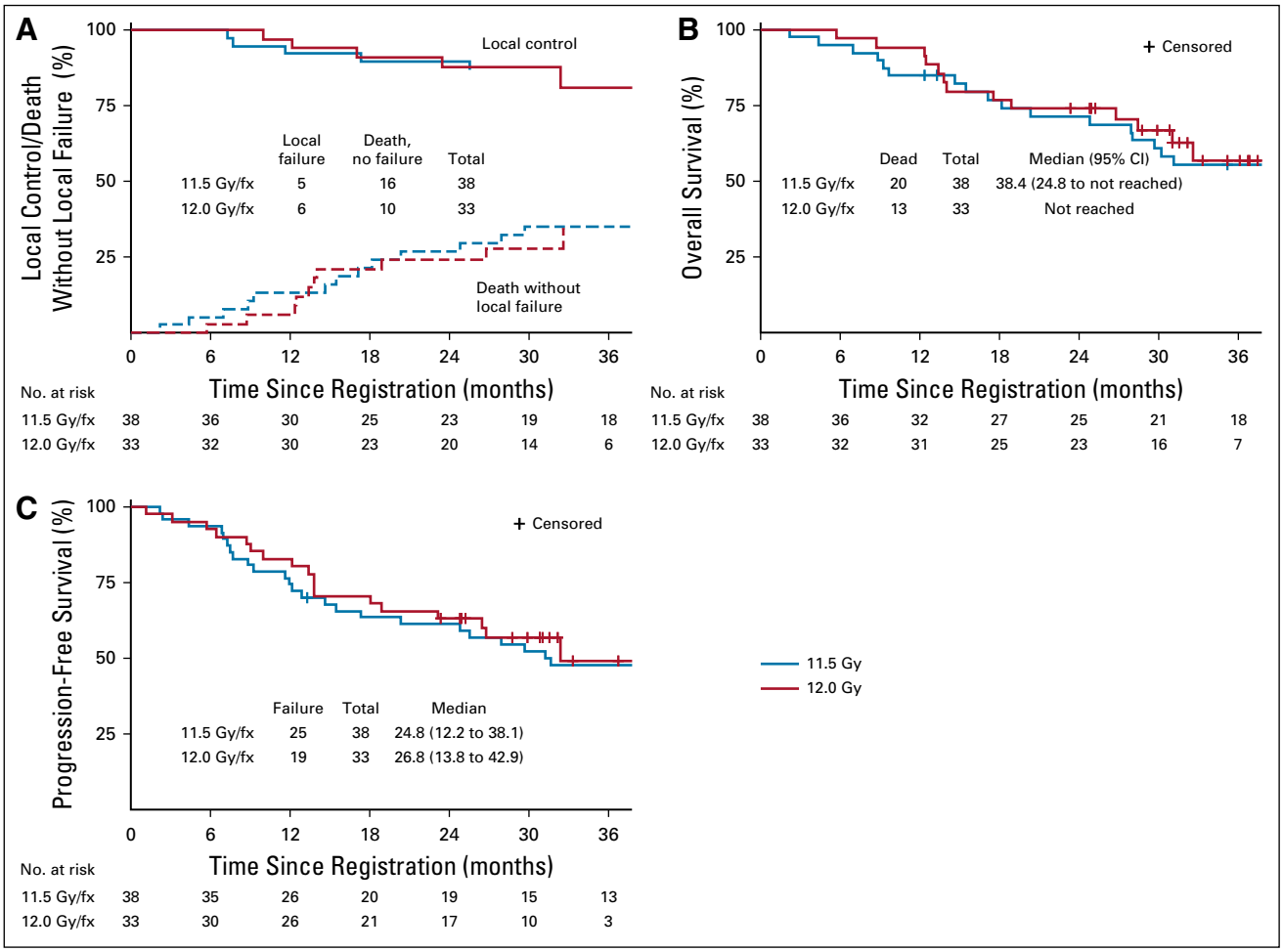

FIG 2. Outcomes for 11.5 and 12 Gy/fx cohorts. (A) Local control rates through 36 months. (B) Overall survival rates through 36 months. (C) Progression-free survival rates through 36 months. fx, fraction.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non–Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial

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No other potential conflicts of interest were reported.

APPENDIX

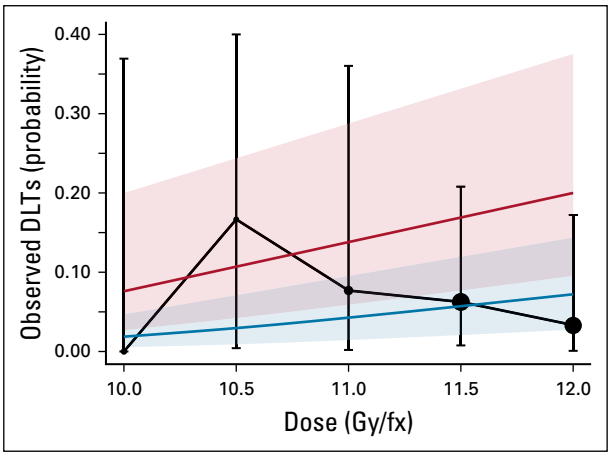

FIG A1. Dose-toxicity function. The red area is the prior distribution of the dose-toxicity function, and the blue area is the posterior distribution. Black lines connect the observed probabilities of dose-limiting toxicities (DLTs), and the diameters of the dots are proportional to the number of participants treated at each dose.

