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ORIGINAL REPORT

Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
Patients with stage IV non–small-cell lung cancer (NSCLC) who progress through first-line therapy have poor progression-free survival (PFS) and overall survival (OS), most commonly failing in original sites of gross disease. Cytoreduction with stereotactic body radiation therapy (SBRT) may help systemic agents delay relapse.

Patients and Methods
Patients in our single arm phase II study had stage IV NSCLC with no more than six sites of extracranial disease who failed early systemic chemotherapy and were able to receive SBRT and concurrent erlotinib until disease progression. After erlotinib commencement, SBRT with equipotent fractionation was delivered to all sites of disease. PFS, OS, and other end points were evaluated.

Results
Twenty-four patients (13 men and 11 women) with a median age of 67 years (range, 56-86 years) were enrolled with median follow-up of 11.6 months. All patients had progressed through platinum-based chemotherapy. A total of 52 sites were treated with 16 of 24 patients receiving SBRT to more than one site. Lung parenchyma was most often irradiated. Median PFS was 14.7 months, and median OS was 20.4 months. Most patients progressed in new distant sites with only three of 47 measurable lesions recurring within the SBRT field. Two grade 3 toxicities were radiation related. Zero of 13 patients tested were positive for an *EGFR* mutation.

Conclusion
Use of SBRT with erlotinib for unselected patients with stage IV NSCLC as a second- or subsequent line therapy resulted in dramatic changes in patterns of failure, was well tolerated, and resulted in high PFS and OS, substantially greater than historical values for patients who only received systemic agents.

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INTRODUCTION

Stage IV non–small-cell lung cancer (NSCLC), presenting in two thirds of all patients with this disease, remains poorly controlled with 12-month median survival following only first-line chemotherapy.[1-4] Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor originally approved for all patients with locally advanced NSCLC after failure of at least one prior chemotherapy regimen, contributing to a median progression-free survival (PFS) and overall survival (OS) of 2.3 and 6.7 months, respectively.[5]

Stereotactic body radiation therapy (SBRT) is a local radiation technique that delivers high-doses of radiation in limited treatments to extracranial malignant disease.[6-7] SBRT has proven efficacy in the treatment of patients with early-stage, medically inoperable NSCLC,[8] with an emerging indication in the setting of limited metastatic disease.[9-20]

For the majority of patients with stage IV NSCLC who progress through first-line or subsequent systemic therapy without an actionable mutation, options and survival are insufficient.[21-22] Patients with limited metastatic disease, however, could potentially have lengthened PFS if sites of

malignant deposits were controlled locally with surgery or radiation.[23-29] In reviewing patterns of relapse after chemotherapy alone, the majority of treatment failures in the stage IV setting occur at sites of original gross disease. Furthermore, more than half of patients have metastatic distributions amenable to the delivery of SBRT.[30]

We proposed a single-arm phase II study to determine if cytoreductive SBRT plus erlotinib could prolong PFS compared with historical findings at or beyond second-line therapy for patients with metastatic NSCLC with limited sites of disease. This effort tested the tenets of the Norton-Simon hypothesis, which suggests that optimal efficacy in systemic therapy tumor-cell kill is dependent on natural tumor growth kinetics.[31]

PATIENTS AND METHODS

Study Design

This phase II single-arm trial was designed to synergize SBRT in debulking malignant deposits with erlotinib as systemic therapy. The primary objective of this study was 6-month PFS. Secondary objectives included in-field local control, out-of-field disease progression, OS, safety of erlotinib in combination with SBRT, and patient initiation on subsequent line systemic therapy. The study was approved by University of Texas Southwestern and University of Colorado Institutional Review Boards.

Patients

Patients were eligible for enrollment if they were age $\geq$ 18 years, with Karnofsky performance score greater than 60, had biopsy proven stage IV NSCLC with up to six active extracranial lesions ($\leq$ 3 in liver and lung parenchyma each) identified by positron emission tomography and seen on correlative computed tomography (CT)/magnetic resonance imaging within 8 weeks before the initiation of SBRT, and had disease progression through at least one prior chemotherapy regimen. Patients with known pulmonary dysfunction to receive SBRT for lung tumors were required to have a documented forced expiratory volume in 1 second $\geq$ 1L. Conditions for ineligibility included untreated brain metastases or brain metastases treated within the previous 3 months, patients with metastatic disease invading the esophagus, stomach, intestines, mesenteric lymph nodes, or skin, and patients previously treated with EGFR inhibitors.

