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Scientific Article

Stereotactic MR-Guided Online Adaptive Radiation Therapy (SMART) for Ultracentral Thorax Malignancies: Results of a Phase 1 Trial

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Abstract

Purpose: Stereotactic body radiation therapy (SBRT) is an effective treatment for oligometastatic or unresectable primary malignancies, although target proximity to organs at risk (OARs) within the ultracentral thorax (UCT) limits safe delivery of an ablative dose. Stereotactic magnetic resonance (MR)−guided online adaptive radiation therapy (SMART) may improve the therapeutic ratio using reoptimization to account for daily variation in target and OAR anatomy. This study

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assessed the feasibility of UCT SMART and characterized dosimetric and clinical outcomes in patients treated for UCT lesions on a prospective phase 1 trial.

Methods and Materials: Five patients with oligometastatic (n = 4) or unresectable primary (n = 1) UCT malignancies underwent SMART. Initial plans prescribed 50 Gy in 5 fractions with goal 95% planning target volume (PTV) coverage by 95% of prescription, subject to strict OAR constraints. Daily real-time online adaptive plans were created as needed to preserve hard OAR constraints, escalate PTV dose, or both, based on daily setup MR image set anatomy. Treatment times, patient outcomes, and dosimetric comparisons were prospectively recorded.

Results: All initial and daily adaptive plans met strict OAR constraints based on simulation and daily setup MR imaging anatomy, respectively. Four of the 5 patients received ≥1 adapted fraction. Ten of the 25 total delivered fractions were adapted. A total of 30% of plan adaptations were performed to improve PTV coverage; 70% were for reversal of ≥1 OAR violation. Local control by Response Evaluation Criteria in Solid Tumors was 100% at 3 and 6 months. No grade ≥3 acute (within 6 months of radiation completion) treatment-related toxicities were identified.

Conclusions: SMART may allow PTV coverage improvement and/or OAR sparing compared with nonadaptive SBRT and may widen the therapeutic index of UCT SBRT. In this small prospective cohort, we found that SMART was clinically deliverable to 100% of patients, although treatment delivery times surpassed our predefined, timing-based feasibility endpoint. This technique is well tolerated, offering excellent local control with no identified acute grade ≥3 toxicity.

Introduction

Stereotactic body radiation therapy (SBRT) is an established treatment modality for unresectable primary or metastatic thoracic malignancies. Increased radiation dose correlates with increased tumor control, and delivery of a biologically effective dose of 100 Gy or more has been found to improve survival outcomes in SBRT for early-stage lung cancers.[1–3] However, within the central thorax, dose-escalated therapy has previously resulted in excess toxicity because of the proximity of critical organs at risk (OARs).[4,5] Inherent uncertainties in targeting precision and accuracy, attributable to both inter- and intrafraction OAR motion as well as setup and gating inaccuracies, may contribute to this risk.

Toxicity risks of SBRT may be highest in ultracentral thorax (UCT) malignancies. Here we define UCT tumors as those with gross tumor volumes (GTVs) directly abutting the mainstem bronchi, carina, or contents of the mediastinum, although some definitions also include tumors whose planning target volumes abut or overlap these structures.[6,7] Hypofractionated stereotactic radiation therapy is one reported approach to central and ultracentral lesions, predicated on the theory that a more fractionated course, using 6 to 15 fractions (rather than ≤5 as with SBRT), could enhance OAR protection.[8,9] However, in a reported series of hypofractionated stereotactic radiation therapy for ultracentral tumors, toxicity remained a concern and the radiobiologic evidence for improved OAR protection using this method is inconclusive.[6]

As an alternative method, SBRT approaches using improved image guidance and adjusting for changes in tumor and OAR anatomy through online adaptive radiation therapy could also improve OAR protection. Magnetic resonance (MR) image (MRI) guided radiation therapy (MR-IGRT) offers superior soft tissue visualization for sites such as the mediastinum and is increasingly practiced in a variety of disease sites.[10–12] A recently published phase 1 trial of stereotactic MR-guided online adaptive radiation therapy (SMART) described application of this technique in the abdomen.[13] A simulated study of SMART previously indicated potential dosimetric benefits in the UCT, including improvement of the therapeutic index through daily treatment plan reoptimization based on daily volumetric setup imaging and treatment monitoring with cine MR-guided gating during treatment delivery.[14] Prospective clinical evaluation of this technique to improve the therapeutic index of SBRT for UCT disease has not previously been reported.

