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Scientific Article

Dose-Escalated Magnetic Resonance Image–Guided Abdominopelvic Reirradiation With Continuous Intrafraction Visualization, Soft Tissue Tracking, and Automatic Beam Gating

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Abstract

Purpose: Compared with computed tomography, magnetic resonance (MR) image guidance offers significant advantages for radiation therapy (RT) that may be particularly beneficial for reirradiation (reRT). However, clinical outcomes of MR-guided reRT are not well described in the published literature.

Methods and Materials: We performed a single-institution retrospective safety and efficacy analysis of reRT patients treated on the MRIdian Linac to targets within the abdomen or pelvis using continuous intrafraction MR-based motion management with automatic beam triggering. Fiducial markers were not used.

Results: We evaluated 11 patients who received prior RT to a median of 50 Gy (range, 30-58.8 Gy) in 25 fractions (range, 5-28 fractions). The median interval to reRT was 26.8 months. The most frequently retreated sites were nodal metastases (36.4%) and pancreatic cancer (27.3%). The median reRT dose was 40 Gy (range, 25-54 Gy) in 6 fractions (range, 5-36 fractions); ultrahypofractionation (63.6%) was more common than hyperfractionation (36.4%). Daily on-table adaptive replanning was used for 3 patients (27.3%). With a median of 14 months' follow-up from reRT completion (range, 6-32 months), the median and 1-year freedom

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from local progression were 29 months and 88.9%, respectively, and the median and 1-year overall survival were 17.5 months and 70.0%, respectively. One patient (9.1%) experienced acute grade 2 toxic effects; there were no acute or late treatment-related toxic effects of grade 3 or greater.

Conclusions: Magnetic resonance–guided reRT appeared to be feasible and may facilitate safe dose escalation. Additional follow-up is needed to better assess long-term efficacy and late toxic effects. Prospective evaluation of this novel treatment strategy is warranted.

Introduction

Reirradiation (reRT) may provide significant benefit for carefully selected patients with locally recurrent or progressive cancer. However, it must be used with caution because of potentially severe or fatal toxic effects from cumulatively high organ-at-risk (OAR) doses.[1,2] As such, reRT is a complex undertaking in which an appropriate balance must be realized between delivering an effectively high target dose while simultaneously achieving appropriately low OAR doses. Prescription doses for ReRT are typically modest out of necessity to prioritize patient safety.[3,4] However, safely achieving prescription dose intensification may improve long-term local control (LC) and also overall survival (OS).[4-6]

During the past several decades, technological advancements have improved the therapeutic ratio of reRT through improved image guidance, motion management, and more highly conformal delivery techniques.[7-10] The recent advent of magnetic resonance (MR)–guided RT has further contributed to improving outcomes of patients,[11] especially those with cancers in high-risk anatomic locations such as the pancreas and central lung.[12,13]

The unique imaging and on-table adaptive replanning capabilities of MR-guided RT are ideal to minimize OAR dose during reRT and potentially reduce severe toxic effects, although published clinical outcomes of this treatment strategy are limited to case reports.[14,15] The purpose of this analysis was to report our institutional MR-guided reRT outcomes.

Methods and Materials

After obtaining institutional review board approval, we performed a single-institution retrospective analysis of patients who received reRT to the abdomen or pelvis using the ViewRay MRIdian Linac (ViewRay Inc, Oakwood Village, OH) between April 2018 and December 2020. Patient, tumor, treatment, toxic effect, and disease progression details were evaluated.

Simulation for reRT on the MRIdian Linac included a planning 0.35 T balanced steady-state free precession sequence (TrueFISP) MR scan acquired over at least 17 to 25 seconds and immediately followed by a planning computed tomography (CT) scan. Simulation was typically done in the supine position for abdominal targets and in the prone position for pelvic targets to facilitate small bowel displacement and sparing. Fiducial markers were not placed because the treated lesions were directly visualized throughout treatment using continuous intrafraction sagittal plane MR imaging at 4 to 8 frames per second. Intravenous or oral contrast were not used because both the target and OARs can be well visualized without contrast on the TrueFISP MR scan, which served as the primary scan for segmentation and treatment planning.

Target volume and OAR contours were delineated on the TrueFISP MR simulation scan and exported to the MRIdian treatment planning system. The simulation CT was exported to the MRIdian treatment planning system and deformably registered to the simulation MR scan for electron density information for dose calculation purposes. For some cases, bulk density assignment to the vertebral bodies as bone, external as water, and any abdominal gas as air was used to account for changes in anatomy between the simulation CT and MR image (MRI).