Radiation Technique

Patients were immobilized in a vacuum-type or equivalent body mold and a planning CT scan with 3- to 5-mm slices was performed. Contrast was recommended for lesions near mediastinal structures and lesions within the liver/adrenals. At the time of SBRT simulation for thoracic and abdominal lesions, the movement of the diaphragm was observed under fluoroscopy or other acceptable means to define respiratory motion. Patients were assessed for suitability and tolerance of a respiratory control device using a breath-hold technique, respiratory gating, or abdominal compression to limit diaphragmatic motion. For treatment of all sites, each individual gross tumor volume (GTV) was contoured. The planning target volume for each contoured GTV was at least 5 mm larger than the GTV. Four-dimensional CTs were routinely performed on thoracic and abdominal lesions needing treatment, with internal target volumes used for planning. Critical normal structures were contoured for treatment planning purposes.

The SBRT prescription dose was prescribed to the periphery of the planning target volume in 1, 3, or 5 fractions. While allowing physician choice, all compliant doses were considered tumor equivalent according to the Universal Survival Model (alpha = 0.33 Gy$-$1, D_o = 1.25 Gy, Dq = 1.8 Gy).[32-34] Accepted single fraction cumulative doses included 19 to 24 Gy (with minor protocol deviation of $\geq$ 14 Gy and $<$ 19 Gy per fraction and major deviation if $<$ 14 Gy or $>$ 24 Gy per fraction). Accepted 3 fraction cumulative doses included 27 to 33 Gy (with minor protocol deviation with $\geq$ 22 Gy or $<$ 27 Gy cumulative dose in 3 fractions and major protocol deviation if $<$ 22 Gy or $>$ 33 Gy). Accepted 5 fraction cumulative doses included 35 to 40 Gy (with minor protocol deviation if $\geq$ 30 Gy or $<$ 35 Gy cumulative dose in 5 fractions and major protocol deviation if $<$ 30 Gy or $>$ 40 Gy). Patients treated to one site had two to three treatments per week. For those treated to multiple sites, no more than two sites were treated on any given day. Quality assurance by the radiation oncology principal investigators of the study was performed on all cases.

Study Medication

Erlotinib administration began 1 week before SBRT at a dose of 150 mg/day and continued during and after SBRT until disease progression or intolerable toxicity. Evaluation of *EGFR* mutation status was not mandatory in the work-up of patients enrolled on the trial. If a patient experienced protocol defined toxicity from erlotinib, dose adjustments were made based on the greatest degree of toxicity (ie, reducing the dose to the next lowest level, ie, 100 mg/day). If significant toxicity was still apparent, the dose was reduced a second time. Any patient who failed to tolerate treatment of 50 mg/day was withdrawn from the study.

Follow-Up

Evaluation of study end points began from the start of protocol therapy. All patients were followed at 3-month intervals/6-month minimum with CT of the chest/abdomen, physical examination, and laboratory tests including CBC/complete metabolic panel. Subsequent work-up was based on suspicion of progression or toxicity. All evaluations of disease response used RECIST criteria.

Failure of the primary end point occurred with progression at any site. However, progressing patients could remain on study, including continuation of erlotinib, if all progressive sites were outside any previously treated radiation area and amenable to treatment with SBRT. This subset of patients progressing but continuing erlotinib was followed separately for determining long-term sustainability of erlotinib therapy. Local failure (in-field and marginal) was defined as progressive consolidation (CT imaging changes consistent with but not diagnostic of tumor recurrence/progression, also known as progressive enlargement as defined in all of the Radiation Therapy Oncology Group [RTOG] SBRT trials) within 1 cm of SBRT treatment site, typically at standard uptake values similar to pretreatment levels and not consistent with benign radiation-induced changes. As per RTOG guidelines, if such changes were not diagnostic of tumor recurrence, positron emission tomography or tissue-directed biopsy was required to declare a local failure. In cases where this was only clarified with serial imaging, failure was scored from the first radiographic appearance of the abnormality.

