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Evaluation of Safety of Stereotactic Body Radiotherapy for the Treatment of Patients With Multiple Metastases

Findings From the NRG-BR001 Phase 1 Trial

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Key Points

Question

Can ablative radiation schedules designed for single tumors be used when treating patients with 3 to 4 metastases or 2 metastases in close proximity to each other?

Findings

In this National Cancer Institute–sponsored phase 1 trial, 35 patients with oligometastatic breast, prostate, or non–small cell lung cancer were treated with ablative radiation. Standard doses were safe in all 35 evaluable patients, with a median of 3 metastases; there were no protocol-defined dose-limiting toxicities, and more than 50% of patients were alive at 2 years.

Meaning

Standard ablative radiation schedules appear to be safe for patients with oligometastatic disease with 3 to 4 metastases or 2 metastases in close proximity to each other; ongoing National Cancer Institute trials were expanded to include these patients.

This phase 1 nonrandomized controlled trial uses data from NRG Oncology trials to investigate if ablation radiotherapy schedules designed for use with single tumors can be used in patients with oligometastases (2-4 tumors).

Abstract

Importance

Stereotactic body radiotherapy (SBRT) for oligometastases is hypothesized to improve survival and is increasingly used. Little evidence supports its safe use to treat patients with multiple metastases.

Objective

To establish safety of SBRT dose schedules in patients with 3 to 4 metastases or 2 metastases in close proximity to each other.

Design, Setting, and Participants

This phase 1 trial opened on August 4, 2014, and closed to accrual on March 20, 2018. Metastases to 7 anatomic locations were included: bone/osseous (BO), spinal/paraspinal (SP), peripheral lung (PL), central lung (CL), abdominal-pelvic (AP), mediastinal/cervical lymph node (MC), and liver (L). Six patients could be enrolled per anatomic site. The setting was a consortium of North American academic and community practice cancer centers participating

in NRG Oncology trials. Patients with breast, prostate, or non–small cell lung cancer with 3 to 4 metastases or 2 metastases in close proximity (≤5 cm) amenable to SBRT were eligible for this phase 1 study. Statistical analyses were performed from December 31, 2017, to September 19, 2019.

Interventions

The starting dose was 50 Gy in 5 fractions (CL, MC), 45 Gy in 3 fractions (PL, AP, L), and 30 Gy in 3 fractions (BO, SP).

Main Outcomes and Measures

The primary end point was dose-limiting toxicity (DLT) defined by the Common Terminology Criteria for Adverse Events, version 4.0, as specific adverse events (AEs) of grades 3 to 5 (definite or probable per the protocol DLT definition) related to SBRT within 180 days of treatment. Dose levels were considered safe if DLTs were observed in no more than 1 of 6 patients per location; otherwise, the dose at that location would be de-escalated.

Results

A total of 42 patients enrolled, 39 were eligible, and 35 (mean [SD] age, 63.1 [14.2] years; 20 men [57.1%]; 30 White patients [85.7%]) were evaluable for DLT. Twelve patients (34.3%) had breast cancer, 10 (28.6%) had non–small cell lung cancer, and 13 (37.1%) had prostate cancer; there was a median of 3 metastases treated per patient. Median survival was not reached. No protocol-defined DLTs were observed. When examining all AEs, 8 instances of grade 3 AEs, most likely related to protocol therapy, occurred approximately 125 to 556 days from SBRT initiation in 7 patients.

Conclusions and Relevance

This phase 1 trial demonstrated the safety of SBRT for patients with 3 to 4 metastases or 2 metastases in close proximity. There were no treatment-related deaths. Late grade 3 AEs demonstrate the need for extended follow-up in long-surviving patients with oligometastatic disease. Treatment with SBRT for multiple metastases has been expanded into multiple ongoing randomized phase 2/3 National Cancer Institute–sponsored trials (NRG-BR002, NRG-LU002).