To prospectively assess the feasibility and safety of SMART, we a conducted a phase 1 clinical trial of this technique for oligometastatic and unresectable primary malignancies. The primary endpoint was feasibility, defined by delivery of adaptive treatment in <80 minutes of on-table time for >75% of cases. Here we report the results of this study in patients with UCT malignancies. We hypothesized that SMART would be feasible and deliver ablative radiation doses with acceptable rates of acute thoracic toxicity.

Table 1 Patient and disease characteristics

Characteristic	Number or Median (range)
Median age (range), y	64 (45-76)
Median tumor size (range), cm	3.1 (1.1-5.6)
Median prior chemotherapy regimens (range)	1 (0-9)
Median KPS (range)	90 (70-90)
Disease histology	
Primary non-small cell lung cancer	1
Papillary thyroid carcinoma metastasis	1
Colorectal cancer metastasis	1
Spindle cell sarcoma metastasis	1
Renal cell carcinoma metastasis	1
Disease subsite	
Invading pericardium	2
Invading mainstem bronchus	2
Abutting esophagus	1
Acute (within 6 mo) grade 3+ toxicities	0
Late (>6 mo) treatment-related toxicities	1
Esophageal stricture 15 mo posttreatment	1

Abbreviations: KPS = Karnofsky Performance Status.

Methods and Materials

Patient eligibility

This protocol was approved by Washington University's institutional review board (NCT 02264886). Enrolled patients were considered clinical and technical SBRT candidates and had oligometastatic or unresectable primary UCT malignancies. We defined oligometastatic disease as $\leq$3 progressive disease sites. Eligible patients had $\geq$1 site amenable to UCT SBRT, were $\geq$18 years old, had a Karnofsky performance status score of $\geq$70, had the capacity to provide consent, and had disease of solid tumor (nonhematologic) classification, excluding small cell cancers; characteristics are provided in Table 1. Any preceding systemic therapy was held $\geq$1 week before planned start of SMART, with no plans to reinitiate systemic therapy for $\geq$1 week after SMART completion. Exclusion criteria comprised history of radiation within the projected treatment field, ongoing receipt of other investigational agents, uncontrolled intercurrent illness, pregnancy and/or breastfeeding, or any contraindication to MRI.

Simulation and initial plan

The initial treatment planning process and details of treatment simulation, as well as the MR-IGRT treatment device, its built-in dedicated treatment planning system, and imaging characteristics, have been previously described.[13,15–17] Briefly, we used a commercially available MRIdian (ViewRay, Sunnyvale, CA) MR-IGRT unit, consisting of a low-field split-solenoid 0.35 Tesla MRI unit straddling a ringed gantry with 3 multileaf collimator–equipped ^{60}Co heads spaced 120° apart. All patients underwent computed tomography (CT) and MRI simulation with custom immobilization, per standard clinical protocol. Exhale breath-hold simulation CT scans served as primary image sets for treatment planning density information, with registration of simulation MR image sets to aid physician delineation of target volumes and OARs.

Prescription dose for all plans was 50 Gy in 5 fractions, with goal 95% planning target volume (PTV) coverage by 95% of prescription dose (47.5 Gy). Prescription coverage was subject to hard OAR constraints, as delineated in Tables 2 and 3, using a strict isotoxicity approach. A 5-mm volumetric expansion on the GTV was used to generate the PTV. A strict isotoxicity approach was used such that if goal PTV coverage could not be achieved without OAR constraint violation, then coverage of the PTV was sacrificed to meet OAR constraints.