Statistical Analysis

The predicted rate of PFS of treated subjects at a follow-up interval of 6 months was the determinant of sample size. For any individual patient, progressive disease within any SBRT-treated lesion or distantly was scored as progressive disease for that patient. A 6-month PFS rate of 20% or less was not considered worthy of further investigation, whereas PFS probability of 55% or higher was considered worthy of future investigation. An exact binomial test with a nominal 0.050 two-sided significance level was predicted to have 86% power to detect the difference between the null hypothesis proportion of 20% PFS rate and the alternative proportion of 55% PFS rate with the sample size of 20 patients. To assure an adequate number of evaluable patients, allowing for patients who would be lost to follow-up or otherwise nonevaluable, a total of 24 patients were enrolled.

The primary outcome was evaluated using an exact test for a single proportion. The rate of local control of treated lesions, a secondary outcome, was reported with an exact 95% CI. All safety measures were reported using descriptive statistics (mean, median, standard deviation, proportions, and 95% CIs).

There was an early stopping rule for unexpected toxicity. If at any point during the study more than one sixth of patients treated to date experienced treatment-related grade 4 to 5 toxicity of any kind (hematologic, pulmonary, etc), study enrollment would be suspended. Depending on the nature of toxicity and its relevance to erlotinib or SBRT, the dose of either intervention

Table 1. Baseline Characteristics of Patients Treated on Protocol

Characeristic	No.	%
Sex		
Female	11	46
Male	13	54
Age, years		
Median	66.9	
Standard deviation	7.6	
Range	56-86	
Previously treated brain metastases		
No	22	92
Yes	2	8
Follow-up, months		
Mean	16.8	
Standard deviation	14.5	
Range	3.4-60.3	
Study site		
University of Colorado	6	25
UT Southwestern Medical Center	18	75
Survival, last follow-up		
Alive	11	46
Dead	13	54
No. of previous systemic therapy regimens		
1	15	63
2	7	29
3	2	8
Race		
White, Hispanic	23	96
African American	1	4

Table 2. SBRT Treatment Patterns

Treatment Pattern	No.	%
SBRT sites treated per patient		
1	8	33
2	8	33
3	5	21
4	2	9
5	1	4
SBRT courses to specific sites		
18	Lungs (35% of 52 sites treated)	
13	Mediastinum/hilum (25)	
7	Adrenals (13)	
6	Bone/spine/chest wall (13)	
4	Liver/paracaval (8)	
3	Nonmediastinal lymph nodes (5)	
1	Kidney (1)	
Lesions treated with specific SBRT fractionation schemas		
21	3 fx to 27-33 Gy (40)	
21	5 fx to 35-40 Gy (40)	
10	1 fx to 19-20 Gy (20)	

Abbreviations: fx, fractions; SBRT, stereotactic body radiation therapy.

might have been modified by amendment to the protocol, requiring institutional review board reapprovals.

RESULTS

Twenty-four patients with stage IV NSCLC with six or fewer sites of disease after progressing through first-line or subsequent systemic therapy were enrolled onto the study between 2007 and 2013 (Table 1). Mean follow-up was 16.8 months with a standard deviation of 14.5 months (range, 3.4-60.3 months). The majority of patients (21 of 24) received platinum-based chemotherapy, fourteen with docetaxel and seven with pemetrexed as part of a doublet regimen. Fifteen patients were accrued onto trial after failing first-line therapy, seven after failing second-line therapy, and two were added after failing third-line therapy.

All patients had every site of disease treated with SBRT as physician intended (Tables 2 and 3). Forty-eight out of 52 lesions were treated without major study deviation (other lesions treated with dose variation out of patient choice/anatomic consideration). Sixteen of 24 patients had two or more sites treated with SBRT. Lung parenchyma was the most common site of SBRT treatment (18 courses) followed by mediastinal/hilar nodes (13 courses). Twenty-one lesions were treated with 3 fractions, 21 lesions with 5 fractions, and 10 lesions with 1 fraction.

Patients received erlotinib from 1 to 3 weeks before SBRT till taken off study due to progression not further manageable by SBRT or by patient choice. The range of erlotinib use was from 24 days to 847 days. Patients on average stayed on erlotinib for 273 days with a median use of 183 days. Ten out of 24 patients needed an erlotinib dose modification below 150 mg daily due to diarrhea, rash, and fatigue.