The gross tumor volume (GTV) was defined as the visible tumor on diagnostic and simulation scans. For most patients (8 of 11), a clinical target volume was not used; for the 3 others, it was defined by a 5- to 10-mm uniform expansion from the GTV. The planning target volume (PTV) was defined by a 3- to 5-mm uniform expansion of the GTV (or clinical target volume if present). No internal target volume was used.

All patients were treated with continuous intrafraction MR imaging. The treatment delivery system was set so that if more than 5% of the tracking structure, which included the GTV, extended beyond a 3-mm boundary, the beam would be automatically held until the tracking structure returned inside the boundary, at which time treatment delivery would resume (Fig 1). Patients with abdominal targets subject to potentially significant respiratory motion were treated in breath hold, whereas patients with pelvic targets were usually treated with free-breathing beam gating because they were not subject to significant respiratory motion. On-table adaptive replanning was performed for selected patients, especially when gross disease was located within 5 mm of gastrointestinal OARs on simulation scans, to ensure that OAR dose constraints were not exceeded either owing to interfraction anatomic changes or otherwise to compensate for changes in tumor anatomy and position.

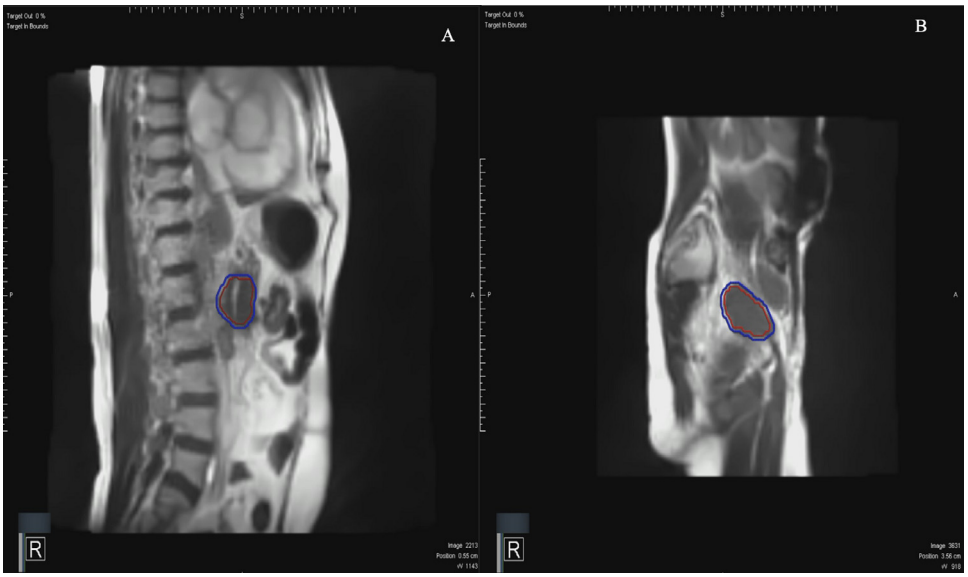

Fig. 1 Intrafraction motion management in the sagittal plane acquired using magnetic resonance imaging on the MRIdian Linac (ViewRay Inc, Oakwood Village, OH) at 8 frames per second with the tracking structure encompassing gross disease in the red region of interest for (A) pancreas and (B) pelvic lymph node reirradiation. Automated beam gating occurred when greater than 5% of the deformed red region of interest moved outside the static 3-mm expanded blue tracking boundary region of interest.

Because different dose fractionation reRT schedules were used, the biologically equivalent schedule in 2-Gy fractions (EQD2) was calculated for all patients using the following formula: $EQD2 = D \times (d + \alpha/\beta) \ / \ (2.0 + \alpha/\beta)$, where D was the total dose, d was the dose per fraction, and α/β was equal to 3 Gy for OARs and 10 Gy for the tumor. There was variability in OAR dose constraints used across different radiation oncologists, given the lack of defined constraints for reRT in the literature. A priority, however, for all physicians was to limit the volume of tissue outside of the PTV that received a dose greater than the prescription dose. Cumulative dose constraints across the original and reRT plans for gastrointestinal luminal organs were not used for plan optimization, although they were reviewed for awareness and routinely exceeded 90 to 100 Gy $EQD2_3$. Dose constraints for both ultrahypofractionated and hyperfractionated plans typically included the duodenum, stomach, small bowel, large bowel, and rectum, each V30 to V35 $\leq$ 0.5 cm^3 and V33 to V38 $\leq$ 0.03 cm^3 on the reRT plan; bladder, V30 to V35 $\leq$ 0.5 cm^3 on the reRT plan; spinal cord, cumulative V50 to V60 $\leq$ 0.03 cm^3 $EQD2_3$; kidneys, cumulative mean $\leq$ 18 Gy $EQD2_3$; and liver, cumulative mean $\leq$ 30 Gy $EQD2_3$.[16]

Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina). Clinical outcomes were assessed using the Kaplan-Meier method from the date of reRT start. Freedom from local progression (FFLP) was defined as the time to local progression and was assessed using Response Evaluation Criteria in Solid Tumors, version 1.1. Progression free survival (PFS) was the time to the first occurrence of local progression, distant progression, or death. Overall survival (OS) was calculated as the time to death or otherwise last follow-up. Toxic effects were assessed per the Common Terminology Criteria for Adverse Events, version 5.0. Acute toxic effects were defined as being present during or within 3 months from the completion of reRT. All toxic effects were assessed by a physician at least once weekly during RT and at each follow-up visit, usually performed at 3-month intervals after completion of reRT.

Results

A total of 11 patients were evaluated (Table 1). The median age was 62 years (range, 34-88 years), and the majority of patients (90.9%) had an Eastern Cooperative Oncology Group performance status of 0 to 1. Most had a primary malignancy of the rectum (36.4%), pancreas or bile duct (36.4%), or cervix (18.2%). Eight patients (72.7%) experienced local progression after definitive surgery and either neoadjuvant or adjuvant RT, and the others experienced progression after definitive chemoradiation therapy. The median total prescription dose for the prior RT course was 50 Gy (range, 30-58.8 Gy) in 25 fractions (range, 5-28 fractions). For most patients (63.6%), chemotherapy was given before reRT after a diagnosis of local progression, whereas surgical resection was also performed for 2 patients (18.2%).

The prior RT and reRT delivered to each patient is summarized in Table 2. The median interval from the completion of prior RT to the start of reRT was 26.8 months (range, 7.6-59.0 months). Most commonly, reRT

Table 1 Patient, tumor, prior therapy, and reirradiation characteristics

Characteristic	Patients, no. (%)* (N = 11)
Age, median (range), y	62 (34-88)
Sex	
Male	9 (81.8)
Female	2 (18.2)
ECOG performance status before reRT	
0	6 (54.5)
1	4 (36.4)
2	1 (9.1)
Primary tumor site	
Rectum	4 (36.4)
Pancreas or bile duct	4 (36.4)
Cervix	2 (18.2)
Lung	1 (9.1)
Histology	
Adenocarcinoma	8 (72.7)
Squamous cell carcinoma	2 (18.2)
Non-small cell carcinoma	1 (9.1)
Initial RT dose and fractionation	
Total dose, median (Gy)	50 (30-58.8)
Number of fractions, median	25 (5-28)
$EQD2_{10}$	56 (40-60)
$EQD2_3$	56 (43.2-100)
Definitive surgery after initial RT	8 (72.7)
Low anterior resection	4 (50)
Pancreaticoduodenectomy	2 (25)
Hysterectomy	1 (12.5)
Total pelvic exenteration	1 (12.5)
Interval from initial RT end to reRT start, median (range), mo	26.8 (7.6-59.0)
Reirradiation site	
Lymph node	4 (36.4)
Pancreas	3 (27.3)
Presacral	2 (18.2)
Rectum	1 (9.1)
Superior mesenteric artery	1 (9.1)
Reirradiation target volumes, median (range), cm^3	
GTV	24.3 (7.6-142.21)
PTV	38.8 (26.3-179)
Reirradiation dose and fractionation, median (range)	
Total dose, Gy	40 (25-54)
Fractions, No.	6 (5-36)
$EQD2_{10}$	44.7 (31.3-83.3)
$EQD2_3$	56.1 (34.3-83.3)
Reirradiation fractionation	
Ultrahypofractionation	7 (63.6)
Hyperfractionation	4 (36.4)
Concurrent chemotherapy during reirradiation	
Xeloda	4 (36.4)
None	7 (63.6)
Tumor resection after reRT	0

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EQD2 = equivalent dose in 2-Gy fractions; GTV = gross tumor volume; RT = radiation therapy; reRT = reirradiation; PTV = planning target volume.

* Data are presented as the number and percentage of patients unless otherwise indicated.