Online plan adaptation

The online plan adaptation and plan quality assurance (QA) processes used in this study were summarized previously.[13,15] In short, patients underwent daily volumetric MRI for localization and setup. The initial plan, comprising either the simulation-based plan or the most recently used adapted plan, was loaded onto the image set of the day, and the treating physician edited contour volumes manually, as needed. The pre-existing plan was then assessed on the anatomy of the day. If OAR violation or an opportunity for PTV coverage improvement was identified, a new adaptive plan was generated while the patient remained on the table. The daily adaptive plan was then assessed and compared with the pre-existing, nonadaptive initial plan on the basis of dose to OARs and target volumes. The patient was then treated with the plan preferred by the treating physician. A fraction-by-fraction, strict isotoxicity approach was used to assess OAR sparing, without OAR point dose accumulation. Any delivered adaptive treatment plan became the default, nonadaptive plan for subsequent treatment days.

Treatment delivery and cine MR gating

Standard clinical practices for use of MR guidance and cine MR gating as performed in this study have been previously described.[13,18] Real-time MR guidance including planar sagittal cine MR gating on the GTV (based on the exhale phase during free breathing) was employed for all fractions. Targets for cine gating window construction and gating settings were chosen by the treating physician at the time of each treatment fraction.

Table 2 Organ-at-risk dosimetry

Organ at risk	Hard constraint	No. of PI constraint violations	Mean ± SD	Median	Range
Uninvolved lung	1500 cm^3 <12.5 Gy	NA	NA	NA	NA
(lung GTV)	1000 cm^3 <13.5 Gy	NA	NA	NA	NA
Trachea max	V50 Gy <0.2 cm^3	3	11.32 ± 1.83 cm^3	10.97 cm^3	9.68-13.30 cm^3
Bronchial tree max	V50 Gy <0.2 cm^3	NA	NA	NA	NA
Esophageal max	V32 Gy ≤0.5 cm^3	3	3.24 ± 1.27 cm^3	3.09 cm^3	2.05-4.58 cm^3
Heart/pericardium	V32 Gy ≤15 cm^3	3	23.38 ± 6.67 cm^3	25.66 cm^3	15.87-28.62 cm^3
Cord	V25 Gy <1.0 cm^3	3	1.87 ± 0.09 cm^3	1.84 cm^3	1.72-1.89 cm^3
Stomach max	V33 ≤0.5 cm^3	1	1.19 cm^3	1.19 cm^3	NA

Abbreviations: GTV = gross tumor volume; NA = not applicable; max = maximum; min = minimum; PI = initial nonadaptive plan; SD = standard deviation.

Treatment time and dosimetry data collection

Feasibility, defined by delivery of adaptive treatment in <80 minutes of on-table time for >75% of cases, was the primary study endpoint. Study physicians subjectively designed this endpoint based on the clinical estimation that patients would not tolerate treatments lasting longer than 80 minutes. This inference was based on treating physician opinion of typical patient tolerance of daily immobilized treatment positioning within the bore of an MR-IGRT device; at the time of the study there was a paucity of preceding prospective radiation therapy data to better estimate patient timing tolerances for MR-IGRT. Timing data, including door-to-door patient treatment time and subcomponents such as imaging, recontouring, replanning, and plan QA times, were prospectively recorded by the treating radiation therapists. Dosimetry metrics, including fraction-by-fraction OAR dose, cumulative GTV/PTV dose, and projected dose that would have been delivered without plan adaptation, were also prospectively recorded. Current technology is insufficient to reproducibly identify point volumes of deformable OARs for dose accumulation. However, GTV/PTV dose accumulation was achieved by a previously described method, using rigid alignment of the daily dose distribution from each fraction to the first fraction, based on the centroid of the GTV volume, and addition of the dose from all fractions.[13]

Patient follow-up, outcomes, and statistical analysis

Patient demographic characteristics and baseline Response Evaluation Criteria in Solid Tumors (RECIST) target tumor measurements of the treated lesion were collected pretreatment and during scheduled study follow-up at 6 weeks, 3 months, and 6 months after treatment. Treatment response by RECIST was prospectively assessed by study physicians at 3 and 6 months after treatment. Acute thoracic toxicity, defined as toxicity within 6 months of radiation therapy completion, was assessed prospectively at 6 weeks, 3 months, and 6 months. Toxicity was graded according to the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4). Late toxicities were evaluated by treating physicians through routine clinical care and detailed retrospective chart review by study physicians. Disease-free, progression-free, and overall survival metrics were prospectively assessed at 3 and 6 months posttreatment. Longer-term outcomes were subsequently determined by study physicians through careful chart review and routine clinical appointments. The Kaplan-Meier method was