Trial Registration

ClinicalTrials.gov Identifier: NCT02206334

Introduction

Systemic therapy is standard treatment for most patients with metastatic cancer. Despite advances in molecularly targeted therapy[1] and immune checkpoint blockade,[2] systemic therapies are rarely curative. Based on better-than-expected patient outcomes after resection of limited

lung[3] and liver[4] metastases, the clinical state of oligometastases has been proposed wherein patients with metastases limited in both number and destination organ may have a more indolent disease course and benefit from metastasis-directed therapies.[5]

Concurrent with increasing acknowledgment of the oligometastatic state has been integration of advanced tumor imaging with novel radiation planning and delivery techniques. By precisely delivering high-dose radiation while restricting surrounding normal tissue exposure (commonly described as stereotactic body radiotherapy [SBRT]),[6] high treated-tumor control rates with a favorable toxicity profile have been reported.[7] Phase 2 studies have demonstrated safe and effective SBRT doses for limited lung,[8] liver,[9] or spine[10] metastases, whereas retrospective analyses demonstrated safety for patients with other single metastasis locations.[7] Stereotactic body radiotherapy provides an alternative to resection for metastasis-directed therapy, minimizing systemic therapy interruptions and expanding the type and location of metastasis[6] amenable to an ablative therapy.[7]

Delivering SBRT to patients with 3 to 4 metastases or those with 2 metastases in close proximity to one another is technically challenging. As the number of metastases treated increases, the cumulative radiation dose to the surrounding organs increases the potential for treatment-related toxicity. Additionally, this challenge is magnified, because many patients with oligometastases have had prior radiotherapy, limiting further permissible dose to surrounding normal tissues. Despite the lack of prospective and well-defined techniques and safety data, practitioners are increasingly using SBRT to treat patients with multiple metastases.[11,12,13] However, many patients with oligometastases now being considered for SBRT have up to 4 metastases or 2 metastases in close proximity to one another. Existing data include mostly treatment of 1 or 2 metastases separated widely from each other and use of differing radiation doses, toxicity reporting, image guidance, and normal tissue constraints.[12] Given the critical need, NRG Oncology NRG-BR001 trial sought to determine the safety of delivering curative-intent SBRT to patients with 3 to 4 metastases or 2 metastases within close proximity to each other. It was hypothesized that by establishing robust treatment planning, delivery parameters, and quality assurance, SBRT could be delivered in 3 to 5 sessions to up to 4 metastases in a condensed time frame with acceptable toxic effects.[14]

Methods

Patients

This phase 1 trial was opened on August 4, 2014, and closed to accrual on March 20, 2018. Patients were considered eligible if they had metastatic breast, prostate, or non–small cell lung cancer (NSCLC) and either 3 to 4 metastases or 2 metastases within 5 cm of each other otherwise amenable to SBRT. Patients also were required to be 18 years or older and have controlled primary tumors, an Eastern Cooperative Oncology Group performance status of 2 or less, and normal organ and marrow function. Patients with brain metastases, severe active comorbid disease, or prior palliative radiation to current metastases were ineligible, as were patients with metastases located within 3 cm of previously irradiated organs (ie, lungs, bowel, stomach, brachial plexus, or spinal cord). The National Cancer Institute Adult Central Institutional Review Board–Early Phase Emphasis approved this study, and all patients signed study-specific informed consent. The trial protocol is available in Supplement 1.

Upon registration, each metastasis was assigned to 1 of 7 metastatic locations (bone/osseous [BO], spinal/paraspinal [SP], peripheral lung [PL], central lung [CL], mediastinal/cervical lymph node [MC], liver [L], or abdominal-pelvic [AP]) based on the potential for toxicity. Protocol-specified radiation doses were derived from phase 2 data for single metastases or by expert consensus when data were not available. The starting dose was 50 Gy in 5 fractions for the CL and MC lymph node locations; 45 Gy in 3 fractions for PL, AP, and L locations; and 30 Gy in 3 fractions for BO and SP locations (eTable 1 in Supplement 2). Therefore, a given patient could have metastases receiving different doses and could contribute to multiple metastatic tumor locations. Flexibility was given to treating physicians to irradiate metastases sequentially or concurrently. However, treatment of all metastases must have been completed within 21 days from the start of SBRT.

Treatment Planning

All patients underwent computed tomography (CT)-based treatment planning in customized immobilization devices with a CT range including all targeted metastases and surrounding normal organs. All metastases with a potential for respiratory-induced tumor motion were required to be evaluated with 4-dimensional CT, implanted fiducial marker, or fluoroscopy during radiation simulation. Tumors with respiratory motion greater than 1 cm were required to have respiratory motion management with a method specified in the protocol, such as including abdominal compression, breath hold, fiducial marker tracking, or gating.

