Advances in Radiation Oncology (2022) 7, 100978

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Multi-Institutional Outcomes of Stereotactic Magnetic Resonance Image Guided Adaptive Radiation Therapy With a Median Biologically Effective Dose of 100 Gy_{10} for Non-bone Oligometastases

Tugce Kutuk, MD,[a] Robert Herrera, BS,[a] Teuta Z. Mustafayev, MD,[b] Gorkem Gungor, PhD,[b] Gamze Ugurluer, MD,[b] Banu Atalar, MD,[b] Rupesh Kotecha, MD,[a,c] Matthew D. Hall, MD, MBA,[a,c] Muni Rubens, MBBS, MPH, PhD,[d] Kathryn E. Mittauer, PhD,[a,c] Jessika A. Contreras, MD,[a,c] James McCulloch, DMP,[a,c] Noah S. Kalman, MD, MBA,[a,c] Diane Alvarez, MSc,[a,c] Tino Romaguera, PhD,[a,c] Alonso N. Gutierrez, PhD, MBA,[a,c] Jacklyn Garcia, BS,[e] Adeel Kaiser, MD,[a,c] Minesh P. Mehta, MD,[a,c] Enis Ozyar, MD,[b] and Michael D. Chuong, MD[a,c,*]

[a]Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida; [b]Department of Radiation Oncology, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey; [c]Department of Radiation Oncology, Herbert Wertheim College of Medicine, Florida International University, Miami, Florida; [d]Department of Clinical Informatics, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida; [e]Herbert Wertheim College of Medicine, Florida International University, Miami, Florida

Received March 17, 2022; accepted April 16, 2022

Sources of support: This work had no specific funding.

Disclosures: Dr Kotecha reports honoraria from Accuray Inc, Elekta AB, ViewRay Inc, Novocure Inc, Elsevier Inc, and Brainlab and institutional research funding from Medtronic Inc, Blue Earth Diagnostics Ltd., Novocure Inc, GT Medical Technologies, AstraZeneca, Exelixis, ViewRay Inc, and Brainlab. Dr Hall reports honorarium from Accuray, Inc.; is a Proton Collaborative Group Executive Committee Institutional Representative and a voting member, Miami Cancer Institute (unpaid); receives grant funding from Live Like Bella Pediatric Cancer Research Initiative, and a Florida Department of Health grant (8LA04). Dr Mittauer reports honoraria, consulting, and research funding from ViewRay Inc and is a cofounder of MR Guidance LLC. Dr Contreras reports consulting fees from Boston Scientific. Kalman reports being an advisory board participant for Naveris. Dr Gutierrez reports honoraria from ViewRay Inc, Elekta AB, IBA S.A, and ownership of uPlan Oncology. Dr Mehta reports consulting fees from Mevion, Zap, Sapience, Blue Earth Diagnostics, IBA, and Xoft, NRG Oncology leadership role, stock or stock options for Chimerix, and is on the Board of Directors of Oncoceutics. Dr Chuong reports honoraria from ViewRay, Sirtex, is on the advisory board for ViewRay, and receives research funding from ViewRay, Novocure, StratPharma. All other authors have no disclosures to declare.

Presented at the American Society for Radiation Oncology 2021 meeting. Chicago, IL. October 26, 2021.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Michael D. Chuong, MD, FACRO; E-mail: MichaelChu@baptisthealth.net

https://doi.org/10.1016/j.adro.2022.100978

Abstract

Purpose: Randomized data show a survival benefit of stereotactic ablative body radiation therapy in selected patients with oligometastases (OM). Stereotactic magnetic resonance guided adaptive radiation therapy (SMART) may facilitate the delivery of ablative dose for OM lesions, especially those adjacent to historically dose-limiting organs at risk, where conventional approaches preclude ablative dosing.

Methods and Materials: The RSSearch Registry was queried for OM patients (1-5 metastatic lesions) treated with SMART. Freedom from local progression (FFLP), freedom from distant progression (FFDP), progression-free survival (PFS), and overall survival (LS) were estimated using the Kaplan-Meier method. FFLP was evaluated using RECIST 1.1 criteria. Toxicity was evaluated using Common Terminology Criteria for Adverse Events version 4 criteria.

Results: Ninety-six patients with 108 OM lesions were treated on a 0.35 T MR Linac at 2 institutions between 2018 and 2020. SMART was delivered to mostly abdominal or pelvic lymph nodes (48.1%), lung (18.5%), liver and intrahepatic bile ducts (16.7%), and adrenal gland (11.1%). The median prescribed radiation therapy dose was 48.5 Gy (range, 30-60 Gy) in 5 fractions (range, 3-15). The median biologically effective dose corrected using an alpha/beta value of 10 was 100 Gy_{10} (range, 48-180). No acute or late grade 3+ toxicities were observed with median 10 months (range, 3-25) follow-up. Estimated 1-year FFLP, FFDP, PFS, and OS were 92.3%, 41.1%, 39.3%, and 89.6%, respectively. Median FFDP and PFS were 8.9 months (95% confidence interval, 5.2-12.6 months) and 7.6 months (95% confidence interval, 4.5-10.6 months), respectively.

Conclusions: To our knowledge, this represents the largest analysis of SMART using ablative dosing for non-bone OM. A median prescribed biologically effective dose of 100 Gy_{10} resulted in excellent early FFLP and no significant toxicity, likely facilitated by continuous intrafraction MR visualization, breath hold delivery, and online adaptive replanning. Additional prospective evaluation of dose-escalated SMART for OM is warranted.