Forty-seven sites of disease treated in 21 patients were evaluable with baseline and minimum 3-month follow-up CT based imaging. The other three patients died or had not otherwise reached this window for evaluation. At the first 3-month follow-up CT scan, 10 of 47 treated lesions were not visible with any obvious tumor volume. Twenty-four other lesions (45% of all evaluable lesions) had at least 30% tumor reduction at month 3. No SBRT-treated lesions progressed until 9 months. On univariable analysis, there was no difference in tumor response based on treatment dose, fractionation, or location of disease.

At last follow-up, 11 of 24 patients were alive. By Kaplan-Meier actuarial analysis, median progression-free survival was 14.7 months and median overall survival 20.4 months (Figs 1 and 2). Thirteen of 24 patients had longer than 6-months follow-up without progression before month 6. Of the 11 patients with less than 6-months follow-up, six patients had progressed and five had not. Since the binomial test does not have a natural mechanism for handling censoring, we estimated the PFS rate at month 6 using Kaplan-Meier analysis to be 69%. Based on the initial statistical discourse, our treatment was considered worthy of further investigation.

There were only three local SBRT failures out of 47 lesions evaluable, presenting at 9 months after treatment. Out of 21 patients, three patients failed within only one of their radiation fields, ten failed at new distant sites outside of their radiation fields, and 10 patients had not recurred at last follow-up (Table 4). Three patients had four recurrences not within original radiation fields and were kept on protocol for analysis of secondary end points while continuing to receive erlotinib. New sites of recurrence in these patients given SBRT

Table 3. Patient Clinical Profiles

Patient ID	KPS	Site	Total Dose/ Fractions	OS From Treatment Start (days)	Time to Progression or Last Follow-Up (days)	Alive	*EGFR* Status	Further Systemic Therapy After Discontinuation From Trial
1	100	Liver	40/5	121	68	No	Unknown	No
2	80	Lung	33/3	203	145	No	Negative	No
2	—	Adrenal	40/5	—	—		—	—
2	—	Adrenal	40/5	—	—		—	—
3	90	Adrenal	40/5	621	322	No	Negative	No
4	90	Lung	33/3	1,809	1,809	Yes	Negative	No
5	70	Adrenal	40/2	299	128	Yes	Unknown	No
5	—	Rib	22/3	—	—		—	—
6	100	Chest wall	19/1	103	103	No	Unknown	No
6	—	Lung	27/3	—	—		—	—
6	—	Scapula	19/1	—	—		—	—
7	100	Lung	40/5	1,020	536	Yes	Unknown	Yes
8	80	Hilum/mediastinum	33/3	120	87	No	Negative	No
8	—	Mediastinum	19/1	—	—		—	—
9	100	Lung	40/5	556	456	No	Negative	Yes
9	—	Spine	20/1	—	—		—	—
10	90	Mediastinum	18/3	204	102	No	Unknown	No
10	—	Axilla	19/1	—	—		—	—
10	—	Mediastinum	18/3	—	—		—	—
10	—	Liver	24/3	—	—		—	—
10	—	Lung	19/1	—	—		—	—
11	90	Axilla	30/5	423	184	No	Unknown	No
11	—	Adrenal	35/5	—	—		—	—
12	100	Lung	40/5	144	70	Yes	Unknown	No
13	90	Lung	35/5	1,281	1,259	Yes	Unknown	No
13	—	Lung	35/5					—
13	—	Lung	35/5					—
14	100	Mediastinum	27/3	612	96	No	Unknown	Yes
14	—	Kidney	35/5	—	—		—	—
15	100	Mediastinum	14.5/1	1026	518	No	Negative	Yes
15	—	Lung	27/3	—	—		—	—
15	—	Lung	30/3	—	—		—	—
15	—	Lung	30/3	—	—		—	—
16	90	Lung	33/3	248	135	No	Negative	Yes
16	—	Ilium	20/1	—	—		—	—
17	90	Lung	33/3	800	800	No	Negative	No
18	100	Adrenal	33/3	862	440	Yes	Negative	Yes
18	—	Hilum	40/5	—	—		—	—
18	—	Hilum	40/5	—	—		—	—
19	90	Supraclavicular basin	35/5	183	68	No	Unknown	No
19	—	Mediastinum	35/5	—	—		—	—
19	—	Lung	33/3	—	—		—	—
20	80	Hilum	40/5	402	312	Yes	Negative	Yes
20	—	Spine	20/1	—	—		—	—
20	—	Liver	19/1	—	—		—	—
20	—	Liver	33/3	—	—		—	—
21	100	Mediastinum	40/5	225	204	Yes	Unknown	No
22	100	Lung	33/3	395	395	Yes	Negative	No
22	—	Mediastinum	33/3	—	—		—	—
23	80	Mediastinum	30/3	297	297	Yes	Negative	No
24	90	Lung	33/3	137	129	Yes	Negative	Yes
24	—	Adrenal	35/5	—	—		—	—