Table 3 Target volume coverage

Target volume	Goal coverage	Projected nonadaptive mean ± SD	Projected nonadaptive median (range)	Cumulative adaptive mean ± SD	Cumulative adaptive median (range)
PTV V50, %	NA	54.9 ± 50.8	77.6 (0-98.9)	73.1 ± 43.3	98.7 (0-100)
PTV V47.5, %	95%	57.4 ± 52.3	86.7 (0.1-100)	75.6 ± 43.1	99.8 (0.5-100)
GTV V50, %	100%	59.3 ± 54.2	96.7 (0-100)	76.2 ± 43.4	100 (0-100)
GTV V47.5, %	100%	60.0 ± 54.0	98.2 (0.5-100)	78.8 ± 43.6	100 (1.1-100)
GTV V45, %	100%	80.7 ± 29.3	99.0 (33.0-100)	86.3 ± 29.8	100 (33.0-100)
GTV max, Gy	NA	58.5 ± 10.5	58.1 (47.8-72.3)	62.5 ± 10.3	64.0 (49.1-76.5)
GTV min, Gy	NA	48.5 ± 11.1	43.5 (37.9-61.0)	53.0 ± 12.0	53.8 (40.3-70.1)

Abbreviations: GTV = gross tumor volume; max = maximum; min = minimum; NA = not applicable; PI = initial nonadaptive plan; PTV = planning target volume; SD = standard deviation.

Table 4 Treatment delivery parameters

Characteristic	Number (%) or Median (range)
Total delivered fractions	25
Total adapted fractions (% of total)	10 (40)
Adapted for ≥1 OAR violation, %	7 (28)
Adapted only to increase PTV coverage, %	3 (12)
Median on-table time (range), min	69 (22-117)
Median imaging (volumetric and gating acquisitions) time (range), min	2 (1-5)
Median recontour time (range), min	8 (2-13)
Median replan time (range), min	11 (8-20)
Median QA time (range), min	4 (2-6)
Median beam-on time (range), min	27 (13-52)

Abbreviations: OAR = organ at risk; PTV = planning target volume; QA = quality assurance.

used to estimate local progression-free survival. Statistical analyses were completed using SAS Version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Patient and tumor characteristics

Five patients were enrolled and treated per protocol to UCT sites. Four of the 5 patients received treatment to oligometastatic lesions, and 1 had an unresectable primary non-small cell lung cancer. Median follow-up time from completion of therapy was 14 months (range, 8-31 months). A complete summary of patient demographics and disease characteristics is available in Table 1.

Treatment planning and delivery

All initial plans met hard OAR constraints (Table 2) based on CT/MRI simulation anatomy. Adaptive plans met identical hard constraints based on daily volumetric setup MRI anatomy. All 5 patients completed planned treatment using a 5-fraction course of SMART, for a total of 25 delivered fractions. Ten of 25 total treatment fractions were delivered using online adapted plans based on superior OAR sparing (7 of 10) or improved PTV coverage (3 of 10) compared with the initial, nonadaptive plan. Four out of 5 patients required adaptive planning for ≥1 fraction. One patient had a tumor invading and attached to the pericardium without other adjacent OARs; the fixed tumor–pericardium spatial relationship was not found to change, and adaptation was not deemed advantageous in that patient. Summarization of disease subsites treated and the clinical reasons for plan adaptation for each patient are available in Tables 1 and 4.

The primary feasibility endpoint of delivery of >75% of treatment fractions in ≤80 minutes was not met. Although median on-table treatment time was 69 minutes (range, 22-117 minutes), only 68% (17 of 25) of treatment fractions were delivered in ≤80 minutes. Instead, 76% (19 of 25) of fractions were delivered in ≤90 minutes. A detailed breakdown of treatment time components is provided in Table 4.

