advances
in radiation oncology

Scientific Article

Can Polymetastatic Disease Be ARRESTed Using SABR? A Dosimetric Feasibility Study to Inform Development of a Phase 1 Trial

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Abstract

Purpose: Phase 2 randomized trials suggest that stereotactic ablative radiation therapy improves progression-free and overall survival in patients with oligometastatic cancer, with phase 3 trials currently testing stereotactic ablative radiation therapy in up to 10 metastases. Whether stereotactic radiation therapy could provide similar benefits in polymetastatic disease (>10 metastases) is unknown. We sought to evaluate the dosimetric feasibility of using stereotactic radiation therapy in polymetastatic disease in preparation for a phase 1 trial.

Methods and Materials: Five craniospinal computed tomography simulations were used to simulate 24 metastatic targets (n = 2 patients), 30 targets (n = 2 patients), and 50 targets (n = 1 patient) that were not present on the initial scan. Creation of radiation therapy plans was attempted for doses up to 30 Gy in 5 fractions, with de-escalation to 24 Gy/4, 18 Gy/3, 12 Gy/2, or 6 Gy/1 if not feasible based on standardized dose constraints. Plans were created using Raystation for delivery on linear accelerators using volumetric modulated arc therapy and validated using Mobius 3D.

Results: A stereotactic radiation therapy treatment plan was generated for each simulated patient. Dose constraints were met to a dose of 30 Gy in 5 fractions for the patients with 24 and 30 lesions. For the patient with 50 targets, dose de-escalation to 12 Gy in 2 fractions was required to meet lung constraints. Estimated beam-on time varied between 18 and 29 minutes per fraction of 6 Gy. Median D95 planning target volume dosimetry ranged from 96.6% to 97.7% of the prescription dose. The conformity index (R100) range was 0.89 to 0.95, and R50 range was 6.84 to 8.72.

Conclusions: Stereotactic radiation therapy treatment plans meeting standardized dose constraints could be created in the setting of 24 to 50 metastatic lesions using volumetric modulated arc therapy. This safety of this approach is being evaluated in a phase 1 trial (NCT04530513).

Introduction

For patients who have metastatic cancer, palliative systemic therapy (such as chemotherapy, targeted therapy, and/or immunotherapy) remains the backbone of standard therapy.[1] Radiation therapy has traditionally been reserved for palliation of sites not readily penetrated by systemic therapy (ie, brain metastases)[2] or for localized symptoms

such as pain, obstruction, and/or bleeding.[3,4] Palliative radiation therapy is typically delivered using low doses and simple radiation planning techniques with the goal of obtaining symptom relief while minimizing treatment toxicity, treatment burden, and financial toxicity.

Recently, patients with oligometastatic cancer have been the subject of numerous trials evaluating the role of aggressive metastasis-directed therapy. The oligometastatic state is typically defined as disease stage where cancer has spread beyond the primary site but is not yet widely metastatic.[5] Although definitions of oligometastatic cancer vary, most would consider the oligometastatic state to represent 1 to 3 or 1 to 5 metastatic lesions.[6,7] Randomized trials in patients with oligometastatic disease have reported improvements in progression-free and overall survival with aggressive treatments to oligometastases,[8-11] including stereotactic ablative radiation therapy (SABR). The effect of SABR on overall survival in patients with 4 to 10 metastatic sites is being evaluated in the SABR stereotactic ablative radiotherapy for comprehensive treatment of 4-10 oligometastatic tumors (COMET-10) trial.[12]

We use the term "polymetastatic" to refer to the widespread dissemination of metastatic cancer.[13] However, there is no clear boundary between an oligo- and polymetastatic state, and these 2 entities may merely be arbitrarily defined states along a continuous distribution of metastases. Emerging randomized evidence supports aggressive radiation therapy to the primary tumor in selected patients with newly diagnosed polymetastatic (low-volume) prostate[14] and nasopharyngeal cancers,[15] with improvements in progression-free and overall survival.