Abbreviations: KPS, Karnofsky performance score; OS, overall survival.

again included the hilum (2 failures), thoracic spine, and liver. PFS after a second round of SBRT was 6 to 9 months.

Univariable Cox regression analysis identified clinical factors that correlated with OS and PFS (Appendix Tables A1 and A2, online only). For OS, the number of SBRT-treated sites was positively associated with higher death rate ($P = .040$, hazard ratio = 1.512). There was 1.5 times greater chance of death for each increment of one site treated. The increase in number of SBRT-treated sites also

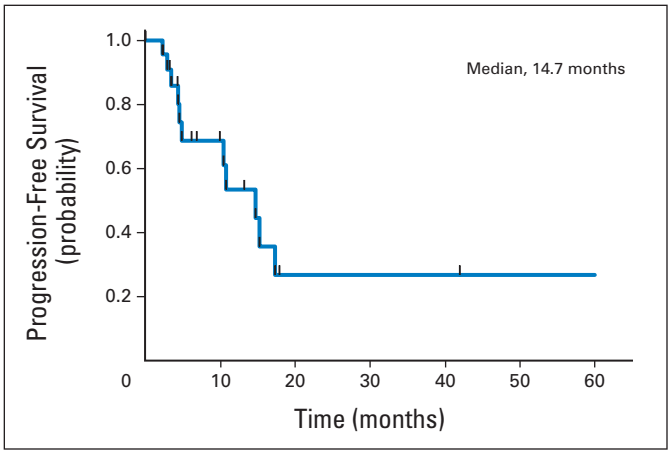

Fig 1. Kaplan-Meier analysis of progression-free survival (PFS) in months for all 24 patients enrolled on the study.

corresponded to patients with greater disease burden, however. Patients with intrathoracic treatment had a lower chance of progression than those receiving extrathoracic treatment (P = .018, hazard ratio = 0.080).

The majority of study patients (19 of 24) presented with Karnofsky performance scores of 90 to 100, which were maintained throughout the trial period. SBRT relevant toxicity included: one of 13 grade 5 toxicities possibly related, one of four grade 4 toxicities possibly attributable to SBRT but three of four definitely related to erlotinib use, and two of 24 grade 3 toxicities definitely related to radiation—pneumonitis and back pain secondary to vertebral compression fracture. The grade 5 toxicity possibly attributable to SBRT involved a patient who developed acute respiratory distress syndrome/pneumonia 3 months after SBRT to three sites—a left parenchymal lung lesion given 27 Gy in 3 fractions, a right scapular metastasis given 19 Gy in 1 fraction, and a right anterior chest wall metastasis given 19 Gy in 1 fraction. This patient presented with reduced pulmonary function by pulmonary function tests and had two previous lines of systemic therapy. The same patient developed hypoxia before the acute respiratory distress syndrome/pneumonia related death and experienced

