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Phase I trial

Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen



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ABSTRACT

Purpose/objectives: SBRT is used to treat oligometastatic or unresectable primary abdominal malignancies, although ablative dose delivery is limited by proximity of organs-at-risk (OAR). Stereotactic, magnetic resonance (MR)-guided online-adaptive radiotherapy (SMART) may improve SBRT's therapeutic ratio. This prospective Phase I trial assessed feasibility and potential advantages of SMART to treat abdominal malignancies.

Materials/methods: Twenty patients with oligometastatic or unresectable primary liver ($n = 10$) and non-liver ($n = 10$) abdominal malignancies underwent SMART. Initial plans prescribed 50 Gy/5 fractions (BED 100 Gy) with goal 95% PTV coverage by 95% of prescription, subject to hard OAR constraints. Daily real-time online-adaptive plans were created as needed, based on daily setup MR-image-set tumor/OAR “anatomy-of-the-day” to preserve hard OAR constraints, escalate PTV dose, or both. Treatment times, patient outcomes, and dosimetric comparisons between initial and adaptive plans were prospectively recorded.

Results: Online adaptive plans were created at time of treatment for 81/97 fractions, due to initial plan violation of OAR constraints (61/97) or observed opportunity for PTV dose escalation (20/97). Plan adaptation increased PTV coverage in 64/97 fractions. Zero Grade ≥ 3 acute (<6 months) treatment-related toxicities were observed.

Discussion: SMART is clinically deliverable and safe, allowing PTV dose escalation and/or simultaneous OAR sparing compared to non-adaptive abdominal SBRT.

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Stereotactic body radiation therapy has revolutionized treatment of medically inoperable cancers [1,2]. Investigation of varying fractionation schedules in disease sites such as the lung demonstrated a critical biologically equivalent dose of approximately 100 Gy, under which local control and survival outcomes were significantly poorer [3,4]. More recently, the role of stereotactic radiation for unresectable pancreatic cancer and limited abdominal metastases has been further investigated [5–7]. Unfortunately, the proximity of gastrointestinal viscous structures and their positional uncertainty has often limited dose [6,8].

It is well known that both intra-fraction respiratory motion and inter-fraction physiologic organ motion contribute to inherent positional uncertainty of abdominal structures [9,10]. Compared to traditional computed-tomography (CT)-based strategies, magnetic resonance (MR) image-guided radiation therapy (IGRT) confers superior soft tissue definition that is potentially advantageous in abdominal disease sites, enabling daily imaging of sufficient quality to permit daily plan adjustments in response to inter-fraction organ motion [11,12]. Such online adaptive radiation therapy (ART) has been previously described by our institution for conventionally-fractionated RT [13]. Recently, our group modeled potential advantages of stereotactic, MR-guided online-adaptive radiotherapy (SMART) for abdominal disease sites and found it allowed PTV dose escalation and/or simultaneous improvements in OAR sparing when compared with non-adaptive SBRT [14].

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To evaluate the feasibility and safety of SMART for abdominal disease sites, we conducted a prospective Phase I clinical trial of this technique for oligometastatic and unresectable primary liver and non-liver abdominal malignancies. The primary endpoint was feasibility, defined by delivery of adaptive treatment in <80 min on-table time for >75% of cases. We hypothesized that SMART would be clinically feasible and deliver ablative radiation doses with low rates of gastrointestinal toxicity.

Methods

Eligibility

Washington University's Institutional Review Board approved this protocol (NCT02264886). Patients with oligometastatic or unresectable primary liver or non-liver-abdominal malignancies who were considered technical and clinical candidates for SBRT were prospectively enrolled. Oligometastatic disease was defined as ≤ 3 progressive disease sites; patients were eligible if ≥ 1 site was amenable to abdominal SBRT. Patients were ≥ 18 -years-old and had Karnofsky Performance Status (KPS) $\geq 70\%$, capacity to provide consent, and disease of solid-tumor (non-hematologic) categorization, excluding small-cell cancers. All patients were required to complete any systemic therapy ≥ 1 week prior to planned start of SMART, with no plans to initiate systemic therapy for ≥ 1 week following completion of SMART. Patients were excluded for prior history of radiotherapy within the projected treatment field, current receipt of other investigational agents, uncontrolled intercurrent illness, pregnancy and/or breastfeeding, or medical contraindication to undergoing MR-imaging.