Each metastasis was targeted on the planning CT, with an additional 5- to 7-mm expansion for setup uncertainty except for spinal metastases, which followed accepted standards.[14] Standard SBRT planning techniques, including 3-dimensional conformal, intensity-modulated, volumetric modulated arc, or robotic radiosurgery delivery, were used. Each radiation treatment plan was prioritized to respect spinal cord, cauda equina, sacral plexus, and brachial plexus dose constraints, followed by prioritizing compact radiation dose distribution and then by meeting other normal tissue tolerances. Ninety-five percent of the target was required to be covered with the prescription dose, unless immediately adjacent to a critical normal organ in which the dose could be reduced to 70% of the prescription dose. The decision to cover the target or reduce coverage to spare surrounding normal organs was left to the treating physician except in cases of critical neural structures as specified previously (eFigure in Supplement 2).

Central Review

To ensure protocol adherence, robust quality assurance evaluated institutional capabilities and radiation planning techniques for the protocol-specified treatment.[15] Each institution was required to complete a dry-run benchmark to demonstrate their ability to use protocol-specified SBRT treatment planning techniques, validate pretreatment imaging quality, and complete a phantom study to prove appropriate dose delivery to multiple nearby targets.[15] Furthermore, a study team of physicists and physicians (S.C., J.S., H.A., M.M.) performed rapid pretreatment reviews of the first radiation treatment plan for each new metastatic location at each treatment center. If the initial plan was not approved, study team feedback was used to generate a revised approved treatment plan before protocol treatment. Antiestrogen, antiandrogen, and anti-*ERBB2* (formerly *HER2* or *HER2/neu*) therapies were allowed concurrently during SBRT. Bevacizumab, cetuximab, and systemic cytotoxic chemotherapies were held and could resume 14 days after protocol treatment.

Statistical Analysis

The primary study objective was to determine the recommended SBRT dose for each metastatic location when treating multiple metastases (based on 2 possible dose levels: an initial and de-escalated dose) resulting from the incidence of predefined dose-limiting toxicities (DLTs) within 180 days of treatment start. Secondary objectives included determining incidence of all treatment-related adverse events (AEs) greater than or equal to grade 3 within 180 days of treatment start, the late AE incidence, and survival. The study was designed to accrue 6 evaluable patients at the initial starting dose level for each metastatic location. Evaluable patients were eligible patients who began protocol SBRT treatment for a given metastatic location and were either (1) monitored for at least 180 days after treatment start or (2) monitored for less than 180 days with a reported DLT. Adverse events were graded with the Common Terminology Criteria for AEs, version 4.0. Specific AEs or grades that counted as DLTs are shown in eTable 2 in Supplement 2. Late AEs were defined as occurring more than 180 days after treatment start. Each patient was assessed every 3 months from SBRT completion for up to 2 years.

For each metastatic location, after 6 evaluable patients were accrued to the initial dose level, accrual was temporarily suspended for DLT assessment. Adverse events were selected to be DLTs based on prior toxicity reports from studies treating a single oligometastasis. If no more than 1 patient experienced a protocol-specified DLT in a given metastatic location, the initial starting dose was determined to be acceptable and would become the recommended SBRT dose. Otherwise, the radiation dose would be de-escalated and another 6 evaluable patients accrued. If no more than 1 patient at the de-escalated dose experienced a DLT, then the de-escalated dose was judged to be acceptable and would become the recommended SBRT dose for that metastatic location. Once safety assessment was determined and the dose cleared without DLT, the metastatic location reopened for accrual only for patients who could contribute to metastatic locations that had not met accrual limits. The study team assessed all AEs monthly. Depending on observed DLTs (and the need to de-escalate) and whether patients had more than 1 metastatic location, a minimum of 42 and a maximum of 84 patients were needed for accrual. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc) from December 31, 2017, to September 19, 2019.

Results

From August 4, 2014, to March 20, 2018, 42 patients were registered; 3 did not receive protocol therapy, leaving 39 eligible patients. Median follow-up for eligible patients was 22.6 (min-max, 2.1-26) months, with only 2 patients having less than 20 months of follow-up. Of the 39 eligible patients, 4 were not evaluable (2 died due to their disease without a DLT event before DLT period completion, 1 entered hospice [day 154], and 1 was alive but lost to follow-up before completion of the DLT period), leaving 35 evaluable patients (mean [SD] age, 63.1 [14.2] years; 20 men [57.1%]; 30 White patients [85.7%]) for the DLT end point. The number of patients accrued and contributing to a given metastatic location are shown in eTable 3 in Supplement 2. Patient and tumor characteristics for all 39 eligible and the 35 DLT evaluable patients are shown in Table 1. Among the DLT evaluable patients, 12 patients (34.3%) had breast cancer, 10 (28.6%) had NSCLC, and 13 (37.1%) had prostate cancer. There was a median (min-

max) of 3 metastases treated per patient (min-max, 2-4), with 23 patients (66%) having 3 to 4 metastases. Twenty-one patients (60%) had received prior radiation away from the targeted metastases.