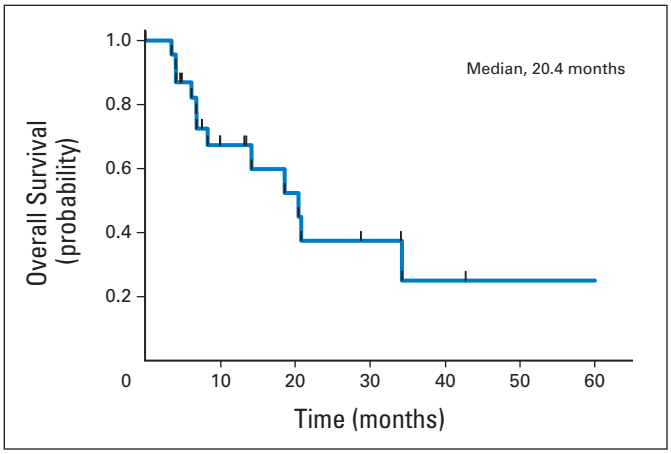

Fig 2. Kaplan-Meier analysis of overall survival (OS) in months for all 24 patients enrolled on the study.

Table 4. Patterns of Failure

Pattern	No. Out of 21 Patients	%	No. Out of 47 Total Evaluable Lesions Treated With SBRT	%
Sites of failure by patient				
Within SBRT-treated area (in-field failure)	3	14	3	6
Outside of SBRT-treated area (OFF)	10*	48	N/A	N/A
No failures	10	48	N/A	N/A

OFF Sites	No. of Failures	Percentage of Total OFFs	Percentage of 10 Patients With OFFs
Thorax	6	43	60
Liver	3	21	30
Brain	2	14	20
Pancreas	1	7	10
Lymph node	1	7	10
Spine	1	7	10

Abbreviations: OFF, out-of-field failure; SBRT, stereotactic body radiation therapy.
*Two of three in-field failures occurred in patients with OFFs.

the only grade 4 toxicity possibly related to SBRT use as well (Appendix Table A3, online only).

At trial commencement, mutational evaluation for *EGFR* was not routine. Mutational analysis was conducted on tumor specimens from 13 of the 24 patients. Of the 13 evaluable lesions, none had an *EGFR* exon 19/21 mutation as determined by polymerase chain reaction.

DISCUSSION

Local therapies including surgery and radiation have impacted cure rates and survival in selected metastatic patients with oligometastases, corresponding to an intermediate step between initial propensity to disseminate and overt, widespread dissemination,[35] particularly in colorectal cancer and sarcomas. In cancers where this window is narrow, like advanced NSCLC, local therapies have been typically only of palliative benefit and life-prolonging treatment has consisted of systemic therapy alone regardless of tumor burden, offering patients without actionable mutations a median OS of 1 year.[1-3] Most who fail first-line therapy do so in original sites of gross disease and have limited options.[21-22] Studies have previously shown that at least 53% of these patients would have lesions amenable to SBRT.[30] While these patients might not be defined as having oligometastatic disease by classic definitions, we nonetheless postulated that an aggressive local and systemic therapy approach may prolong PFS and OS. This trial safely delivered cytoreductive doses of SBRT concurrently with erlotinib in patients with advanced stage NSCLC with up to six locations of metastatic disease who progressed through systemic therapy. SBRT was delivered to a variety of locations and to two or more sites in 15 of 24 patients without unacceptable toxicity.

The PFS (14.7 months) and OS (20.4 months) for patients in our cohort were superior to patients with stage IV NSCLC who historically

received systemic therapy and progressed through first and subsequent lines of cytotoxic chemotherapy (2- to 4-month median PFS, 6- to 9-month OS).[21-22] Furthermore, the survival benefits were significantly higher than patients with stage IV disease who respond to first-line therapy and go on to receive maintenance chemotherapy.[36] Our approach dramatically changed the pattern of relapse, with a shift in failure from existing sites (ie, local) to new sites (ie, distant). One third of patients were able to receive additional cytotoxic chemotherapy after progression on our trial, with SBRT potentially allowing this subset to tolerate subsequent agents by delaying continued use.

EGFR status was evaluated in 13 of 24 patient tumors with none harboring mutations. The absence of an *EGFR* mutation in more than half of the cohort suggests that SBRT was the driver of the prolonged PFS. We conducted the log-rank test and found no significant differences in OS ($P = .552$) and PFS ($P = .408$) between patients with unknown versus negative *EGFR* tumor mutation status. With inclusion of patients with *EGFR* mutation positive tumors or an alternative systemic therapy, PFS and OS may have been even greater with SBRT.