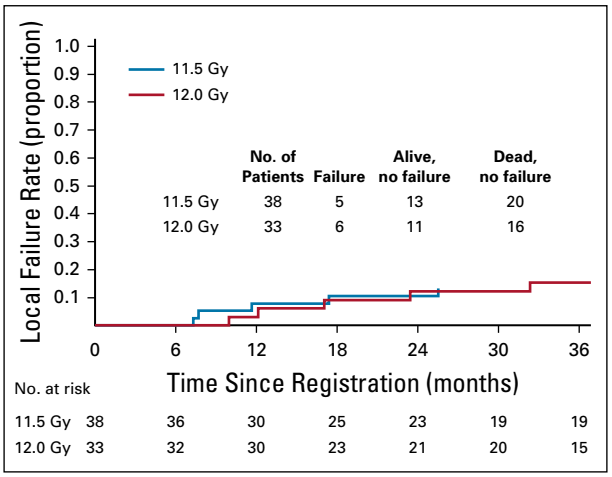

FIG A2. Local failure rate for the 11.5- and 12-Gy cohorts.

TABLE A1. Conformality Indices as Specified in the Protocol: PTV

	Deviation							
	Ratio of Prescription Isodose Volume to PTV		Ratio of 50% Prescription Isodose Volume to the PTV		Maximum Dose* (Gy)		Percent of Lung Receiving ≥ 20 Gy Total	
PTV (mL)	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

Abbreviation: PTV, planning target volume.
*In percentage of dose prescribed at 2 cm from PTV in any direction.

TABLE A2. Dose Limits Indices as Specified in the Protocol: Organs at Risk

Tissue	Volume (mL)	Volume Max, Gy (Gy/fx)	Max Point Dose, Gy (Gy/fx)	Avoidance End Point
Serial				
Spinal cord	< 0.25	22.5 (4.5)	30 (6)	Myelitis
	< 0.5	13.5 (2.7)		
Ipsilateral brachial plexus	< 3	30 (6)	32 (6.4)	Neuropathy
Skin	< 10	30 (6)	32 (6.4)	Ulceration
Parallel*				
Lung (right and left side)	1,500	12.5 (2.5)		Basic lung function
Lung (right and left side)	1,000	13.5 (2.7		Pneumonitis
Serial				
Esophagus, nonadjacent wall	< 5	27.5 (5.5)	105†	Stenosis/fistula
Heart/pericardium	< 15	32 (6.4)	105†	Pericarditis
Great vessels, nonadjacent wall	< 10	47 (9.4)	105†	Aneurysm
Trachea and ipsilateral bronchus, nonadjacent wall	< 4	18 (3.6)	105†	Stenosis/fistula

Abbreviations: fx, fraction; Max, maximum.
*Listed are critical volume and critical volume dose maximum.
†Percentage of planning target volume (PTV) prescription.

TABLE A3. Prespecified Dose-Limiting Toxicities

System	Adverse Events
Cardiac disorders, grades 3-5	Pericardial effusion Pericarditis Restrictive cardiomyopathy
GI disorders, grades 4-5	Dysphagia Esophagitis Esophageal fistula Esophageal obstruction Esophageal perforation Esophageal stenosis Esophageal ulcer Esophageal hemorrhage
Nervous system disorders, grades 3-5	Brachial plexopathy Recurrent laryngeal nerve palsy Myelitis
Respiratory, thoracic, and mediastinal disorders, grades 3-5*	Atelectasis (grade 4-5 only) Bronchopulmonary hemorrhage Mediastinal hemorrhage Pleural hemorrhage Tracheal hemorrhage Bronchial fistula Pulmonary fistula Bronchopleural fistula Tracheal fistula Hypoxia (provided grade 3 is worse than baseline) Bronchial obstruction Tracheal obstruction Pleural effusion Pneumonitis Pulmonary fibrosis
Changes in PFTs per the SBRT pulmonary toxicity scale, grades 3-5	FEV_1 decline (< 0.5 times the patient's baseline value) FVC decline (< 0.5 times the patient's baseline value)
Any grade 5 adverse event attributed to treatment	

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PFT, pulmonary function test; SBRT, stereotactic body radiotherapy.
*Except as noted.

TABLE A4. Causes of Death as Reported by Investigators

Cause of Death	Level 5: 10.0 Gy/fx (n = 8), No. (%)	Level 6: 10.5 Gy/fx (n = 6), No. (%)	Level 7: 11.0 Gy/fx (n = 9), No. (%)	Level 8: 11.5 Gy/fx (n = 25), No. (%)	Level 9: 12.0 Gy/fx (n = 20), No. (%)
As a result of the disease	1 (12.5)	2 (33.3)	1 (11.1)	9 (36.0)	4 (20.0)
Second primary or other malignancy	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
Protocol treatment	0 (0.0)	0 (0.0)	0 (0.0)	3 (12.0)	1 (5.0)
Other cause	2 (25.0)	2 (33.3)	3 (33.3)	7 (28.0)	10 (50.0)
Unknown	4 (50.0)	2 (33.3)	5 (55.6)	6 (24.0)	4 (20.0)

NOTE. Cause of death is as reported by the site.
Abbreviation: fx, fraction.