Introduction

Resection can result in improved long-term outcomes and even cure for some patients with limited metastatic disease.[1-3] Oligometastases (OM) can also be effectively treated with stereotactic ablative radiation therapy (SABR), which has emerged as a noninvasive alternative to surgery. When used in addition to chemotherapy, SABR may improve freedom from local progression (FFLP), progression-free survival (PFS), and overall survival (OS) in patients with OM compared with chemotherapy alone.[4-7]

Although SABR is well tolerated for most patients, severe toxicity is possible. In the SABR-COMET trial, 3 patients (4.5%) experienced treatment-related death.[4] Other studies have reported that moderate or severe toxicity is not infrequent, especially when treating lesions in the abdomen and central lung.[8-11] Moreover, the proximity of certain organs at risk (OARs) may necessitate that the prescribed dose be constrained to limit toxicity.

Magnetic resonance-guided radiation therapy (MRgRT) is particularly well suited to deliver ablative dose with ultrahypofractionation even for lesions in challenging anatomic locations that otherwise may be prescribed a lower dose using computerized tomography (CT) guidance.[12] A primary reason for this is the ability to visualize both the target and critical surrounding OARs on a daily basis, as well as during the delivery of each fraction, and responding to change from 1 day to the next through adaptation, and change during treatment delivery through beam gating/hold. This is distinctly different from all other radiation therapy technology platforms, where continuous intrafraction tracking usually relies on a surrogate fiducial, rather than the complex and dynamic anatomic interplay between the target and OARs. The feasibility of stereotactic magnetic resonance-guided adaptive radiation therapy (SMART) has been demonstrated for tumors in the chest, abdomen, and pelvis.[13-19] However, most of the supporting literature consists of small retrospective and phase 1 trials. The intent of this analysis was to evaluate multi-institutional outcomes of SMART for OM to better understand the benefits of this novel technology.

Methods and Materials

The Radiosurgery Society RSSearch Registry was queried for patients treated with MRgRT for OM, defined as 5 or fewer metastatic lesions. RSSearch is managed by the Radiosurgery Society, a nonprofit professional medical society. A description of the methodology, database design and initial patient and treatment characteristics of patients enrolled in RSSearch has been previously reported.[20] After receiving institutional review board approval, we performed a retrospective analysis of safety and efficacy outcomes in these patients. All patients were treated using the ViewRay MRIdian Linac (Oakwood Village, OH) between September 2018 and September 2020 at 2 tertiary cancer care institutions.

Simulation, treatment planning, and treatment delivery on the MRIdian Linac have been previously published

Table 1 Dose constraints used for 50 Gy in 5 fraction (biologically effective dose: 100 Gy_{10}) stereotactic magnetic resonance image guided adaptive radiation therapy in oligometastases

Organ at risks	Hard constraints
Spinal cord	Maximum dose less than 30 Gy; V25 Gy ≤0.5 cm^3
Liver	700 cm^3 <18 Gy; Mean <15 Gy
Large bowel	V33 Gy ≤0.5 cm^3; V40 Gy ≤0.03 cm^3
Stomach	V33 Gy ≤0.5 cm^3; V40 Gy ≤0.03 cm^3
Duodenum	V30 Gy <5 cm3; V33 Gy <1 cm^3; V36 Gy <0.5 cm^3; V40 Gy ≤0.03 cm^3
Small bowel	V30 Gy <5 cm^3; V33 Gy <1 cm^3; V36 Gy <0.5 cm^3; V40 Gy ≤0.03 cm^3
Kidney (combined)	Mean <10 Gy; 2/3 of each kidney ≤14 Gy
Kidney (single)	V12 Gy <10%
Vessels	Maximum dose <53 Gy; D47 <10 cc
Rectum	V25 Gy <20 cm^3; V33 Gy <10 cm^3; V34 Gy <5 cm^3; V36 Gy <1 cm^3; V38 Gy <0.1 cm^3
Bladder	V33 Gy <15 cm^3; V36 Gy <1 cm^3; V38 Gy <0.1 cm^3
Esophagus	V27.5 Gy ≤5 cm^3; V35 Gy ≤0.03 cm^3
Chest wall	V30 Gy ≤30 cm^3; V50 Gy ≤3 cm^3
Trachea	V40 Gy ≤0.03 cm^3
Heart	V40 Gy ≤0.03 cm^3
Lungs	V12.5 Gy ≤1500 cm^3; V13.5 Gy ≤1000 cm^3; V20 Gy ≤10%
Brachial plexus	V32 Gy ≤0.03 cm^3
Ribs	V52.5 Gy ≤0.03 cm^3

in detail.[16,17] Briefly, patients were simulated in the supine position typically with at least the ipsilateral arm raised above the head. Simulation scans were acquired on the MRIdian Linac in breath hold over 17 to 25 seconds based on a balanced free precession technique. Intravenous or oral contrast was not used as the tumor and normal anatomy are well-visualized due to the superior soft tissue contrast provided by the magnetic resonance imaging (MRI) scans. The simulation MRI scan was used as the primary scan for contouring and planning while a simulation CT scan was obtained for electron density. The gross tumor volume (GTV) encompassed visible tumor as defined on the simulation imaging as well as diagnostic scans with a 3 to 8 mm (median 3 mm) set up margin expansion to the planning target volume (PTV). Dose constraints used during planning and on-table adaptive review are presented in Table 1.