OAR constraints

A total of 70% (7 of 10) of plan adaptations were due to need to reverse ≥1 hard OAR constraint violation that would have otherwise occurred had the initial, nonadaptive plan been delivered. An example case of plan adaptation to reverse OAR constraint violation that would have otherwise occurred is illustrated in Figure 1. OARs that would have received excess dose without adaptive planning included the esophagus (n = 3 averted violations), heart (n = 3), trachea (n = 3), stomach (n = 1), and spinal cord (n = 3). The magnitude by which constraints would have been exceeded was variable, as were the volumes of OARs that would have received excess dose; Figure 2 and Table 2 provide detailed summaries of OAR violations. With online adaptation, 100% of OAR violations that would have occurred were prevented.

Target volume coverage

Online plan adaptation had variable effects on target coverage. Plan adaptation was performed in 3 of 10 adapted fractions for the primary indication of improved PTV coverage (Fig 1). By contrast, in most (5 of 7) fractions in which adaptation was indicated to reverse an OAR constraint violation, GTV and PTV coverage were reduced to protect OARs. An example of such reduction in target coverage to reverse multiple OAR constraints is demonstrated by the dose-volume histogram in Figure 1. In 2 fractions, OAR violations could be reversed concomitantly with improvements in PTV coverage. One patient treated for a spindle cell sarcoma metastasis invading the pericardium required dose reduction in the original CT simulation plan to 35 Gy to 95% of the PTV to meet the hard cardiac constraint. No change in tumor/OAR geometry was identified during daily MR-guided treatments, adaptation was not advantageous at any fraction, and the delivered dose remained 35 Gy to the PTV. Despite need to protect OARs, however, the mean and median cumulative GTV and PTV coverage were superior with SMART compared with the projected coverage that would have been delivered with nonadaptive SBRT. Improved cumulative coverage with SMART was found across all recorded metrics of GTV and PTV coverage (Table 3). In Figure 3, a dose-volume histogram demonstrates dose accumulation to the GTV for an example patient.