A precedent for treating extensive metastatic disease with radiation exists using hemi-body radiation therapy for palliation of diffuse bone metastases,[16] radio-ligand or systemic radiopharmaceuticals for the treatment of metastases,[17] and radiosurgery for multiple brain metastases.[18] Although delivering SABR in the polymetastatic setting is unlikely to be curative, SABR may allow a temporary delay in cancer growth, similar to systemic therapy.[19]

Given that SABR has shown promise in providing progression-free and overall survival advantages in treating oligometastases, we postulate that the benefits of stereotactic radiation therapy may not be limited only to those with oligometastases. As part of the development of the phase 1 dose escalation trial ARREST (NCT04530513), we sought to evaluate the dosimetric feasibility of delivering stereotactic radiation therapy to patients with polymetastatic cancer.

Methods and Materials

Patient selection/target delineation

Five anonymized computed tomography (CT) simulation data sets, originally obtained for the clinical purpose of planning craniospinal radiation therapy, were used in our study. Twenty-four (n = 2 patients), 30 (n = 2 patients), and 50 (n = 1 patient) gross tumor volumes (GTVs) were simulated and contoured on the craniospinal CT scans. These tumor targets were not present on the initial CT scans and were contoured by the study authors in a random fashion to be plausible in size and location based on clinical experience. Patients were originally simulated arms down, a position that has been shown to be safe for lung radiation therapy,[20] with a thermoplastic shell. Slice thickness was 3 mm. CT images were transferred to RayStation V7 (RaySearch Laboratories, Stockholm, Sweden). The GTVs were created such that they would meet inclusion/exclusion criteria for our planned phase 1 trial, with key considerations including the following: all lesions must be ≤5 cm, except brain metastases, which must all be ≤3 cm, and total volume <30 cm^3. Lesions could not involve the brain stem, gastrointestinal tract, mesentery, skin, epidural space, or be diffuse/miliary (ie, lymphangitic spread, malignant pleural effusion). We assumed the patient had not received previous radiation therapy. No clinical target volume expansion was used. A 2-mm planning target volume (PTV) expansion on brain/spine metastases was used, and a 5-mm PTV expansion was used for all other targets. Normal structures in proximity to each target were contoured. Research ethics board approval was provided by the Western University Research Ethics Board (#116871).

Simulated treatment planning

Treatment planning was conducted using Raystation V7. Volumetric modulated arc therapy was used using Varian Truebeam linear accelerators equipped with millennium or high definition 120 multi leaf collimators. Treatment planning was conducted to meet criteria outlined in our planned phase 1 trial, with key considerations including prioritizing organ-at-risk dosimetry over target coverage, minimizing the number of isocenters treated per day, and using the least number of arcs to shorten treatment time. Treatment volumes were selected in the longitudinal direction to avoid beam overlap and minimize scatter. We used the treat function to dedicate different beams to specific targets. The optimization procedure accounted for radiation scatter between the different beams.

We considered 5 dose levels of radiation: 6 Gy in 1 fraction, 12 Gy in 2 fractions, 18 Gy in 3 fractions, 24 Gy in 4 fractions, and 30 Gy in 5 fractions, with each fraction delivered 1 week apart. The best possible treatment plan was generated for 30 Gy in 5 fractions, and if it did not meet organ-at-risk constraints, the number of fractions delivered was decreased until a treatment plan compliant with our constraints was created. Organ-at-risk

constraints used are available in Appendix E1 and are based on existing clinical trials[12,21] and SABR guidelines.[22,23]

Target coverage goals were ≥95% of the PTV to receive ≥95% of the prescription dose. The maximum hot spot allowed was 120%. If compromising PTV coverage was required to meet organ-at-risk constraints, our planned phase 1 protocol indicates that it is acceptable for ≥95% of the GTV to receive ≥95% of the prescription dose, so long as ≥90% of the targets meet the PTV coverage criteria.

Treatment plans underwent independent quality assurance (QA) using Mobius 3D (Varian Medical Systems, Palo Alto, CA). Mobius 3D is a second-check dosimetry system that uses the patient's CT images.[24,25] The dose for all treatment plans was recalculated on Mobius 3D for each treatment region. Passing rates represent global 3-dimensional gamma passing rates with gamma criteria of 3-mm distance and 5% dose difference. A 95% pass rate would represent that 95% of the points have less than 5% dose difference within 3-mm distance.