All treatments were planned using a step-and-shoot intensity modulated radiation therapy technique. During daily set-up for treatment, a volumetric MRI is obtained to visualize the target volume and OARs. Tumor target volumes were registered rigidly from the simulation MRI to the daily localization MRI scan, and OAR volumes undergo deformable registration using an intensity-based algorithm. GTV contours were manually adjusted by the attending physician and relevant OAR contours were adjusted to reflect the anatomy of the day (Fig 1). For each fraction, predicted dose was computed (ie, the baseline plan was recalculated on the anatomy of the day and a reoptimized adaptive plan was generated). The adaptive plan was used for treatment if superior (ie, insufficient target volume coverage; <95% of PTV receives 100% of the dose) or OARs dose violations significantly exceeding the predicted dose. Before treatment, calculation fidelity was verified through a secondary Monte Carlo-based quality assurance (QA) dose calculation. After QA, treatment was delivered during breath hold, guided by visual biofeedback provided to the patient with an in-room monitor that projected the real-time MRI 2-dimensional sagittal at 4 or 8 frames per second. The time for workflow steps was documented for each patient and included time-stamps of setup, 3-dimensional MRI localization, segmentation, dose prediction and reoptimization with QA, real-target cine MRI, beam delivery, and any unexpected treatment disruptions.

The Common Terminology Criteria for Adverse Events version 4.0 criteria[21] was used to score treatment-related toxicities during follow-up visits by treating physicians. Toxicities were acute when occurring within 90 days from completion of SMART, and any afterward was considered late. Treatment response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[22] Patients were followed every 3 months with CT, positron emission tomography, CT, or

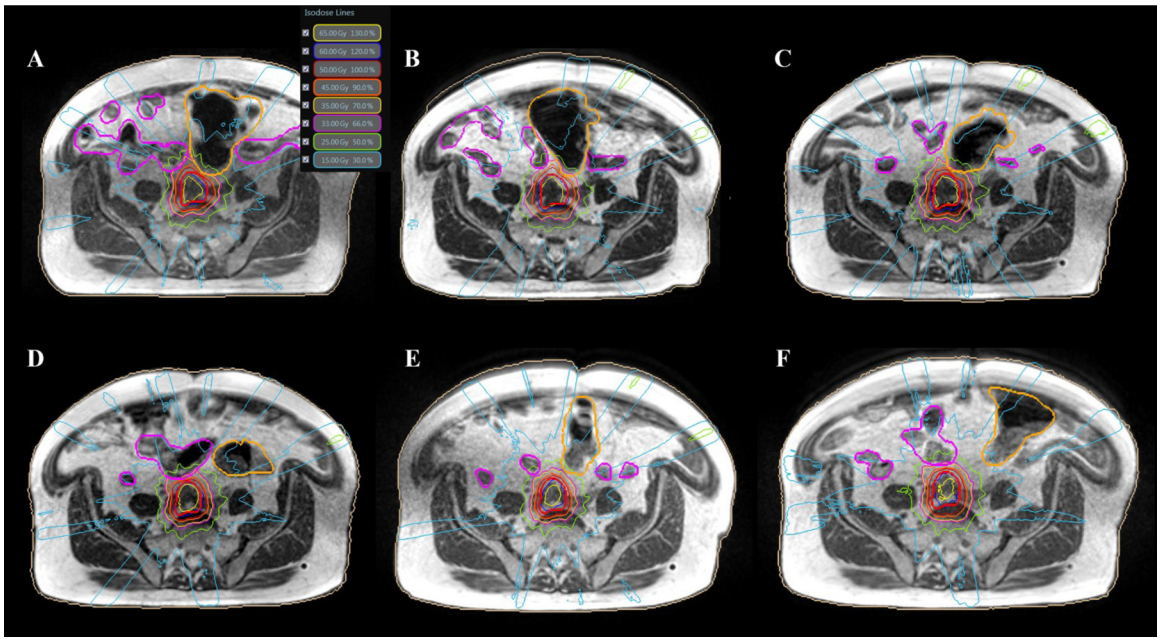

Fig. 1 Isodose distributions from the original treatment plan (A) compared with each daily fraction (B-F) achieved with on-table adaptive replanning to ensure organ at risk constraints are met due to interfraction anatomic changes of a patient with lung carcinoma with abdominopelvic lymph node metastasis.

MRI. OS was calculated from the date of initiating SMART to the day of last follow-up or death. Freedom from distant progression (FFDP), PFS, FFLP and OS were estimated using the Kaplan-Meier method. Statistical analysis was performed using SPSS, version 27 (SPSS Inc, Chicago, IL).

Results

From September 2018 to September 2020, 108 OM lesions in 96 consecutive patients met inclusion criteria for this study. Patient demographics and disease characteristics are described in Table 2. The median age was 61.5 years (range, 23-89 years) and 53.1% were male. The most common primary tumor sites were lung (31.5%) followed by colorectal (26.8%) and gynecologic malignancies (13.0%). The most common treatment sites for SMART were abdominal/pelvic lymph nodes (52 lesions, 48.1%), lung (20, 18.5%), liver and intrahepatic bile ducts (18, 16.7%), adrenal gland (12, 11.1%), and subcutaneous soft tissues (6, 5.6%). All patients had good performance status (Eastern Cooperative Oncology Group 0-1). Seventy-nine lesions (73.2%) were metachronous and 27 (25.0%) were synchronous OM. The primary tumor was definitively managed in 34.7% patients and 50% received chemotherapy for OM before SMART. All patients were treated without fiducial markers and with real-time MR-based tumor tracking and automated beam gating, allowing for intra- and interfraction visualization of both the target and the critical OARs.

All patients completed planned treatment with SMART and required adaptive planning for ≥1 fraction. The reasons for plan adaptation were insufficient target coverage in 233 (54.2%) fractions, OARs dose violations in 111 (25.8%) fractions, and both target coverage and OARs dose violations in 86 (20.0%) fractions (Table 2). A total of 571 fractions were delivered and 430 fractions (75.3%) were reoptimized. The median prescribed dose and fraction number were 48.5 Gy (range, 30-60 Gy) and 5 fractions (range, 3-15 fractions), respectively. The median biologically effective dose corrected using an alpha/beta value of 10 (biologically effective dose [BED]) was 100 Gy_{10} (range: 48-180). The median GTV and PTV were 7.1 cm^3 (range, 0.4-452.4 cm^3) and 14.5 cm^3 (range, 1.5-567.8 cm^3), respectively. The median time in the treatment room for set-up was 45 minutes per fraction (interquartile range, 35 to 56 min) and median treatment delivery time with gating was 21 min per fraction (interquartile range, 14-27 min).