Simulation and initial plan

Details of the initial treatment planning process, simulation, MR-IGRT treatment device, imaging characteristics and dedicated MR-IGRT treatment planning system (TPS) have been previously published [13,15,16]. Full detail description is available in the [Supplemental Material](#). Prescribed dose for all plans was 50 Gy/5 fractions (fx), with goal 95% planning target volume (PTV) coverage by 95% of prescription dose (47.5 Gy), subject to hard OAR constraints (Table 2). The PTV was defined as a 5 mm volumetric expansion upon the gross tumor volume (GTV). If goal PTV coverage could not be met without violation of hard OAR constraints, then PTV coverage was sacrificed in accordance with a strict isototoxicity approach.

Daily online plan adaptation

Our online plan adaptation and plan QA processes have been previously published [13]. A complete description is available in the [Supplemental Material](#). Briefly, each patient underwent volumetric MRI imaging for setup and localization. The initial/prior fraction's plan was loaded onto the daily image and contours were manually edited, as needed, by physicians. The prior plan was then assessed on the daily image. If there was either a violation in an OAR maximum dose constraint or an opportunity for PTV coverage improvement, a daily adaptive plan was generated. Maximum target dose was 60 Gy at 15 Gy per fraction, permitting treating physicians to condense the treatment to four fractions if all OAR constraints could be met. Adaptive plans were evaluated and compared to the prior, non-adaptive plans based on dose to OARs and PTV coverage without dose accumulation, using a fraction-by-fraction, strict isototoxicity approach. The superior plan was then delivered. Any delivered adaptive plan became the default, non-adaptive plan for the subsequent fraction.

Treatment delivery and cine gating

All treatment fractions were delivered with real-time MR-guidance including cine-MR gating on the GTV based on the exhale phase during free breathing. Gating window targets and settings were selected by physicians and evaluated on each treatment day. Details of MR-guidance and cine-MR gating, as implemented at our institution for standard clinical practice, have been previously published [17]; a complete description is available in [Supplemental Materials](#).

Dosimetric and timing data collection

The prospective primary endpoint of the study was feasibility, defined by delivery of adaptive treatment in <80 min on-table time for >75% of cases. This endpoint was subjectively chosen based on study physician anticipation that patients would not tolerate treatments exceeding 80 min. Door-to-door patient treatment, imaging, physician segmentation, re-planning, and plan QA times were prospectively recorded at each fraction by treating radiation therapists. Prospectively recorded dosimetry included OAR dose, cumulative GTV/PTV dose, and projected dose that would have been delivered by non-adaptive plans. Current technology is insufficient to reproducibly identify point volumes of deformable OARs for dose accumulation. GTV/PTV dose accumulation was performed, with detailed description provided in the [Supplemental Materials](#).

Patient follow-up, quality-of-life metrics, and statistical analysis

Pre-treatment collection of patient data included patient demographics, baseline Response Evaluation Criteria in Solid Tumors (RECIST) criteria target tumor measurements of the treated lesion, and baseline European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) Version 3.0 quality of life (QOL) scores. Patients had planned follow-up at 6, 12, and 26 weeks post-treatment. Study physicians prospectively assessed treatment response of treated-lesions using RECIST at pre-planned time points of three and six months post-treatment. Disease-free, progression-free, and overall survival were prospectively assessed at 12 and 26 weeks post-treatment and subsequently through chart review and routine clinical appointments. Acute (defined as within six months of therapy completion) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 gastrointestinal toxicity was prospectively assessed at 6, 12, and 26 weeks by clinical research coordinators (CRCs) through the Washington University clinical trials office. Subsequent late toxicities occurring after the six month study period were rigorously assessed by the treating physicians through routine clinical care and retrospective chart review. CRCs also prospectively assessed patient-reported QOL scores at zero, six, and 26 weeks post-treatment. Repeated measures analysis was used to assess for change in QOL scores. Kaplan Meier analysis was used to estimate local progression-free survival. Statistical analyses were performed by the study statistician using SAS, Version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Patient and tumor characteristics

Patient demographics and disease characteristics are described in [Table 1](#). A total of 20 evaluable patients were enrolled and treated per protocol; ten patients received treatment for hepatic lesions and ten underwent treatment for non-liver abdominal sites. Of 20 patients enrolled, 11 had oligometastatic disease, while nine

Table 1
Patient, tumor, and treatment delivery characteristics.