Despite the complexity of the treatment protocol, SBRT was delivered per protocol or with acceptable variations in all but 1 case. The median time to complete protocol SBRT was 8 (min-max, 3-27) days. Of 39 treated patients, 33 (85%) underwent rapid reviews, of whom 25 (76%) passed and 8 (24%) required 1 to 3 resubmissions. There were no unacceptable variations in target coverage and only 1 unacceptable variation in dose to normal tissues demonstrating strict compliance with protocol-specified therapy.

Dose-Limiting Toxicity

There were no protocol-specified DLTs reported in any of the 7 metastatic locations as summarized in Table 2. Dose-limiting toxicity analyses were based on 6 evaluable patients for all but the liver metastatic location, which was based on 5 patients evaluable for DLT. When the DLT assessment period was completed without any reported DLTs for 5 evaluable patients with liver metastasis, the 6 other metastatic locations had already been determined to be safe. Trial accrual was thus closed, because the accrual of a sixth patient with liver metastasis could not affect the DLT evaluation. Given this, the initial starting dose (eTable 1 in Supplement 2) is the recommended SBRT dose for each metastatic site.

Adverse Events

There were 50 AEs of grade 3 to 4 (45 grade 3 and 5 grade 4) reported in 18 patients regardless of relationship to treatment. Each AE grade 3 to 4 was evaluated with respect to the time from SBRT start, time of progression, and the radiation treatment plan to elucidate a mechanism of relationship to protocol therapy. Of the 50 AEs of grade 3 to 4, 18 AEs (36%) were reported by the treating site as at least possibly related to protocol therapy, as shown in Table 3. These AEs were distributed among 9 patients with 16 grade 3 and 2 grade 4 AEs (Table 3). Six of the 18 AEs occurred within 180 days and the rest after 180 days; all of these AEs did not meet the defined criteria for DLT as outlined in eTable 2 in Supplement 2.

The study team further reviewed these AEs to determine whether they were mechanistically associated with the protocol treatment (Table 3). Ten of these AEs were not considered mechanistically related to protocol therapy, as they were metabolic, infectious, mood, and hematologic AEs not expected or known to occur with SBRT, were present before the study therapy, or occurred with progressive disease without confirmatory evidence of relation to protocol treatment. The other 8 AEs, on central review, were determined to be mechanistically related to protocol therapy. One patient with breast cancer who was treated for 3 metastases (in the CL, PL, and MC lymph node locations) developed grade 3 pneumonitis 125 days from start of SBRT, and another patient with NSCLC who was treated for 3 metastases (2 in the L and 1 in the AP region) developed a grade 3 gastric ulcer 131 days from start of SBRT. After central review of the treatment plans, these AEs were scored as most likely related to protocol therapy. Six grade 3 treatment-related AEs in 6 patients were reported more than 180 days after treatment start, including bone pain, pulmonary fibrosis, bronchial fistula, bronchial stenosis, spinal fracture, and humeral fracture. These AEs included 2 late treatment-related grade 3 AEs occurring in patients receiving SBRT to the pulmonary hilum: the grade 3 bronchial stenosis and the

grade 3 bronchial fistula. Review of the radiation treatment plans revealed that both patients received a full protocol radiation dose to the hilum. The 18-month and 2-year cumulative incidences of late grade 3 to 4 treatment-related AEs based on site reporting were 17% (95% CI, 7%-32%) and 20% (95% CI, 9%-35%), respectively, as shown in Figure 1. Review of the treatment plans revealed no significant deviations from the protocol.

Survival

For all 39 eligible patients, with a median follow-up of 23.9 (min-max, 2.1-26) months for surviving patients, 15 patients had died (5 of 13 [38%] of breast cancer, 6 of 13 [46%] of lung cancer, 4 of 13 [30%] of prostate cancer), all from metastatic cancer. The median survival was not reached. The estimated 2-year overall survival was 57% (95% CI, 38%-72%) (Figure 2).