Median follow-up time from completion of SMART was 10 months (range, 3-25 months). Thirty-five (36.4%) patients received chemotherapy and 16 (16.7%) patients received immunotherapy after SMART. Complete radiographic response occurred in 61 (56.5%) OM lesions, stable disease in 24 (22.2%) lesions, partial response in 16 (14.8%), and local progression in 7 (6.5%) lesions. Distant progression occurred in 63 cases (58.3%). There was no treatment-related grade 3+ toxicity after SMART. We

Table 2 Patient, tumor, and treatment characteristics

Characteristics	N (%/range)
Total no. patients	96
Total number of lesions	108
Median age, y	61.5 (23-89)
Sex	
Women	45 (46.9%)
Men	51 (53.1%)
Primary tumor location	
Lung	34 (31.5%)
Colorectal	29 (26.8%)
Cervix/uterus/ovary	14 (13.0%)
Breast	6 (5.6%)
Esophagus/gastric	5 (4.6%)
Other	20 (18.5%)
Location of treated lesion	
Abdominal/pelvic lymph nodes	52 (48.1%)
Lung	20 (18.5%)
Liver and intrahepatic bile ducts	18 (16.7%)
Adrenal gland	12 (11.1%)
Connective, subcutaneous and other soft tissues	6 (5.6%)
ECOG	
0	85 (78.7%)
1	23 (21.3%)
Oligometastases type	
Synchronous	27 (25.0%)
Metachronous	79 (73.2%)
Unknown	2 (1.8%)
Median number of oligometastases	1 (1-5)
Prior chemotherapy	
Yes	54 (50.0%)
No	54 (50.0%)
Total delivered fractions	571
Total adapted fractions	430 (75.3%)
Clinical reasons for plan adaptation	
Insufficient target coverage	233 (54.2%)
OARs dose violations	111 (25.8%)
Target coverage and OARs dose violations	86 (20.0%)
Median prescribed dose (Gy)	48.5 (30-60)
Median fraction number	5 (3-15)
Median BED_{10} (Gy)	100 (48-180)
Median GTV volume (cm^3)	7.1 (0.4-452.4)
Median PTV volume (cm^3)	14.5 (1.5-567.8)

Abbreviations: BED = biologically effective dose; ECOG = Eastern Cooperative Oncology Group; GTV = gross tumor volume; OARs = organs at risk; PTV = planning target volume.

recorded grade 1 toxicity in 11 (10.2%) patients and grade 2 toxicity in 3 (2.8%) patients. One-year FFLP, FFDP, PFS, and OS were 92.3% (95% confidence interval [CI], 86.3%-98.3%), 41.1% (95% CI, 30.2%-52.0%), 39.3% (95% CI, 28.6%-50.0%), and 89.6% (95% CI, 82.6%-96.6%), respectively (Fig 2 A-D). Median FFDP and PFS were 8.9 months (95% Cl, 5.2-12.6 months) and 7.6 months (95% Cl, 4.5-10.6 months), respectively. Median OS and FFLP were not reached yet.

Discussion

SABR for patients with OM may improve survival for certain subsets of patients. MRgRT represents a promising ablative treatment modality for OM lesions due to its excellent soft tissue contrast, motion management and automatic beam gating, and online adaptive replanning capability that enables safe dose escalation even to lesions in proximity to radiosensitive OARs such as the stomach and bowel. In what is, to our knowledge, the largest analysis of SMART for none-bone OM to date, no patient experienced grade 3 or higher toxicity. This is noteworthy given the predominance of lesions, especially abdominopelvic lymph nodes, treated with dose escalation in proximity to gastrointestinal OARs, which are notably underrepresented in previous OM trials and compares favorably to prospective trials such as SABR-COMET.[4]

Despite increasing enthusiasm for SABR in OM disease, questions remain about the optimal therapeutic approach due to its higher toxicity.[3-5,8] The potential to cause severe or fatal toxicity should not be overlooked for the utilization of SABR for oligometastatic disease. Three (4.5%) grade 5 treatment-related toxicities occurred in the SABR-COMET trial.[4] Recently, Olson et al[11] presented the results of SABR-5 trial that also included one (0.3%) grade 5 toxicity. Clinical outcomes and toxicity rates for select OM trials are summarized in Table 3. Moreover, the most frequently prescribed fractionation in OM was 35 Gy in 5 fractions in the SABR trials, and the median BED was about 60 Gy_{10} which can be a suboptimal for achieving durable FFLP.