Results

A treatment plan was generated for each simulated patient. The first 4 simulated patients (24 and 30 GTVs) could be planned at the 30 Gy in 5 fraction dose level. The dose prescription for the fifth simulated patient (50 GTVs) had to be de-escalated to 12 Gy in 2 fractions to meet prespecified lung dose constraints. Other than the lung dose constraints, all other organ-at-risk dose constraints were satisfied at the 30 Gy in 5 fraction dose level.

Details regarding GTV/PTV size, dosimetric coverage, conformity indices, beam-on time, and treatment plans are available in Table 1. GTV volumes ranged from 0.21 to 37.33 cm^3. Three of the treatment plans required sacrificing of PTV coverage to meet organ-at-risk constraints. Estimated treatment time ranged from 18 minutes 11 seconds to 29 minutes 50 seconds per fraction. R100 (ratio of the volume receiving ≥ prescription dose to the PTV volume) ranged from 0.89 to 0.95, and R50 (ratio of the volume receiving ≥ 50% prescription dose to the PTV volume) ranged from 6.84 to 8.72. Sample dose distributions from simulated patient 4 and 5 (30 and 50 GTVs, respectively) are available in Figure 1. A description of GTV locations is available in Appendix E2.

Treatment plan QA using Mobius 3D was clinically acceptable for all patients. The average QA passing rate for the treatment volumes was 99.9% and 99.1% for simulated patients 1 and 2, respectively (24 GTVs). For simulated patients 3 and 4 (30 GTVs), the average QA passing rates were 97.6% and 95.1%. For the fifth simulated patient (50 GTVs), the average QA passing rate was 99.0%.

Discussion

In our dosimetric study, we found it was feasible to generate radiation therapy treatment plans for patients with 24 (n = 2 patients), 30 (n = 2 patients), and 50 (n = 1 patients) GTVs that met standard accepted dose constraints. However, it is unknown whether these standard dose constraints remain acceptable in the setting of polymetastatic disease, and whether such treatments can be delivered with acceptable toxicity. As a result, the ARREST phase 1 trial will be a 3 + 3 dose escalation study beginning at 12 Gy in 2 weekly fractions. Each dose level will increase by 6 Gy in 1 weekly fraction until the maximum dose level, 30 Gy in 5 weekly fractions, is reached. We anticipate that delivering radiation therapy in polymetastatic disease will raise new challenges to our field and have designed ARREST to conform to three major guiding principles: minimization of toxicity, minimization of treatment burden, and strict adherence to dose constraints. Although the highest dose level in ARREST may not be a truly ablative dose, we anticipate it should provide durable control while balancing potential toxicity and treatment burden. This concept is analogous to the dose de-escalation used in the SABR-COMET 10 trial from typical ablative doses with biologically effective dose > 100 Gy$_{10}$.

Only the fifth patient could not be planned at the highest dose level owing to the inability to meet lung constraints. We believe this was due to 2 factors: a total of 17 targets overlapped with the lungs (9 GTVs in the lung, 3 in the mediastinum, 2 in vertebrae, 1 in the clavicle, 1 in the rib, and 1 in the superior liver) and the small lung volumes in this patient (lung minus GTV = 2100 cm^3). By using a strategy of weekly fractions of 6 Gy, treatment planning was simplified by generating a single "best" treatment plan and subtracting fractions should the plan not be able to meet dose constraints. As creating multiple radiation therapy plans would be resource intensive, we felt this approach will help minimize treatment planning workload.