Discussion

The National Cancer Institute trial NRG-BR001 demonstrated that up to 4 separate metastatic sites can be safely treated with curative-intent SBRT doses with acceptable rates of grade 3 to 4 toxicity and no grade 5 toxicity. The protocol-specified recommended SBRT doses were associated with acceptable short-term toxicity, and the safety profile of SBRT treatment for multiple metastases was shown to be similar to that reported from treatment of single metastases and primary tumors.[16,17,18,19,20] This technically challenging treatment was delivered appropriately and safely using comprehensive guide-defining strict parameters for tumor dosing, normal tissue avoidance, image guidance, and motion management for moving targets.[14] Based on the results from NRG-BR001, the recommended SBRT doses for each of the metastatic locations are as follows: 30 Gy in 3 fractions for BO and SP metastases; 45 Gy in 3 fractions for PL, L, and AP metastases; and 50 Gy in 5 fractions for CL and MC lymph node metastases. Additionally, NRG-BR001 directly informs ongoing randomized phase 2/3 trials, such as NRG-BR002 and NRG-LU002, by providing safety data and rationale for rigorous technical standards.

There is growing interest in adding metastasis-directed therapy for patients with oligometastatic disease with the goal of improving progression-free and overall survival. Prior published series of definitive radiotherapy for oligometastases have mostly treated 1 to 2 metastases.[7,16,17] The safety of treating more metastases or more technically challenging cases was previously not reported. In the previously reported Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)[21] randomized phase 2 trial including patients with 1, 2, and 3 metastases treated in 46%, 29%, and 18% of patients, respectively, 5% of patients treated with SBRT had grade 5 toxicity despite treatment for a median of only 1 metastasis per patient.

The present study's requirements consisted of the completion of a very challenging benchmark case to ensure familiarity with protocol requirements[15] and quality preradiation image guidance. Completion of the benchmark case ensured that radiation treatment delivery would be completed as planned by treatment of a phantom study and that the first case from each treating institution was rapidly reviewed by the study team before treatment.[14] Within the confines of this rigorous review, this technique was found to have acceptable short-term (within 180 days from treatment start) toxic effects. It is strongly encouraged that all practitioners offering this type of treatment adopt such rigorous standards and education. Given the potential

for ablative radiotherapy to improve outcomes of patients with oligometastatic cancer,[17,18,20] the finding that SBRT is safe when delivered to 3 to 4 metastases or 2 metastases in close proximity to one another is important and serves as the foundation for ongoing randomized trials.

Overall, the rate of grade 3 to grade 4 AEs was consistent with that seen in systemic therapy trials of patients with metastatic NSCLC and metastatic prostate and breast cancer. Most of the grade 3 to grade 4 AEs reported after protocol SBRT were unrelated to protocol therapy and were often related to disease progression. Some grade 3 to grade 4 AEs were consistent with prior reports of SBRT used to treat primary early-stage NSCLC (including dyspnea, pulmonary fibrosis,[22] and chest wall pain[23]) and spinal metastases[6] reconsidered acceptable via a standard risk/benefit profile. Importantly, there were no grade 5 toxicity events, and the reported grade 4 toxicity events were not mechanistically attributable to protocol SBRT based on central review.

An important finding from this trial was the detection of 2 late treatment-related grade 3 to grade 4 AE toxic effects in the CL or hilar region after the DLT observation period. The starting CL dose on NRG-BR001 was selected from a dose-finding trial for central, early-stage primary NSCLCs, which demonstrated acceptable toxicity in early reports.[16] Two additional patients with metastases treated near the hilum did not have toxic effects. Additionally, no late grade 3 to grade 4 AEs were seen in patients treated near nonhilar airways in the PL, CL, or MC lymph node cohorts. No toxic effects were seen in patients who received lower doses to hilar structures, indicating a dose response supported by other emerging reports.[19] These findings suggest that hilar lymph nodes may be considered a separate metastatic location, given the proximity of the hilar lymph nodes to multiple bronchi, and support a cautious approach when treating patients with a life expectancy of more than 1 year when the full circumference of the bronchus will be irradiated in these situations, as late toxic effects could be significant. The survival in this cohort is similar to that seen in the SABR-COMET study, and the NRG-BR001 population had a higher median number of metastases, associated in prior analyses with worse outcomes in other analyses.[24]