There is increasing evidence that at least LC is correlated with increased radiation therapy dose.[20-22] A meta-analysis of 1006 patients who received SABR for adrenal metastasis demonstrated a strong correlation between prescribed dose and 1- and 2-year LC; BED 60 Gy_{10} versus 100 Gy_{10} was associated with 2-year LC of 47.8% versus 85.6%, respectively.[23] A multi-institutional analysis of SABR for 381 colorectal OM concluded that BED $\geq$120 Gy_{10} was significantly associated with improved LC on multivariate analysis.[24] However, non-ablative dose regimens are routinely used to minimize the risk of severe toxicity especially for lesions in challenging anatomic locations and in proximity to certain OARs such as the

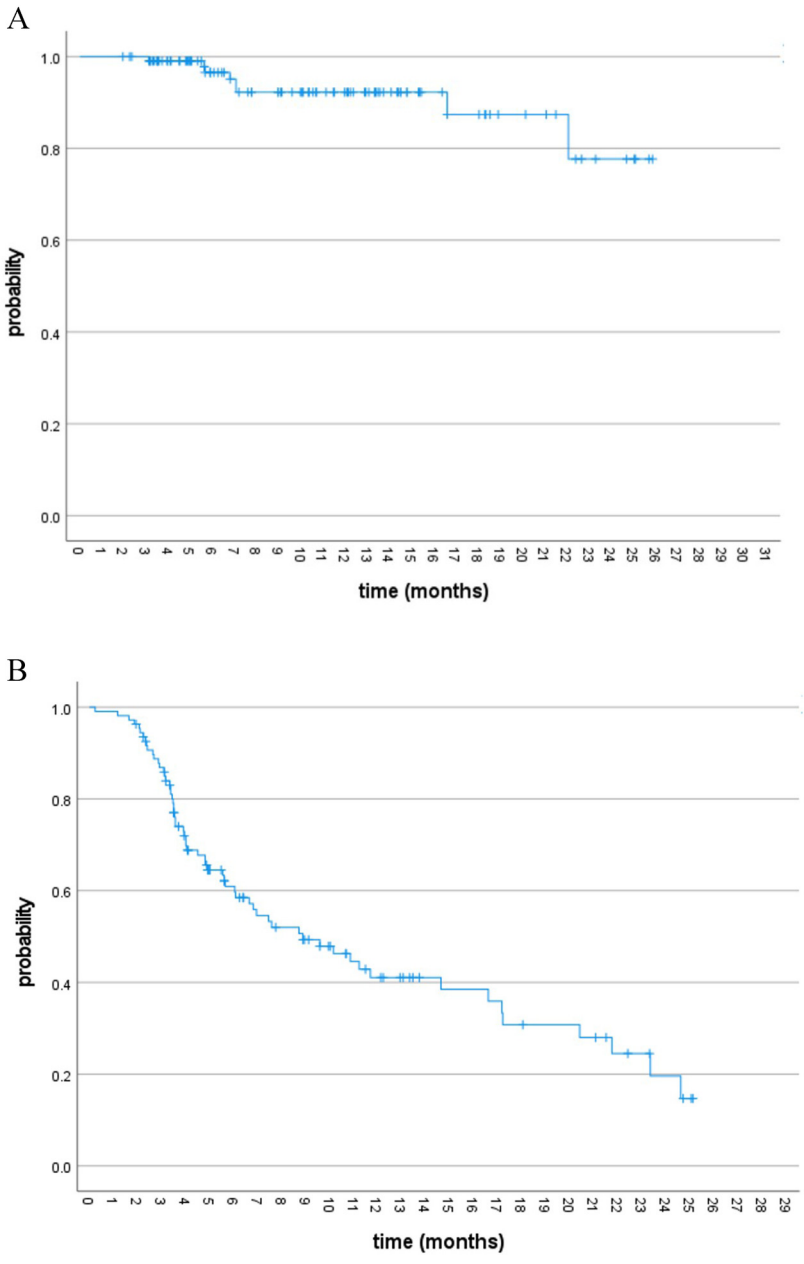

Fig. 2 (A) Kaplan-Meier Freedom from local progression, (B) Freedom from distant progression, (C) Progression free survival, (D) Overall survival.

bowel. The most common regimen used in the SABR-COMET trial, for example, was 35 Gy in 5 fractions (BED = 59.5 Gy_{10}).[4] Despite the majority of lesions in our study being in proximity to gastrointestinal luminal OARs, the median prescribed BED was 100 Gy_{10} that resulted in excellent 1-year FFLP with minimal severe toxicity, likely facilitated by online adaptive replanning.[25]

There is a growing body of evidence that supports safe dose escalation using SMART for OM. Henke et al[15] demonstrated the importance of the SMART approach with 50 Gy in 5 fractions (BED 100 Gy_{10}) in their phase 1 trial including 20 patients with OM or unresectable abdominal tumors, where adaptive plans were created for 83.5% of fractions and in which PTV coverage was increased in 66% of fractions. No patient developed grade 3+ toxicity. Henke et al also published results of a phase 1 trial of SMART for ovarian OM showing that dose escalation was safe.[26] Ugurluer et al[19] evaluated SMART in 21 patients treated to 24 liver metastases to a median total dose of 50 Gy in 5 fractions (BED = 100 Gy_{10}) and 83.7% of fractions were reoptimized; no grade 3+ toxicity was reported. In our study, there was no reported grade 3 or higher toxicity