Median age (range)	64 (48–79)
Median tumor size in cm (range)	3.5 (1.6–11)
Median prior chemotherapy regimens (range)	2 (0–5)
Median KPS (range)	90 (80–100)
Liver	10
Colorectal cancer metastasis	4
Primary intra-hepatic cholangiocarcinoma	1
Primary hepatocellular carcinoma	4
Hepatocellular carcinoma metastasis	1
Non-liver abdomen	10
Non-small cell lung cancer adrenal metastasis	2
Recurrent pancreatic adenocarcinoma	3
Primary pancreatic adenocarcinoma	2
Para-aortic lymph node metastasis	3
Total delivered fractions	97
Total adapted fractions (% of total)	81 (83.5)
Delivered liver fractions	47
Adapted liver fractions (%)	31 (47)
Adapted for ≥ 1 OAR violation (%)	17 (36.2)
Adapted only to increase PTV coverage (%)	14 (29.8)
Delivered non-liver abdomen fractions	50
Adapted non-liver abdomen fractions (%)	50 (100)
Adapted for ≥ 1 OAR violation (%)	44 (88)
Adapted only to increase PTV coverage (%)	6 (12)
Median on-table time in min (range)	79 (36–160)
Median re-contour time in min (range)	9 (2–24)
Median re-plan time in min (range)	10 (1–19)
Median QA time in min (range)	4 (1–14)

had unresectable primary lesions. Median follow-up time from completion-of-therapy (COT) was 15 months (range 4–22 mos).

Treatment planning and delivery

All initial plans from simulation met hard OAR constraints. All 20 patients completed planned treatment with SMART. A total of 97 fractions were delivered. Seventeen patients received a 5fx course, while three patients were treated with a condensed course of 60 Gy/4fx. At time of treatment delivery, a daily adapted plan was determined to be superior to the initial plan or previously adapted fraction for 83.5% (81/97) of fractions. All patients required adaptive planning for ≥ 1 fraction. Fig. 1 summarizes the clinical reasons for plan adaptation for each patient. Overall, 100% of non-liver-abdomen fractions were adapted and 31/47 (66%) of liver fractions benefitted from online adaptation.

Table 2

Hard dose constraints and target volume coverage goals for initial non-adaptive plans and adaptive plans, with recorded organ-at-risk violation metrics for application of initial plan to the treatment-day anatomy as well as cumulative dose metrics for GTV and PTV coverage by both initial and adaptive plans.

Organ at risk	Hard constraint	# of PI constraint violations	Mean (Std Dev)	Median	Range
Uninvolved liver (liver – GTV)	700 cm ³ < 20 Gy	1	968 cm ³	968 cm ³	NA
	V25Gy < 33%	1	45.21%	45.21%	NA
	Mean < 20 Gy	1	24.73 Gy	24.73 Gy	NA
Stomach max	V33Gy < 0.5 cm ³	22	3.18 \pm 3.49 cm ³	1.97 cm ³	0.63–13.21 cm ³
Duodenum max	V35Gy < 0.5 cm ³	14	2.41 \pm 2.64 cm ³	1.09 cm ³	0.51–9.11 cm ³
Small bowel max	V30Gy \leq 0.5 cm ³	37	5.48 \pm 7.01 cm ³	3.72 cm ³	0.57–33.91 cm ³
Large bowel max	V35Gy \leq 0.5 cm ³	4	2.31 \pm 1.50 cm ³	2.23 cm ³	0.80–3.97 cm ³
Heart/Pericardium	V32Gy \leq 15 cm ³	5	18.55 \pm 2.52 cm ³	17.85 cm ³	16.39–22.09 cm ³
Cord	V25Gy < 0.5 cm ³	1	0.72 cm ³	0.72 cm ³	NA
Kidney (combined)	Mean < 18 Gy	0	NA	NA	NA
Target volume	Goal coverage	Projected non-adaptive mean (Std Dev)	Projected non-adaptive median (Range)	Cumulative adaptive mean (Std Dev)	Cumulative adaptive median (Range)
PTV V50	NA	66.3 \pm 26.1%	69.3 (0.1–98.9)%	70.4 \pm 27.7%	76.7 (15.6–100)%
PTV V47.5	95%	76.2 \pm 26.2%	81.6 (0.4–100)%	79.4 \pm 24.1%	88.6 (20.7–100)%
GTV V50	100%	81.0 \pm 26.8%	91.0 (0–100)%	85.0 \pm 21.9%	97.8 (26.0–100)%
GTV V47.5	100%	85.6 \pm 24.4%	94.7 (0–100)%	89.6 \pm 17.2%	99.3 (33.1–100)%
GTV V45	100%	88.5 \pm 23.0%	97.1 (0–100)%	92.2 \pm 14.8%	99.6 (39.5–100)%
GTV Max	NA	61.0 \pm 7.2 Gy	59.4 (43.8–74.1)%	64.1 \pm 5.1 Gy	64.6 (54.9–72.7) Gy
GTV Min	NA	36.8 \pm 14.7 Gy	37.6 (2.0–59.1)%	42.5 \pm 13.7 Gy	42.8 (19.3–62.0) Gy