Strengths and Limitations

The strengths of this trial included the unique design that can be thought of as 7 phase 1 trials in 1. Unlike typical dose-escalation phase 1 trials, this trial started with the organ-specific maximum doses for a single metastasis and would only de-escalate if sufficient DLTs were observed. The use of uniform quality assurance, real-time radiation plan reviews, and minimum motion management requirements further strengthened the safety conclusions. A potential weakness is that although no dose reductions were needed, the possibility exists that when deployed on a wider scale without real-time reviews and quality assurance, there may be higher rates of toxicity. As a phase 1 trial, efficacy is not able to be robustly estimated.

Conclusions

This phase 1 trial found that patients with multiple metastases can be treated with curative-intent SBRT doses developed for a single metastasis or primary tumors with acceptable short-term toxic effects. Patients should be monitored carefully for the development of late toxic effects. These dosing schemes are important, as the use of SBRT to treat multiple metastases is

increasing with mounting randomized evidence. These recommended doses from NRG-BR001 are being used in ongoing trials, including NRG-BR002, the phase 2R/3 trial to determine the role of this treatment for patients with metastatic breast cancer.

Notes

Supplement 1.

Trial Protocol

Supplement 2.

eTable 1. Dose Per Fraction According to Metastatic Site

eFigure. Flexible Prioritization of Tumor Coverage or Organ at Risk Avoidance

eTable 2. Dose-Limiting Toxicity Definitions by Metastatic Site

eTable 3. NRG-BR001 Accrual/Eligibility

Supplement 3.

Data Sharing Statement

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Figures and Tables

Table 1.

Patient and Tumor Characteristics

Characteristic	No. (%)	
	All treated patients (n = 39)	Patients evaluable for DLT assessment (n = 35)
Patient or tumor characteristic		
Age, y		
≤49	8 (20.5)	8 (22.9)
50-59	5 (12.8)	3 (8.6)
60-69	10 (25.6)	9 (25.7)
70-79	11 (28.2)	11 (31.4)
≥80	5 (12.8)	4 (11.4)
Sex		
Male	21 (53.8)	20 (57.1)
Female	18 (46.2)	15 (42.9)
Race		
American Indian/Alaska Native	1 (2.6)	0
Black or African American	4 (10.3)	3 (8.6)
White	31 (79.5)	30 (85.7)
Unknown or not reported	3 (7.7)	2 (5.7)
Ethnicity		
Hispanic or Latino	1 (2.6)	0
Not Hispanic or Latino	34 (87.2)	31 (88.6)
Unknown	4 (10.3)	4 (11.4)
Primary site of disease		
Breast	13 (33.3)	12 (34.3)
Lung	13 (33.3)	10 (28.6)
Prostate	13 (33.3)	13 (37.1)
Performance status (ECOG)		
0	26 (66.7)	24 (68.6)
1	10 (25.6)	9 (25.7)
2	3 (7.7)	2 (5.7)
No. of distinct metastases		

Abbreviations: DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group.

Table 2.

Summary of Dose-Limiting Toxicity (DLT) Results

Metastatic location (starting dose)	No.		
	Patients enrolled for DLT assessment	Patients evaluable for DLT assessment	DLT events
Bone/osseous (30 Gy in 3 fractions)	8	6	0
Spinal/paraspinal (30 Gy in 3 fractions)	7	6	0
Peripheral lung (45 Gy in 3 fractions)	7	6	0
Abdominal-pelvic (45 Gy in 3 fractions)	9	7[a]	0
Central lung (50 Gy in 5 fractions)	8	7[a]	0
Liver (45 Gy in 3 fractions)	9	5	0
Mediastinal/cervical lymph node (50 Gy in 5 fractions)	7	6	0

[a] The DLT analysis was based on the first 6 of these 7 patients.