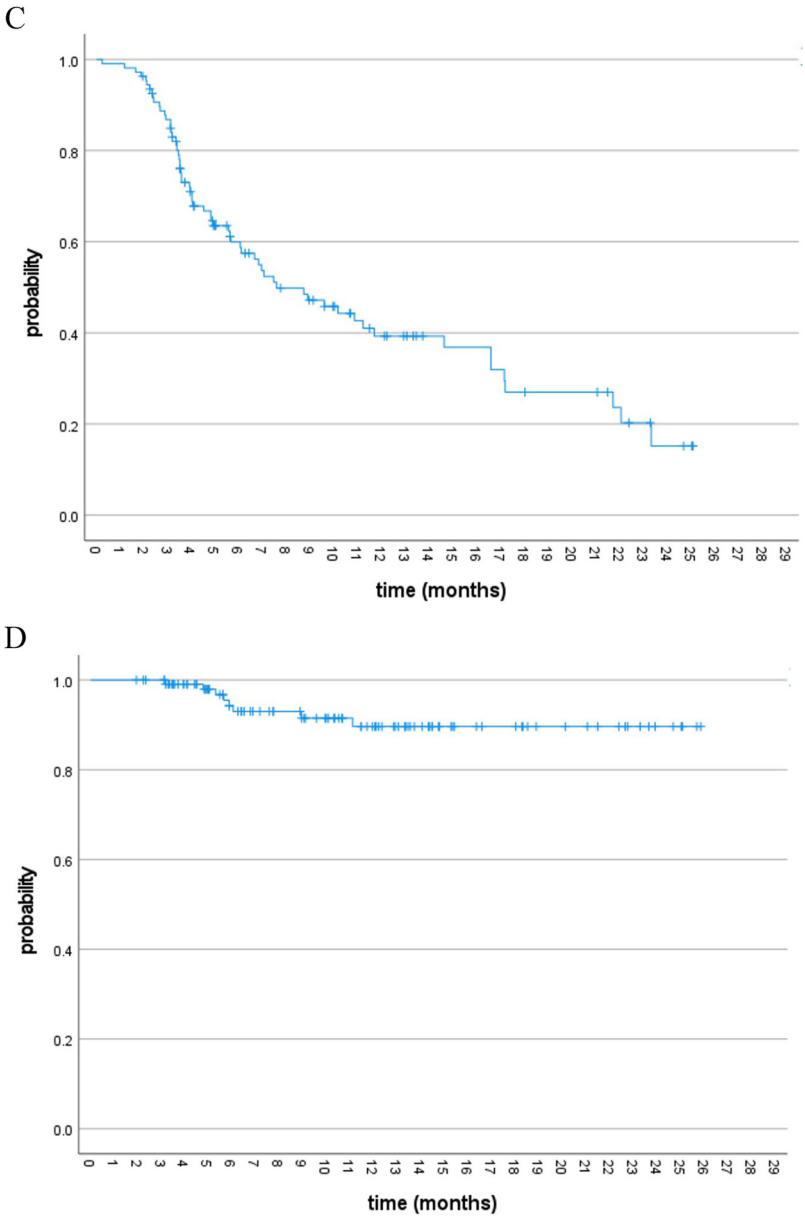

Fig. 2 **Continued.**

despite the median prescribed BED of 100 Gy_{10}, adding to the evidence suggesting that SMART is an ideal strategy to deliver ablative dose even to lesions in challenging anatomic locations, such as lymph nodes in the abdomen and pelvis.

Oligometastatic involvement of lymph nodes appears in 15% to 20% of cancer cases and depends on primary tumor type and histology.[27] Although several studies have shown improved survival after complete resection of abdominopelvic lymph node metastases, resection of such nodal metastases is technically challenging, and radiation therapy offers an effective alternative.[28,29] Previous evidence from several disease sites suggests that an increased BED is associated with improved survival.[30-32] Augugliaro et al[33] reported a retrospective analysis of 13 OM patients with bladder primary who received most commonly 25 Gy in 5 fractions (BED = 37.5 Gy_{10}) to abdominopelvic lymph nodes, but this nonablative dose showed in-field progression among 38% of patients within 3 months. Franzese et al[34] reported the SABR results of 278 patients with 418 oligometastatic lymph nodes with a median follow-up of 15.1 months and local control was 87.2% at 1 year. In their study, they showed that better local control was associated with BED greater than 75 Gy_{10}. In a recent study, Sheikh et al[24] reported the outcomes of 235 patients with a total of 381 OM colorectal cancer lesions. On multivariable analysis, a BED of more than 120 Gy_{10} was associated with a reduction in local recurrence compared

Table 3 Summary of selected clinical reports of SABR and SMART for oligometastatic disease

Study	Median follow-up (months)	Patients	Lesions treated with radiation therapy	Primer histology	Treatment site	Median BED10	Treatment regimen	Local control	Overall survival	Toxicity
SABR studies										
Palma et al[4] (SABR-COMET)[4]	26	66	127	Multiple	Adrenal 7; bone 45; liver 16; lung 55; other 4	60	35 Gy in 5 fx most common	75% at median follow-up	41 months	29% grade 2+ 4.5% grade 5
Iyengar et al[35]	9.6	14	31	NSCLC	Lung 17; adrenal 3 mediastinal ln; 4 bone; 2 liver; 2 Other 3	NA	21-37.5 Gy in 1-5 fx	NA	Not reached	28.6% grade 3+
Zelevsky et al[36]	52	117	154	Multiple	Bone 103; LN 10; bone + LN 4	81.6 vs 51.3	24 Gy in 1 fx vs 27 Gy in 3 fx	3 y 94.2% vs 78%	NA	9.1% grade 2+ 5.8% grade 3+
Olson et al (SABR-5)[11]	28	399	NA	Multiple	Lung 33%; nonspine bone 28%; spine 14%; ln 13%; liver 5%; adrenal 3%	NA	15-60 Gy in 1-8 fx	NA	NA	18.7% grade 2+ 4.5% grade 3+ 0.3% grade 5 (liver, adrenal and LN lesions toxicity 18.5%-27.3% grade 2+)
Chalkideu et al[5]	13	1422	1421	Multiple	Lung 411; spine 132; bone 169; adrenal 41; liver 135; ln 439; other 77	NA	24-60 Gy in 3-8 fx	1 y 86.9% 2 y 72.3%	1 y 92.3% 2 7 79.2%	6.0% grade 3+
SMART studies										
Henke et al[15]	15	20	20	Multiple	Liver 10; pancreas 5; abdominopelvic ln 3; adrenal 2	100	50 Gy in 5 fx	90% at median follow-up	1 year 75%	0
Ugurluer et al[19]	11.6	21	24	Multiple	Liver	100	50 (40-60) Gy in 5 (3-8) fx	1-y intrahepatic control 89.7%	1-y 93.3%	0
Yoon et al[37]	20.4	106 (46			oligometastases)	121	Multiple	Liver 46; pancreas 26; adrenal 7; prostate 6; pelvic side wall; 6 other 22	72	40 (24-60) Gy in 5 (3-5) fx
1 y 87% 2 y 74%	1 y 79% 2 y 57%	Acute 0.9% grade 3+; late 7.3% grade 3 +								
de Mol van Otterloo et al (MOMENTUM)[38]	NA	516 (116			oligometastases)	NA	Multiple	Prostate 223; LN 106; rectum 57; liver 30; pancreas 21; oropharynx 12; brain 7	NA	Variable
NA	NA	4% grade 3+								
Henke et al[26]	17.1	10	17	Ovarian	LN 14; soft tissue 3	60-100	35 Gy in 5 fx (dose escalation until 50 Gy in 5 fx)	3-mo 94%	1 year 80%	Acute 5.9% grade 3+; late 0 grade 3+