The primary endpoint of delivery of adaptive treatment in <80 min for >75% of cases was not met. 52% of fractions were completed in <80 min and >75% of cases were completed in \leq 90 min instead of <80. However, SMART remained clinically deliverable, and all 20 patients completed therapy with median on-table-time of 79 min/fx (range 36–160 min). On table-time comprised MR-imaging set up (median 3.5 min, range 1–14 min), time for physician arrival (median 4 min, range 0–15 min), patient localization/shift application (median 2 min, range 0–14 min), median re-segmentation (median 9 min, range 2–24 min), re-planning (median 10 min, range 2–24 min), QA (median 4 min, range 1–14 min), and beam-on time (median 33.5 min, range 16–107 min). If adaptation was not required, then the re-segmentation, replanning, and QA times were zero/not applicable.

Organ-at-risk constraints

Of adapted fractions, 61/81 (75%) were adapted for the primary purpose of reversing an OAR constraint violation that occurred when the prior plan was applied to anatomy-of-the-day on treatment days (Fig. 1). Fig. 2 illustrates an example case. Within non-liver abdomen fractions, 44/50 (88%) required adaptive plan creation to reverse ≥ 1 OAR violations, most often comprising small-bowel ($n = 37$). Of liver fractions, 17/47 (36.2%) were adapted to reverse OAR violations. Severity of OAR violations that would have occurred without plan adaptation was variable, both in terms of magnitude by which constraints were violated (Fig. 3) and volume of OARs that received excess dose (Table 2). Table 2 and Fig. 3 summarize OAR violations. Adaptive plans successfully reversed 100% of OAR violations.

Target volume coverage and dose escalation

Twenty fractions were adapted with sole intent to increase dose coverage to 95% of the PTV by the prescribed isodose line (Fig. 1). These included 6/50 non-liver-abdomen fractions and 14/47 liver fractions. Target coverage was not necessarily compromised by plan adaptation to meet organ-at-risk constraints. In 35/61fx where adaptive plans were required for OAR violation reversal, improved PTV coverage was simultaneously achieved (example, Fig. 2). In the other 26fx, PTV dose de-escalation was required to meet OAR constraints (example, Fig. 4c). However, mean and med-

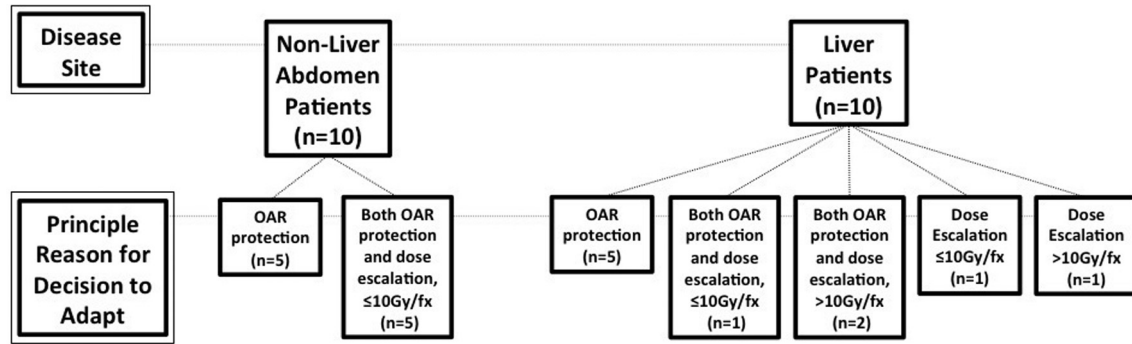


Fig. 1. Flow diagram of the primary clinical reason for plan adaptation for each study patient. Reasons for adaptation included reversal of organ-at-risk (OAR) violation, planning target volume (PTV) dose increase, or for both.