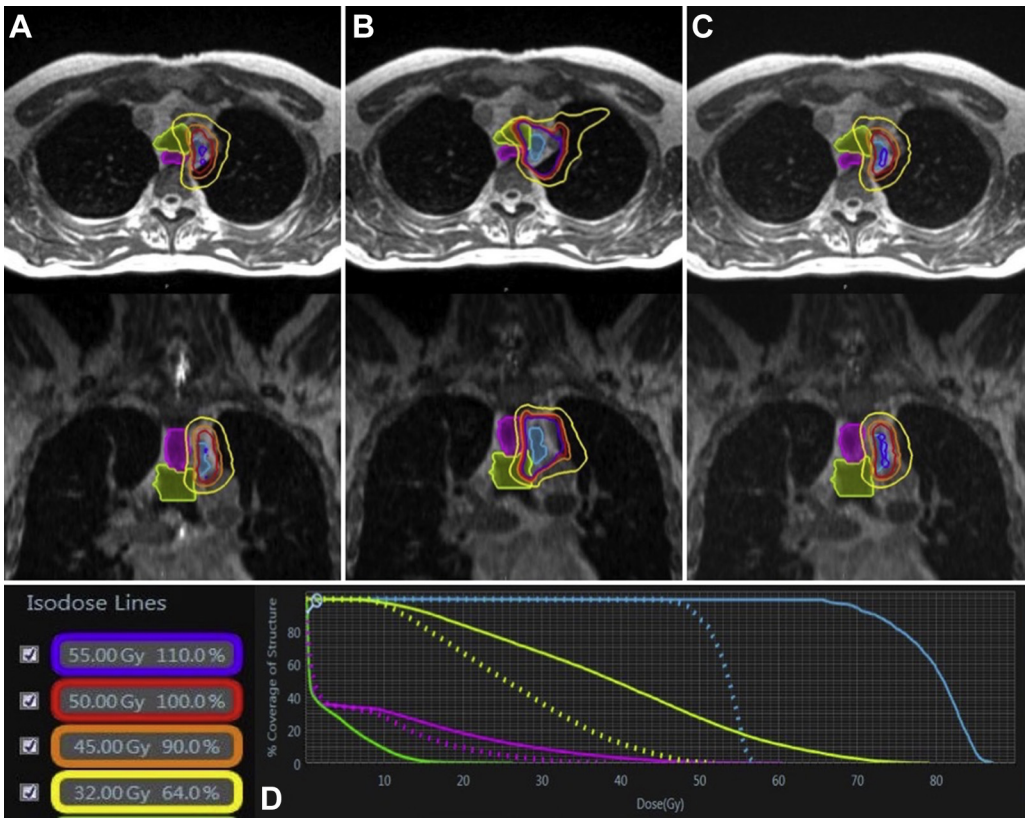

Figure 1 (A) A magnetic resonance (MR)–based, adaptive plan for fraction 1 (fx1) met all organ-at-risk (OAR) constraints based on daily setup anatomy from fx1. (B) Application of the fx1 plan to the fx2 MR image of a patient with an upper paratracheal metastasis (blue colorwash) abutting the esophagus (pink colorwash) resulted in violation of hard esophageal and trachea (green colorwash) constraints. (C) Daily adaptive planning for fx2 achieved OAR violation reversal while preserving target volume coverage, as determined by dose-volume histogram comparison (D). (A color version of this figure is available at https://dx.doi.org/10.1016/j.adro.2018.10.003.)

Toxicity

Acute grade $\geq$3 CTCAE v4 treatment-related toxicity events, defined as occurring within 6 months of SMART completion, were not identified. With regard to late toxicity, 1 patient treated for an upper paratracheal spindle cell sarcoma nodal metastasis abutting the esophagus developed a CTCAE v4 grade 3 benign esophageal stricture 15 months after completion of radiation therapy, causing dysphagia and requiring elective endoscopic dilation. A second patient treated for a pericardial renal cell carcinoma metastasis (requiring a reduced dose of 35 Gy as per earlier) had regional progression 8 months after treatment, including pericardial studding and a metastasis in the left ventricular outflow tract, and developed a symptomatic pericardial effusion requiring pericardial window placement with subsequent heart failure. This grade 4 toxicity 8 months after radiation therapy completion could not be ruled out as possibly related to radiation treatment but was deemed likely secondary to disease progression.

Tumor control and survival

Local control of the treated lesion, defined as stable disease, partial response, or complete response by RECIST criteria, was 100% at 3 and 6 months. Local progression–free survival was 100% at 3 and 6 months and 80% at 12 months by Kaplan-Meier estimate. One locoregional failure outside the high-dose region was identified at 8-month follow-up. Overall survival was 100% at 6 months and 60% at 12 months. At last follow-up, 2 patients had no evidence of disease (19-month and 12-month follow-up), including the patient treated for a primary non-small cell lung cancer (adenocarcinoma). One patient had locoregional progression resulting in death from disease (9-month follow-up), and 2 patients had both regional and distant metastatic progression resulting in cancer-related death (14- and 16-month follow-up).

Discussion

In this prospective trial, we evaluated the feasibility of delivering SMART to UCT tumors. Although our

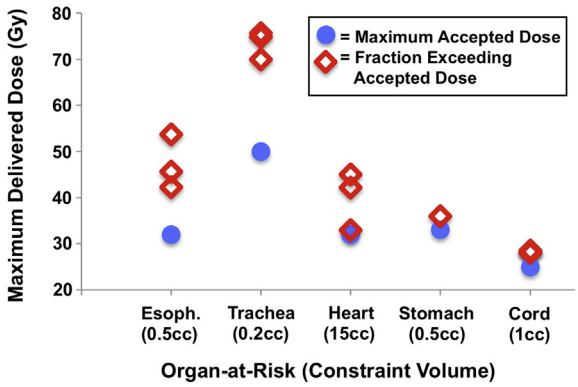

Figure 2 Maximum scaled point doses projected to be delivered to constraint volumes of organs at risk (OARs) when initial nonadaptive plans were applied to daily anatomy. Blue circles indicate goal OAR constraints over 5 fractions. (A color version of this figure is available at https://dx.doi.org/10.1016/j.adro.2018.10.003.)