One aspect of ARREST that will be carefully evaluated on trial is the effect of low doses of radiation therapy to large volumes of the body. The volume of the planning CT scan did not encompass the entire body in any of the included patients in this study, often ending at the bottom of the pelvis, which would result in overestimation of the total body dosimetry, which was measured against the external contour of the planning CT. Nonetheless, low-dose spillage remains a pertinent issue in ARREST, with up to 45.79% of the external contour receiving a dose of 5 Gy in this study. It is estimated that single exposure total-body radiation dose expected to cause death in 50% of a normal human population without medical intervention is approximately 3.5 to 5.5 Gy.[26-28] In ARREST, each fraction will be given weekly. We will also limit the

Table 1 Summary of target and radiation delivery parameters

	Simulated patient number				
	1	2	3	4	5
Number of GTVs	24	24	30	30	50
Prescription dose	30 Gy/5 fx	30 Gy/5 fx	30 Gy/5 fx	30 Gy/5 fx	12 Gy/2 fx
GTVs (cm^3)					
Median	4.27	3.07	3.29	3.14	2.29
Range	0.73-37.33	0.68-36.59	0.21-16.76	0.22-33.73	0.26-18.35
Sum	183.09	153.89	133.20	158.08	176.07
PTVs (cm^3)					
Median	14.37	11.83	9.55	10.58	8.41
Range	1.87-54.74	1.73-74.16	0.85-43.38	0.88-73.31	0.85-51.11
Sum	480.50	420.72	387.15	417.21	563.03
Number of targets not meeting PTV coverage criteria*	2	0	3	0	5
GTV dosimetry (D95, % of prescription dose)					
Median	104.4%	104.1%	104.5%	106.2%	105.2%
Range	95.4%-109.9%	101.8%- 107.9%	95.6%- 100.6%	100.3%- 109.1%	99.9%- 111.3%
PTV dosimetry (D95, % of prescription dose)					
Median	97.7%	97.4%	97.3%	97.5%	96.6%
Range	83.2-100.3%	96.0%-100.5%	81.4%-101.3%	95.1%-100.0%	86.6%-99.8%
Maximum hot spot	116.6%	114.3%	115.4%	118.8%	119.8%
Treatment plan details					
Number of isocenters	7	6	5	5	9
Number of arcs	12	13	11	15	20
Median MU per arc	580.14	653.18	1176.72	830.24	743.23
Range of MU per arc	434.79-1198.21	418.32-1537.11	846.01-1448.35	580.15-1331.22	488.71-987.55
Total MU per fx	8305.12	10,304.58	12,431.10	13,581.03	15,082.48
Estimated treatment time / fx	18 min 11 sec	20 min 55 sec	21 min 34 sec	26 min 38 sec	29 min 50 sec
Total body dosimetry (percent of external contour, including GTV)					
V30 Gy	0.85%	0.93%	0.76%	0.67%	n/a
V20 Gy	3.50%	3.32%	3.04%	2.22%	n/a
V10 Gy	16.69%	17.92%	14.55%	15.19%	2.87%
V5 Gy	35.48%	45.79%	39.4%	43.13%	17.12%
Conformity indices					
R100†	0.89	0.95	0.95	0.95	0.93
R50‡	7.46	6.84	8.05	7.14	8.72

Abbreviations: fx = fraction; GTV = gross tumor volume; MU = monitor unit; PTV = planning target volume.

* A plan was still considered clinically acceptable if ≥ 95% of the GTV received ≥95% of the prescription dose and the ≥ 90% PTV received ≥ 95% of the prescription dose.

† R100 is defined as the volume of patient receiving prescription dose or greater divided by the PTV volume.