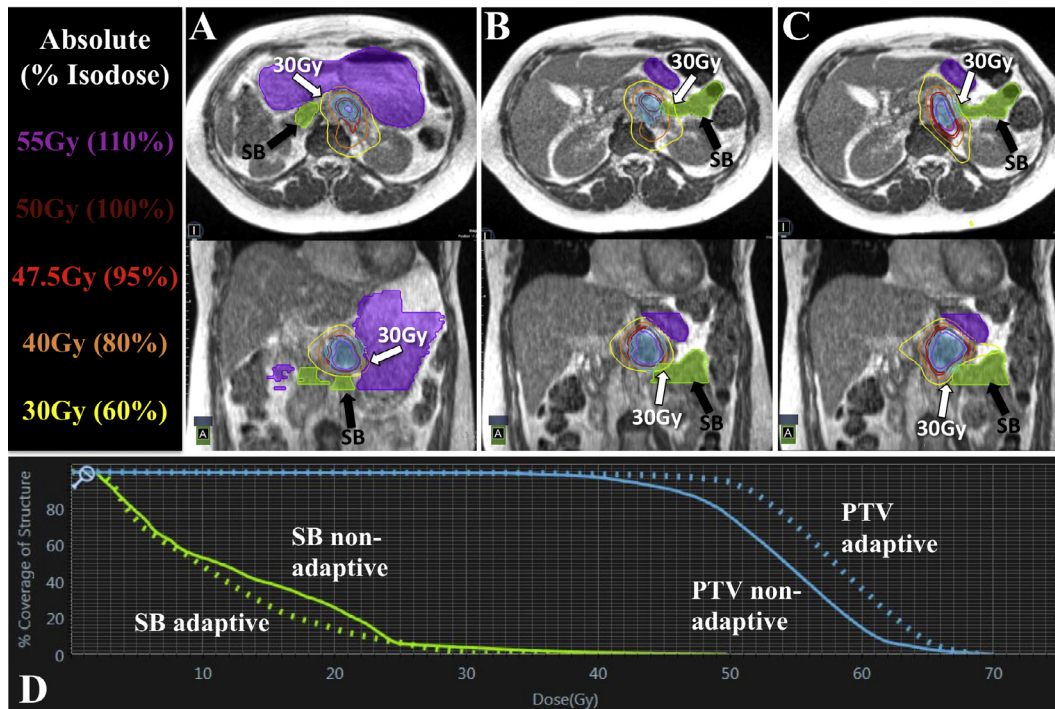


Fig. 2. A fraction 1 plan met all organ-at-risk (OAR) constraints based on day 1 anatomy-of-the-day (a). Application of the fx1 plan as the initial plan to fx2 anatomy-of-the-day for this patient with a para-aortic metastasis (blue colorwash) resulted in small-bowel (green colorwash) constraint violation (b). Daily adaptive planning achieved OAR constraint violation resolution while also improving planning target-volume (PTV) coverage (c and d).

ian cumulative GTV and PTV dose coverage was superior with SMART compared to projected non-adaptive SBRT.

Dose escalation beyond 10 Gy/fx, while maintaining hard OAR constraints, was not feasible for any non-liver-abdomen cases. In 3/10 dose-escalated liver patients, favorable day one anatomy permitted dose escalation beyond 10 Gy/fx and persisted, such that treatment courses could be condensed to four fractions and fx1 adaptive plans were reused without change for all subsequent fractions (example DVH, Fig. 4d). In this manner, a total of 12/47fx were dose-escalated beyond 10 Gy/fx (median 15 Gy/fx). Table 2 provides complete summary of projected non-adaptive versus adaptive cumulative GTV and PTV dose. Example cumulative GTV DVH comparisons for adaptive versus initial plans are illustrated in Fig. 4.

Toxicity and quality-of-life

We observed zero acute (within six months), treatment-related CTCAEv.4 Gr3+ toxicities, with all patients accounted for at six-

months' follow-up. One patient developed an asymptomatic Gr2 gastric-antrum ulcer outside the high-dose field (within the 10–15 Gy low-dose region), discovered on follow-up imaging 4 mo after COT. This resolved with proton-pump-inhibitor therapy. Two patients had Gr4 anemia and thrombocytopenia deemed unrelated to radiotherapy. These instances were following full-dose gemcitabine and FOLFIRINOX chemotherapy at 1.5 and 3.5 months post-radiotherapy, respectively. Of note, zero Grade 3 or higher late toxicities (occurring > 6 mos after RT) were observed, with 15-month median follow-up.