Abbreviations: fx = fraction; LN = lymph node; NA = not allowed; NSCLC = non-small cell lung cancer; SABR = stereotactic ablative radiation therapy; SMART = stereotactic magnetic resonance guided adaptive radiation therapy.

with less than 93.6 Gy_{10}. However, with SABR, dose escalation to BED 100 Gy_{10} in the abdominopelvic region may not be possible due to the location of OARs around the target lymph nodes.[5,7,27] By using real-time visualization and online adaptive capability, SMART can be more suitable for abdominopelvic lymph nodes due to the ability to visualize and track several critical organs such as the stomach and bowel. In previous studies of SMART, patients with abdominopelvic lymph nodes were underrepresented. In our study, of the 108 treated lesions, 52 (48.1%) were abdominopelvic lymph nodes. We believe that this study can contribute to the literature regarding the usage of SMART for abdominopelvic lymph node metastases.

Our study has several limitations including the fact that this is a retrospective study that may underreport toxicity, has short follow-up time, and includes a heterogeneous group of primary diagnosis and treatment doses. We reported the short-term toxicity experience in our study due to the median 10-months follow-up; however, longer follow-up is needed to draw conclusions on long-term safety and efficacy. Furthermore, the important toxicities on SABR-5[11] and SABR-COMET[4] trials occurred outside of the short-term period used in this study, we are planning to report long-term follow-up results in a forthcoming analysis to better understand late toxicity and long-term clinical outcomes and compare with SABR trials once mature date become available. Finally, because most fractions were adapted, the cumulative dose was not evaluated in terms of clinical outcomes.

Conclusions

This study demonstrates that SMART is feasible with at least no significant short-term toxicity for delivering ablative dose to OM near OARs. These outcomes are noteworthy given the predominance of OM, especially LNs, treated with dose escalation despite their proximity to gastrointestinal OARs; such lesions are notably underrepresented in SABR OM trials. In fact, in this report, there were no bone lesions treated, a significant departure from conventional trials of OM. Since our study has only 10 months median follow-up, longer follow-up required to better understand both long-term safety as well as durability of local control consequential to these high-dose radiation therapy regimens (BED $\geq$ 100 Gy_{10}). Furthermore, to overcome the biases associated with retrospective evaluations, a prospective trial is planned at our institution to evaluate the outcomes of SMART with OM.

References

1. Divisi D, Barone M, Zaccagna G, et al. Surgical approach in the oligometastatic patient. *Ann Transl Med*. 2018;6:94.
2. Fernandez RAS, Lau RWH, Ho JYK, et al. Evidence for surgical resections in oligometastatic lung cancer. *J Thorac Dis*. 2019;11:S969–S975.
3. Salama JK, Chmura SJ. Surgery or ablative radiotherapy for breast cancer oligometastases. *Am Soc Clin Oncol Educ Book*. 2015:e8–e15.
4. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. *Lancet*. 2019;393:2051–2058.
5. Chalkidou A, Macmillan T, Grzeda MT, et al. Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: A prospective, registry-based, single-arm, observational, evaluation study. *Lancet Oncol*. 2021;22:98–106.
6. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: The oriole phase 2 randomized clinical trial. *JAMA Oncol*. 2020;6:650–659.
7. Al-Shafa F, Arifin AJ, Rodrigues GB, et al. A review of ongoing trials of stereotactic ablative radiotherapy for oligometastatic cancers: Where will the evidence lead? *Front Oncol*. 2019;9:543.
8. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol*. 2006;24:4833–4939.
9. Chmura S, Winter KA, Robinson C, et al. Evaluation of safety of stereotactic body radiotherapy for the treatment of patients with multiple metastases: Findings from the NRG-BR001 phase 1 trial. *JAMA Oncol*. 2021;7:845–852.
10. Lindberg K, Grozman V, Karlsson K, et al. The Hilus-Trial-A prospective Nordic multicenter phase 2 study of ultracentral lung tumors treated with stereotactic body radiotherapy. *J Thorac Oncol*. 2021;16:1200–1210.
11. Olson WJ, Liu MC, Bergman A, et al. Population based phase II trial of stereotactic ablative radiotherapy (sabr) for up to 5 oligometastases: Preliminary results of the SABR-5 trial 2021. *BMC Cancer*. 2018;18:954.
12. Hall WA, Paulson ES, van der Heide UA, et al. The transformation of radiation oncology using real-time magnetic resonance guidance: A review. *Eur J Cancer*. 2019;122:42–52.
13. Mittauer K, Paliwal B, Hill P, et al. A new era of image guidance with magnetic resonance-guided radiation therapy for abdominal and thoracic malignancies. *Cureus*. 2018;10:e2422.
14. Henke LE, Olsen JR, Contreras JA, et al. Stereotactic MR-guided online adaptive radiation therapy (smart) for ultracentral thorax malignancies: Results of a phase 1 trial. *Adv Radiat Oncol*. 2019;4:201–209.
15. Henke L, Kashani R, Robinson C, et al. Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. *Radiother Oncol*. 2018;126:519–526.
16. Chuong MD, Bryant J, Mittauer KE, et al. Ablative 5-fraction stereotactic magnetic resonance-guided radiation therapy with on-table adaptive replanning and elective nodal irradiation for inoperable pancreas cancer. *Pract Radiat Oncol*. 2021;11:134–147.
17. Kutuk T, McCulloch J, Mittauer KE, et al. Daily online adaptive magnetic resonance image (MRI) guided stereotactic body radiation therapy for primary renal cell cancer. *Med Dosim*. 2021;46:289–294.
18. Seravalli E, Kroon PS, Buatti JM, et al. The potential role of MR-guided adaptive radiotherapy in pediatric oncology: Results from a SIOPE-COG survey. *Clin Transl Radiat Oncol*. 2021;29:71–78.
19. Ugurluer G, Mustafayev TZ, Gungor G, et al. Stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of liver metastases in oligometastatic patients: Initial clinical experience. *Radiat Oncol J*. 2021;39:33–40.