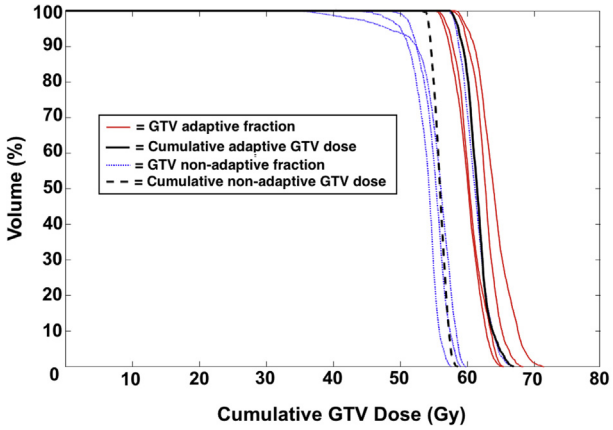

Figure 3 Example dose-volume histogram (DVH) demonstrating the fraction-by-fraction delivered gross tumor volume (GTV) dose using online adaptation for a typical patient with an ultracentral right upper lobe lung metastasis. Proximity to the heart required plan adaptation for multiple fractions, with variable adaptive GTV dose escalation and de-escalation, but cumulative GTV dose remained at goal. Dose from adaptive fractions (red lines) and the projected dose from the original simulation plan that would have been delivered by nonadaptive fractions (blue dashed lines) are shown for comparison, as are the cumulative adaptive versus nonadaptive dose. The treatment fraction depicted here exemplifies the typical cumulative dose profile for all patients included in the study. (A color version of this figure is available at https://dx.doi.org/10.1016/j.adro.2018.10.003.)

subjective, clinician-determined timing endpoint was not met, we found that SMART was clinically deliverable and treatment was tolerated by 100% of patients. SMART offered dosimetric gains, including improved OAR sparing and greater target coverage. Acute grade 3 or higher toxicities within 6 months of radiation therapy were not identified, and control of the treated lesion was 100% at 3 and 6 months. Our findings suggest that SMART may offer a safe and novel approach to deliver ablative doses of radiation therapy to lesions within the UCT.

The primary endpoint of this study was feasibility of SMART. Before study initiation, the criteria for feasibility were subjectively designed by study physicians based on the perception that patients would not tolerate >80-minute treatment sessions. Given that this was the first prospective clinical trial of MR-IGRT and of SMART, there were no available preceding data regarding patient tolerance of remaining immobilized within an MRI bore in the treatment position, and thus this endpoint was chosen. Our endpoint of delivery of >75% of fractions in ≤80 minutes was unmet, although we did achieve delivery of >75% of fractions in ≤90 minutes, with a median treatment time of 69 minutes. Nevertheless, although the subjective feasibility criteria set for this study were unmet, we still conclude that SMART is clinically deliverable to the UCT. This is based on the observation that although treatment required more time than patients were anticipated to tolerate, treatment was successfully delivered for all patients, and all patients tolerated all treatment fractions, despite the length of time for delivery. We note that first implementations of multiple therapy modalities (that have since become standard of care in radiation oncology), including intensity modulated radiation therapy and nonadaptive robotic SBRT, initially required much longer delivery times.[19,20] Since the time of the present study, multiple improvements to the online adaptive process have been implemented at our institution, resulting in reduced treatment times. These include hiring of advanced radiation therapists to assist with recontouring, a more focused resegmentation window, improved instructions for covering physicians, and streamlining of QA procedures.[21,22] In addition, we recently installed a commercially available MR-guided linear accelerator, which may offer reduced beam-on times compared with the tri-cobalt source used in this study. Although treatment times were somewhat longer than anticipated in this early application of SMART, it is reasonable to anticipate that organized efforts toward process and technology improvements will improve future time demands of MR-IGRT.[23]