Patient-reported QOL was prospectively recorded by clinical research coordinators at zero, six, and 26 weeks follow-up using the EORTC QLQ-C30. Median global QOL scores were not significantly different during treatment and the acute post-therapy window by repeated measures analysis (Supplemental Fig. 1; $P = 0.29$). Single-item QOL scores that might indicate low-level toxicity such as for diarrhea, constipation, nausea, emesis, appetite, pain or activity tolerance, were also unchanged.

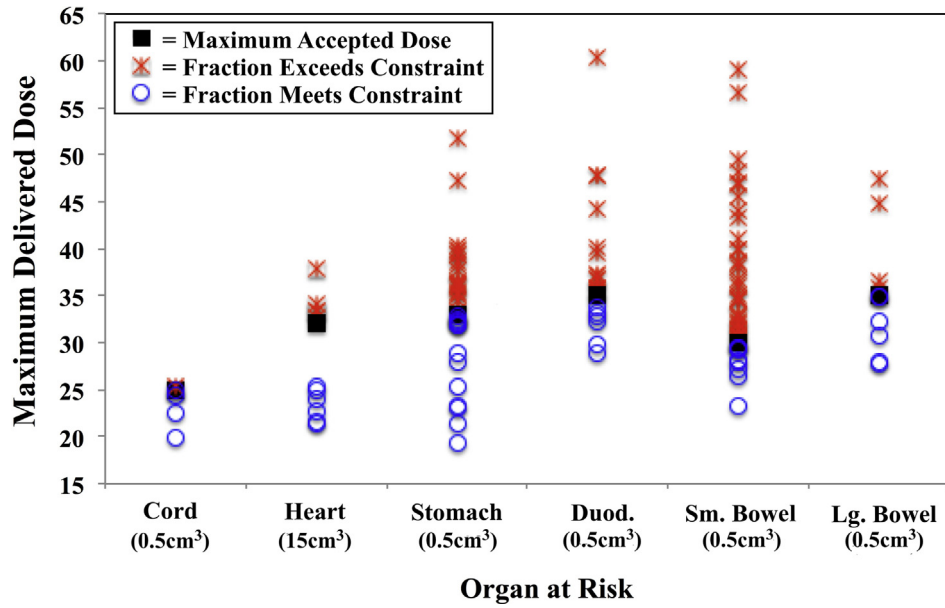


Fig. 3. Maximum scaled fractional point-dose (red marks) to constraint volumes of organs-at-risk (OARs) that violated constraints and would have been delivered to OARs in absence of plan adaptation. Black squares indicate goal OAR constraints over five fractions. Blue circles represent maximum, scaled doses delivered to OARs in the same patients on fractions that did not require adaptation.