20. Davis JN, Medbery 3rd C, Sharma S, et al. The research registry: Patterns of care and outcomes research on patients treated with stereotactic radiosurgery and stereotactic body radiotherapy. *Radiat Oncol*. 2013;8:275.
21. Common terminology criteria for adverse events (CTCAE) v4.0. Available at: https://ctep.Cancer.Gov/protocoldevelopment/electronic_applications/ctc.Htm#ctc_40. Accessed January 31, 2022.
22. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised recist guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
23. Chen WC, Baal JD, Baal U, et al. Stereotactic body radiation therapy of adrenal metastases: A pooled meta-analysis and systematic review of 39 studies with 1006 patients. *Int J Radiat Oncol Biol Phys*. 2020;107:48–61.
24. Sheikh S, Chen H, Sahgal A, et al. An analysis of a large multi-institutional database reveals important associations between treatment parameters and clinical outcomes for stereotactic body radiotherapy (SBRT) of oligometastatic colorectal cancer. *Radiother Oncol*. 2022;167:187–194.
25. Rodriguez LL, Kotecha R, Tom MC, et al. CT-guided versus MR-guided radiotherapy: Impact on gastrointestinal sparing in adrenal stereotactic body radiotherapy. *Radiother Oncol*. 2021;166:101–109.
26. Henke LE, Stanley JA, Robinson C, et al. Phase I trial of stereotactic MRI-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic ovarian cancer. *Int J Radiat Oncol Biol Phys*. 2022;112:379–389.
27. Burkon P, Selingerova I, Slavik M, et al. Stereotactic body radiotherapy for lymph node oligometastases: Real-world evidence from 90 consecutive patients. *Front Oncol*. 2020;10: 616494.
28. Jereczek-Fossa BA, Ronchi S, Orecchia R. Is stereotactic body radiotherapy (SBRT) in lymph node oligometastatic patients feasible and effective? *Rep Pract Oncol Radiother*. 2015;20:472–483.
29. Matsushita H, Jingu K, Umezawa R, et al. Stereotactic radiotherapy for oligometastases in lymph nodes-a review. *Technol Cancer Res Treat*. 2018;17: 1533033818803597.
30. Reyngold M, Parikh P, Crane CH. Ablative radiation therapy for locally advanced pancreatic cancer: Techniques and results. *Radiat Oncol*. 2019;14:95.
31. van Dams R, Wu TC, Kishan AU, et al. Ablative radiotherapy for liver tumors using stereotactic mri-guidance: A prospective phase I trial [e-pub ahead of print]. *Radiother Oncol*. doi:10.1016/j.radonc.2021.06.005, accessed January 31, 2022.
32. Finazzi T, Haasbeek CJA, Spoelstra FOB, et al. Clinical outcomes of stereotactic MR-guided adaptive radiation therapy for high-risk lung tumors. *Int J Radiat Oncol Biol Phys*. 2020;107:270–278.
33. Augugliaro M, Marvaso G, Ciardo D, et al. Recurrent oligometastatic transitional cell bladder carcinoma: Is there room for radiotherapy? *Neoplasma*. 2019;66:160–165.
34. Franzese C, Badalamenti M, Comito T, et al. Assessing the role of stereotactic body radiation therapy in a large cohort of patients with lymph node oligometastases: Does it affect systemic treatment's intensification? *Radiother Oncol*. 2020;150:184–190.
35. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. *JAMA Oncol*. 2018;4: e173501.
36. Zelefsky MJ, Yamada Y, Greco C, et al. Phase 3 multi-center, prospective, randomized trial comparing single-dose 24 Gy radiation therapy to a 3-fraction SBRT regimen in the treatment of oligometastatic cancer. *Int J Radiat Oncol Biol Phys*. 2021;110:672–679.
37. Yoon SM, Luterstein E, Chu FI, et al. Clinical outcomes of stereotactic magnetic resonance image-guided adaptive radiotherapy for primary and metastatic tumors in the abdomen and pelvis. *Cancer Med*. 2021;10:5897–5906.
38. de Mol van Otterloo SR, Christodouleas JP, Blezer ELA, et al. Patterns of care, tolerability, and safety of the first cohort of patients treated on a novel high-field MR-linac within the momentum study: Initial results from a prospective multi-institutional registry. *Int J Radiat Oncol Biol Phys*. 2021;111:867–875.