We also found that SMART offered dosimetric gains, both for OAR sparing and tumor coverage, compared with nonadaptive SBRT, with no observed grade 3+ acute toxicity. Online adaptive planning uncovered multiple unintended OAR constraint violations that would have otherwise occurred with nonadaptive SBRT. Although some constraints were minimally exceeded (Fig 2) and may not have resulted in toxicity, other violations were severe and may represent the historic portion of patients experiencing high-grade acute toxicities in SBRT to the central thorax.[4] SMART reversed 100% of these constraint violations, including multiple point dose

violations to the heart and proximal airways. Only 1 patient did not gain dosimetric advantage for OAR protection through online adaptive planning; in this patient, the tumor was fixed to the adjacent critical OAR (the heart). This particular case may highlight a key concept of online adaptive planning: Therapeutic gains through adaptation are likely to be most pronounced in clinical scenarios in which the spatial relationship between tumors and OARs is variable, whether by tumor response during therapy or mobility of the OAR relative to the tumor.

Although the size of our cohort (5 patients) is limited, zero grade 3+ acute toxicities and only 1 radiation-related reversible late grade 3 toxicity were identified, despite the high-risk disease site treated. Although the cohort in this pilot study is small, a prior study evaluating similarly ablative dose schedules with SBRT near the central bronchi reported acute grade 3 or higher toxicity rates of 33% for central thorax patients.[24] Similarly, in the classic report by Timmerman et al,[4] 46% of patients experienced severe toxicity within 2 years of treatment. Although these experiences of substantial toxicity have discouraged use of highly ablative regimens in the UCT, it is possible that use of SMART may mitigate some toxicity risks.

Importantly, improvements in OAR sparing across the cohort did not compromise cumulative target coverage. Both cumulative GTV and PTV coverage were improved, on average, with SMART compared with projected nonadaptive plans. In several fractions, favorable daily anatomy was observed such that online adaptive planning could be performed specifically to increase target coverage. Local control of the treated lesion was excellent and compares favorably with other reports of SBRT to the central and peripheral thorax, with 100% of patients having control by RECIST criteria at 3 and 6 months posttreatment.[25] The combined dosimetric and clinical findings of treatment safety and tumor control with improved target coverage suggest that SMART may offer a widened therapeutic index for ablative radiation therapy treatment in the UCT.

We acknowledge several limitations to this study. First, although fraction-by-fraction OAR dose was reduced using SMART in this small initial cohort, point dose accumulation to OARs was not performed. Dose deformation and accumulation of dose to OARs is the subject of ongoing research at our institution. However, reproducible methods to identify point volumes of deformable OARs to cumulatively track dose are not offered by current technology. Our fraction-by-fraction isotoxicity approach is therefore conservative, although it does beneficially ensure that no point volume of OAR can receive excess dose. Additionally, the on-board imaging component of the MR-IGRT device used in this study allowed for cine MR monitoring and gating in a single 2-dimensional plane, and it is possible that unobserved tumor/OAR motion in other planes during treatment delivery could diminish the therapeutic gains achieved through daily online adaptive planning. Although 3-dimensional volumetric real-time MR guidance and techniques to manage and adjust for intrafraction motion are of interest and may represent future standards of care, they are not clinically available at this time.[26,27] The imaging component of the device used in this study is also not of diagnostic quality, with magnet strength of 0.35 T. However, this low-field MRI component has been found to be sufficient and effective for clinical use in several clinics, including for SBRT and online adaptive applications.[12,21,28] Finally, although new prospective evidence is emerging to support a survival benefit of ablative treatment for oligometastatic disease (as performed for the majority of patients in this study), use of oligoablation remains debatable in many tumor histologic types and is the subject of ongoing study.[29–31] However, this clinical question is beyond the scope of our study, which primarily sought to determine feasibility of SMART as a novel radiotherapeutic approach to the UCT.

Conclusions

We found that SMART is a clinically deliverable, dosimetrically advantageous, and well-tolerated technique for ablation of UCT malignancies. SMART results in increased OAR sparing and simultaneous improvements in target coverage compared with traditional SBRT. Our future interests include further validation of SMART to the UCT in an expanded patient cohort as well as process improvements to streamline the clinical integration of online adaptive techniques for widespread clinical use.

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