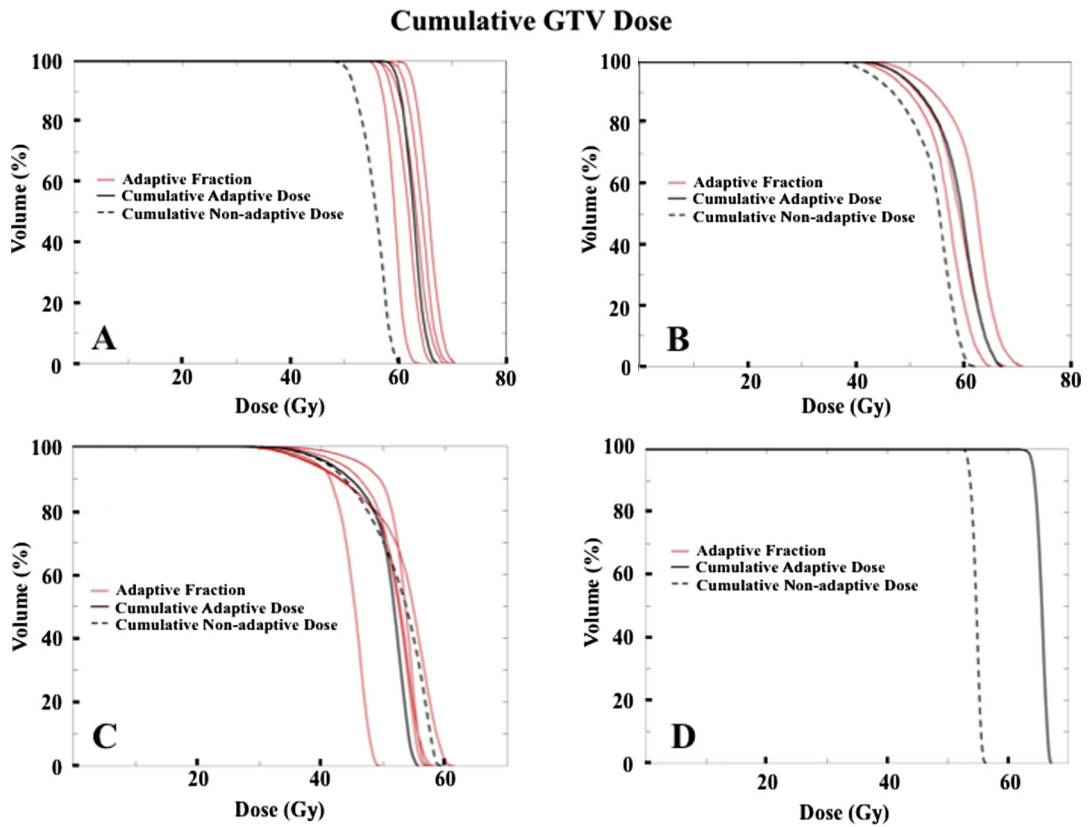


Fig. 4. Cumulative dose delivered to gross tumor volumes (GTV) via adaptive planning versus projected dose delivered by non-adaptive planning. Frames 4a and 4b demonstrate dose–volume histograms for patients with para-aortic and liver metastases. In 4c, organ-at-risk proximity to a pancreas tumor required adaptive GTV dose de-escalation for several fractions. In 4d, dose-escalation to a liver tumor beyond 10 Gy/fx was feasible with magnetic-resonance-guidance and a condensed course of 60 Gy/4fx was delivered using a single, fx1 plan adaptation.

Tumor control and survival

RECIST local progression-free survival (defined here as stability, partial response, or complete response of the treated lesion) was 95% and 89.1% by Kaplan Meier analysis at three and six months' follow-up. At median follow-up of 15 months (range: 7.5–21 mo), only two patients – both with recurrent, locally advanced pancreatic cancer (LAPC) – experienced RECIST progression. At one year, nine patients had no evidence of active disease and 1-year overall survival for all-comers was 75% (15/20). Among the 11 patients with oligometastatic disease at enrollment, 1-year overall survival was 91% (10/11) and 1-year systemic progression-free survival was 45%. Notably, among patients with unresectable primaries, the two patients treated for primary LAPC were both alive without progression at 50 and 56 weeks follow-up.

Discussion

This is the first prospective, clinical study of stereotactic MR-guided online-adaptive radiotherapy (SMART) and of daily online-adaptive external-beam radiotherapy. In this Phase I trial, we evaluated the feasibility and safety of SMART for oligometastatic and unresectable primary abdominal malignancies using ablative doses. The secondary study intent was to characterize potential dosimetric and clinical advantages of this approach within the abdomen for both OAR sparing and target volume coverage. While our primary feasibility endpoint of treatment delivery for >75% of fractions in under 80 min was not met, our results support SMART as an approach that is clinically deliverable, dosimetrically advantageous, and results in minimal gastrointestinal toxicity.

Our primary endpoint was unmet. Nevertheless, all patients completed therapy as planned, with median on-table time of 79 min. Our feasibility goal of delivery of >75% of fractions in <80 min was chosen because study authors anticipated longer treatment times would not be tolerated by patients or supported by clinic workflow. However, this pre-determined limit of tolerance was inaccurate, as demonstrated by all patients completing treatment as delivered. Since study completion, process changes including more focused daily re-segmentation, improved software tools, improved tumor and OAR instructions for covering physicists/physicians, and consolidation of QA procedures have decreased this time. While time required is longer than typical SBRT fractions, it matches that of other radiation therapy procedures, such as brachytherapy, and is similar to initial implementations of intensity modulated radiotherapy (IMRT) and robotic SBRT [18–21]. It is reasonable to assume that organized efforts to advance MR-IGRT technology, including development of MR-guided linear-accelerator systems and ongoing improvements in auto-segmentation of normal structures, will reduce future treatment times considerably [22–25].