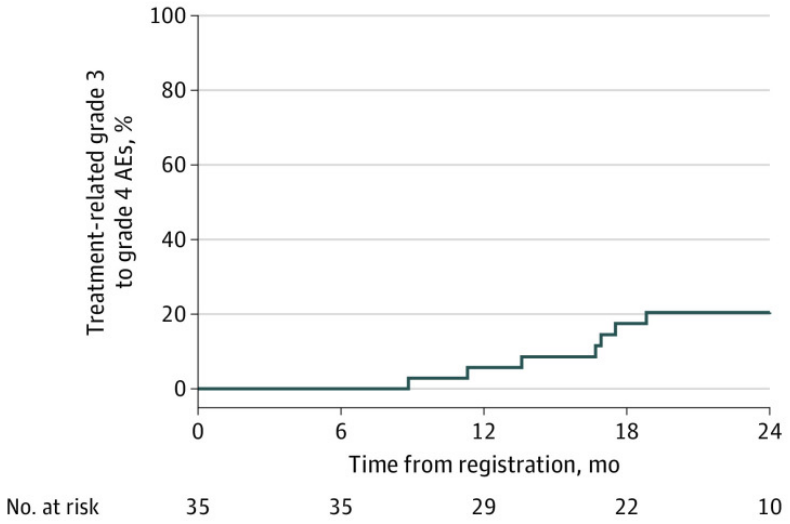
Table 3.

Grade 3 of Higher Treatment-Related Adverse Events by Patient That Did Not Constitute a Dose-Limiting Toxicity

Patient ID	Primary site	No. of metastatic sites treated	Metastatic locations to which patient contributed (No. of metastases treated)	Adverse events (site-reported attribution)	Central review: mechanistically related to treatment	Days from SBRT start
AA	Breast	4	Peripheral lung (1) Central lung (1) Liver (2)	Grade 3 dyspnea (possible)	No	95
				Grade 3 hypoalbuminemia (possible)	No	97
				Grade 3 platelet count decreased (possible)	No	106
BB	Lung	4	Peripheral lung (2) Central lung (2)	Grade 4 hypercalcemia (probable)	No	392
				Grade 3 anemia (possible)	No	280
				Grade 3 anorexia (possible)	No	392
				Grade 3 depression (probable)	No	412
				Grade 3 fatigue (possible)	No	392
				Grade 3 bone pain (definite)	Yes	362
CC	Breast	3	Peripheral lung (1) Central lung (1) Mediastinal/cervical lymph node (1)	Grade 3 pneumonitis (probable)	Yes	125
				Grade 3 pulmonary fibrosis (possible)	Yes	243
DD	Breast	3	Central lung (3)	Grade 3 bronchial fistula (definite)	Yes	337
EE	Lung	3	Bone/osseous (1) Abdominal-pelvic (2)	Grade 3 fracture [right humerus] (definite)	Yes	556
FF	Breast	3	Bone/osseous (2)	Grade 3 bronchial	Yes	496

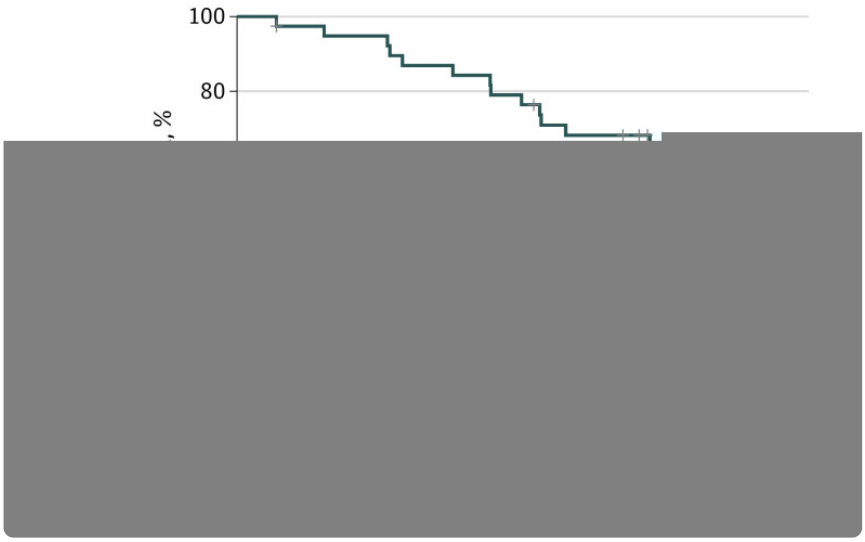
Abbreviation: ID, identification; SBRT, stereotactic body radiation therapy.

Figure 1.



Time to Treatment-Related Grade 3 to Grade 4 Adverse Events (AEs) Occurring Greater Than 180 Days After the Start of Stereotactic Body Radiation Therapy for All Evaluable Patients

Figure 2.



Overall Survival of All Treated Patients

The plus signs indicate censored values.