‡ R50 is defined as the volume of patient receiving 50% or greater of the prescription dose divided by the PTV volume.
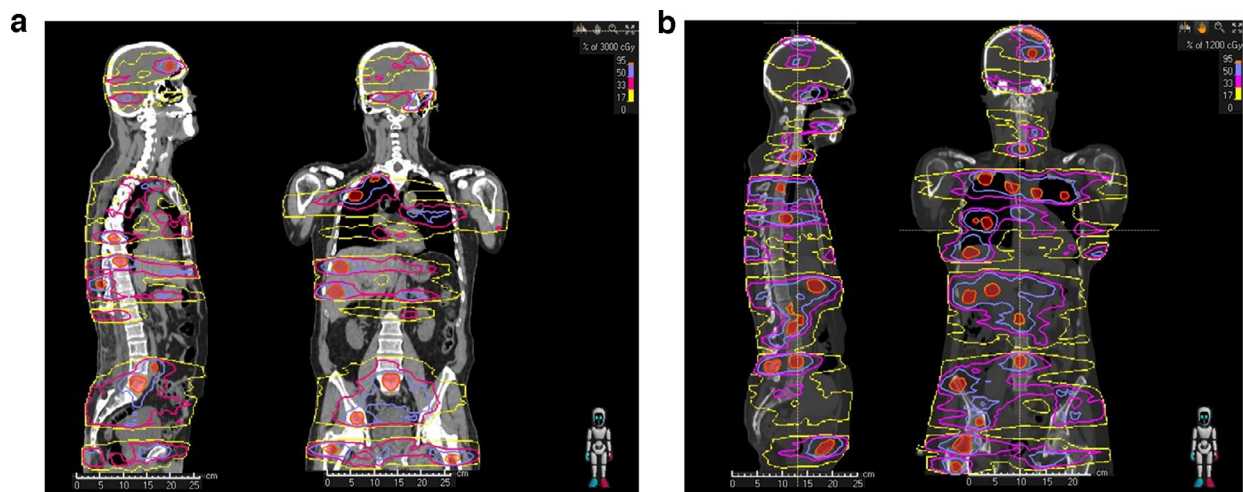
Fig. 1 Sagittal and coronal slices of simulated treatment plans in patients with (a) 30 gross tumor volumes treated to 30 Gy in 5 fractions and (b) 50 gross tumor volumes treated to 12 Gy in 2 fractions. Yellow, pink, purple, and orange isodose lines represent 17%, 33%, 50%, and 95% of prescription isodose lines, respectively. Planning target volumes are shaded contours in red.

number of isocenters treated per day to 3, therefore each fraction may be delivered over up to 3 treatment days. As a precaution, all patients will have weekly bloodwork drawn before the second and subsequent fractions of radiation therapy.

QA of treatment planning was evaluated using Mobius 3D, and we found the average passing rate using Mobius 3D was acceptable for each simulated patient. Ideally, we could have used physical phantoms to QA our treatment plans, but this was not feasible to implement for this study given resource limitations at our center. On ARREST, we plan on performing additional secondary QA analyses using physical phantoms.

One outstanding question is whether these treatment plans will be deliverable to patients. Estimated treatment time in our study only represents "beam-on" time and does not account for patient set-up, cone beam CT, or matching. Toxicity will need to be carefully monitored. We propose that patients should receive regular antiemetics before each treatment, and bone marrow function be monitored with regular bloodwork. The total body dose of radiation therapy is also an anticipated challenge. In our study, the inferior aspect of the craniospinal CT scan often stopped at the bottom of the pelvis, therefore the whole-body doses reported are likely overestimates relative to a whole body dose. Nonetheless, the integral dose of radiation therapy is an important issue encountered in our feasibility study and will be carefully monitored on trial. Either from a departmental or patient perspective, it may be necessary for delivery of each radiation therapy fraction to take more than 1 calendar day; therefore, nearby treatment arcs are to be delivered on the same day owing to overlapping treatment volumes and scatter.

Our study was limited by using simulated GTVs contoured by the study investigators. This was done for pragmatic purposes because the only patients undergoing near whole-body CT scans were those simulated for craniospinal radiation therapy, where GTVs eligible for inclusion in our proposed phase 1 trial would not have been present. Our sample size was small, meant to represent a proof-of-concept to determine whether it would even be feasible to proceed with a phase 1 trial. Given that metastasis patterns are widely variable, it is unlikely we could account for every possible situation where stereotactic radiation therapy may be investigated in our trial, regardless of the number of patients we simulated. Based on the findings of this dosimetric feasibility study, ARREST will be limited to patients with 50 GTVs. The phase 1 X trial is now activated and accruing patients and at the time of this publication, the first three patients on dose level I (12Gy/2) have been accrued and successsfully treated without any limiting toxicities noted within the 6 week post treatment follow-up.

Conclusions

The ARREST phase 1 trial is implementing the approach explored here among patients who have exhausted (or refused) standard-of-care systemic therapies. Should the technique prove safe and feasible to deliver, subsequent trials will need to explore the benefit of this approach in terms of quality of life and survival in this patient population and also potentially among patients at earlier time points in their disease course.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j. adro.2021.100734.

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