We also observed that SMART was advantageous for OAR sparing. Online-adaptive planning revealed frequent, unintended OAR constraint violations that would have occurred in non-adaptive fractions (63%), and all successfully were reversed with SMART. This high number of non-adaptive OAR violations observed is consistent with previous reports of interfractional organ motion and matches the rate predicted by our simulation study using identical MR-IGRT technology [10,14]. It is possible that not all OAR violations prevented by SMART would have been clinically meaningful. However, prior studies delivering high dose therapy to the abdomen while comparatively accounting for tumor motion resulted in prohibitive levels of gastrointestinal toxicity [26]. By comparison, to date, our observed Gr3+ toxicity rate was zero, despite ablative doses. Importantly, patient-reported QOL scores – including specific scores for nausea, pain, and other

indicators of bowel toxicity – were also not adversely impacted by therapy, suggesting that any low-level, unreported gastrointestinal toxicity was clinically insignificant. Coupled together, these factors suggest that the observed dosimetric benefits of SMART for OAR sparing may translate to reduced toxicity, although further study is needed.

Adaptive planning also increased tumor dose in a majority of fractions and improved overall mean/median target coverage. Notably, in 100% of fractions where patient anatomy-of-the-day was favorable and did not result in OAR constraint violation, target coverage improvement was achieved by adaptive planning. Dose escalation beyond 10 Gy per fraction was possible in a subset of three patients, to up to 15 Gy per fraction, resulting in a higher BED. This small subset of patients uniquely had hepatic lesions located >2 cm from the luminal gastrointestinal tract proximity, enabling consistent delivery of escalated dose with less overall risk to OARs. Our institutional practice has since shifted to use MR-localization and cine gating without adaptation for more central hepatic lesions. It may be unnecessary to escalate dose beyond 50 Gy in 5 fractions for oligometastatic lesions, although achievement of an increased BED has been shown to be of utility in some primary malignancies [3,4]. For all comers, local control was excellent at 6 months, with both cases of treated-tumor progression occurring in the setting of recurrent pancreatic cancer, which carries a particularly poor prognosis [27]. Without use of online-adaptive planning, dose to abdominal sites has historically been limited to sub-ablative levels due to normal tissue toxicity [8]. While data on the utility of radiotherapy for certain primary abdominal malignancies, such as LAPC, may be mixed, local control of oligometastatic disease does correlate with increased dose [7,28–30]. However, local control benefit of dose escalation enabled by SMART was not the focus of this feasibility trial and requires future study.

The application of SMART to enable oligometastasis ablation with minimal toxicity is supported by our cohort. Of our oligometastatic patients, 8/11 were alive without toxicity or advancement of systemic disease state at last follow-up. Ongoing randomized trials aim to confirm benefit of an ablative approach for the oligometastatic state [31,32]. If benefits are demonstrated, SMART may be an optimal strategy to maximize the therapeutic ratio for oligometastatic patients.

We acknowledge several limitations to our study. First, current technology is insufficient to reproducibly identify point volumes of deformable OARs including bowel for accurate calculation of cumulative dose. Our fraction-by-fraction isototoxicity approach, while favorably guaranteeing that no point-volume of OAR will exceed dose constraints, may be excessively conservative. OAR dose accumulation and delineation of “true” abdominal dose constraints based on the accurate inter- and intra-fraction imaging information that real-time MR-guidance affords are of future research interest.

Similarly, although our use of 2D-cine gating permitted target monitoring during treatment, it is possible that unobserved intra-fraction OAR motion degrades dosimetric benefits achieved by adaptation. Use of three-dimensional volumetric MR-gating may be possible in the future and could mitigate this concern. Efforts to manage motion and adapt plans based on intra-fraction imaging feedback may represent a future gold-standard but remain far from clinical implementation [33,34]. Additionally, the PTV margins chosen for this study were conservative, at 0.5 cm from the GTV, an expansion that was selected to match that of typical CT-guided SBRT, in order to avoid excessive departures from standard-of-care SBRT practice in this first application of SMART. However, given the soft tissue visualization improvements of MR-IGRT, reduced PTV margin size has now been applied in select MR-guided scenarios and is of ongoing interest in future studies [35].

In summary, we found that SMART remains clinically deliverable, safe, and dosimetrically advantageous compared to non-adaptive SBRT. By permitting PTV dose escalation and/or concomitant sparing of normal tissues, SMART improves the therapeutic ratio of abdominal SBRT. A randomized controlled Phase II trial is now open to directly compare toxicity rates between SMART and non-adaptive MR-localized SBRT to abdominal oligometastatic/unresectable primary disease.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.radonc.2017.11.032>.

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