Caveats of the trial include the relatively small sample size, absence of randomization, and the lack of known *EGFR* mutation positive patients. Classically, oligometastatic patients have few lesions (1-3 to 1-5) that are targeted with surgery or SBRT with durable PFS and OS. Experiences in treating oligometastatic stage IV NSCLC have been primarily single institution or retrospective in nature but have shown promising results.[9-16] Our study enriched for patients with limited metastatic disease amenable to SBRT, introducing some advantage when comparing our outcomes with those of second-line or maintenance studies with all comers of stage IV NSCLC. We acknowledge that our local therapy approach may not be ideal for all patients with metastatic NSCLC, especially those with widespread disease. Furthermore, patients with limited metastases may have biology that allows them to have longer survival independent of the success of local or systemic therapies. However, with studies suggesting that 53% of patients that advanced NSCLC would have SBRT-treatable metastases after first-line therapy, a significant proportion of patients could potentially benefit.

Future studies may involve SBRT as part of first-line approaches for limited metastatic disease with systemic therapy or as stand-alone treatment. A multi-institutional study is currently accruing patients with advanced cancers, randomizing to standard therapy or SBRT plus standard therapy in the setting of limited metastatic disease.[37] It is likely that the European study and future studies in the United States will attempt to identify the subset of patients most likely to benefit from aggressive local therapy.[38] Our group and others have initiated trials comparing maintenance therapies with SBRT plus maintenance therapies for limited metastatic disease in the extended first-line setting.

In conclusion, our phase II study demonstrated a significant outcome for SBRT and erlotinib use in patients with mutation unselected, limited metastatic NSCLC who progressed through chemotherapy. A median PFS of 14.7 months and OS of 20.4 months in a group of patients who historically have done poorly encourages consideration of a new treatment paradigm with the inclusion of aggressive noninvasive local therapy in the form of SBRT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Appendix

Table A1. Univariable Cox Regression Analysis for Overall Survival

Variable	Parameter Estimates	Standard Error	*P*	Hazard Ratio
Age	−0.042	0.043	.326	0.959
Female	0.137	0.564	.808	1.147
Erlotinib dose reduction	−0.769	0.617	.212	0.463
Intrathoracic	−0.924	0.634	.146	0.397
Prior systemic regimens	−0.040	0.429	.925	0.961
SBRT-treated sites	**0.413**	**0.202**	**.040**	**1.512**

NOTE. The number of treated sites was positively associated with higher death rate. There is 1.5 times higher chance of death for an increment of 1 site treated. Bolded data shows that stepwise Cox regression analysis was conducted to identify the prognostic features associated with time to death. Number of SBRT-treated sites was the only significant prognostic factor associated with time to death, correlating with overall disease burden.
Abbreviation: SBRT, stereotactic body radiation therapy.

Table A2. Univariable Cox Regression Analysis for Progression-Free Survival

Variable	Parameter Estimates	Standard Error	*P*	Hazard Ratio
Age	−0.058	0.045	.202	0.944
Female	0.072	0.615	.907	0.931
Erlotinib dose reduction	−0.845	0.639	.186	0.430
Intrathoracic	**−2.530**	**1.071**	**.018**	**0.080**
Prior systemic regimens	0.422	0.400	.291	1.525
SBRT-treated sites	0.426	0.227	.061	1.530

NOTE. Patients with intrathoracic SBRT treatments had significantly less chance of progression than those with extrathoracic SBRT treatments.
Abbreviation: SBRT, stereotactic body radiation therapy.

Table A3. Toxicity

Adverse Events	Number (% of all events)
Grade 5	13*
Grade 4	4†
Grade 3	24‡

*Only one patient with acute respiratory distress syndrome (ARDS)/pneumonia had a possible toxicity attribution to stereotactic body radiation therapy (SBRT). Other patient deaths were not attributable to therapy on trial but progression of disease or other medical event.
†Out of four grade 4 events, diarrhea and fatigue were definitely related to therapy (erlotinib); hypoxia was possibly related to SBRT (same patient who developed grade 5–related ARDS); and motor neuropathy unlikely related to SBRT.
‡Only two of 24 events were definitely attributable to SBRT—vertebral body compression and radiation pneumonitis.