Table 2 Summary of patients treated with reirradiation on the ViewRay MRIdian Linac

Patient number	Age	Primary cancer	Prior RT dose, median, Gy/fx	Interval to reRT,mo	ReRT location	ReRT PTV, cm^3	ReRT total dose/ fx	ReRT schedule	ReRT $EQD2_{10}$, median, Gy	ReRT $EQD2_3$, median, Gy	On-table adaptive replanning	Concurrent chemotherapy	Local progression	Grade ≥3 toxic effects
1	88	Pancreas	30/5	12.8	Pancreas	31.31	25/5	QD	31.3	40	No	No	No	No
2	58	Rectum	50.4/28	30.1	Presacral	160.71	54/36	bid	51.8	48.6	No	Xeloda	21.9 mo after reRT	No
3	62	Rectum	45/25	26.8	LN	33.24	40.8/34	bid	38.1	34.3	No	Xeloda	32.3 mo after reRT	No
4	60	Lung	40/5	7.6	LN	43.4	40/5	QD	60	88	Yes	No	No	No
5	70	Pancreas	59.4/33	11.9	Pancreas	190.2	50/5	QD	83.3	130	Yes	No	No	No
6	34	Rectum	58.8/28	59.0	Presacral	38.84	42/28	bid	40.3	37.8	No	Xeloda	8 mo after reRT	No
7	42	Cervix	59.4/33	31.4	LN	28.34	33/6	QD	42.6	56.1	Yes	No	No	No
8	62	Cervix	59.4/33	10.7	LN	26.26	32.5/5	QOD	44.7	61.8	No	No	No	No
9	76	Pancreas	50.4/28	13.7	Pancreas	37.84	40/5	QD	60	88	No	No	No	No
10	80	Rectum	50.0/25	43.4	Rectum	143.45	42/28	bid	40.3	37.8	No	Xeloda	No	No
11	78	Bile duct	56/28	32.4	SMA	53.25	40/6	QOD	55.6	77.3	No	No	No	No

Abbreviations: bid = twice daily; EQD2 = equivalent dose in 2-Gy fractions; fx = fraction; LN = lymph node; PTV = planning target volume; QD = daily; QOD = every other day; reRT = reirradiation; RT = radiation therapy.

was delivered to abdominal or pelvic nodal metastasis (36.4%), the pancreas (27.3%), or a presacral recurrence (18.2%). The median GTV and PTV volumes were 24.3 cm^3 (range, 7.6-142.21 cm^3) and 38.8 cm^3 (range, 26.3-190.2), respectively.

The median total prescription reRT dose for all patients was 40 Gy (range, 25-54 Gy) in 6 fractions (range, 5-36 fractions). The corresponding median reRT prescription $EQD2_{10}$ and $EDQ2_3$ were 44.7 Gy (range, 31.3-83.3 Gy) and 56.1 Gy (range, 34.3-130 Gy), respectively. Ultrahypofractionation (5 or 6 fractions) was used to retreat nearly two-thirds (63.6%) of patients, predominantly to the nodal metastasis or the pancreas. The median prescription dose for those who received ultrahypofractionation was 40 Gy (range, 25-50 Gy) in 5 fractions (range, 5-6 fractions) delivered daily (5 patients) or every other day (2 patients). The corresponding median reRT prescription $EQD2_{10}$ and $EDQ2_3$ were 55.6 Gy (range, 31.3-83.3 Gy) and 77.3 Gy (range, 40-130 Gy), respectively. All other patients (36.4%) were treated with hyperfractionation to a median total prescription dose of 42 Gy (range, 30-54 Gy) in 28 fractions (range, 25-36 fractions) twice daily. The corresponding median reRT prescription $EQD2_{10}$ and $EDQ2_3$ were 40.3 Gy (range, 38.1-51.8 Gy) and 37.8 Gy (range, 34.3-48.6 Gy), respectively.

The median follow-up from reRT completion was 14 months (range, 6-32 months). The median and 1-year FFLP for all patients was 29 months and 88.9%, respectively (Fig 2A). The median and 1-year PFS were 21 months and 52.0%, respectively (Fig 2B). Six patients (54.5%) were dead at the time of last follow-up, all owing to distant progression and none because of local progression or reRT. The median and 1-year OS were 17.5 months and 70.0%, respectively (Fig 2C). The only 3 patients during the study period who experienced local progression after reRT had rectal cancer; all were retreated using hyperfractionation to a median of 42 Gy (range, 40.8-54 Gy) in 34 fractions (range, 28-36 fractions) twice daily and experienced local progression at a median of 21.9 months (range, 8.1-32.3 months) after reRT on the MRIdian Linac.

Treatment was well tolerated with no observed or reported acute or late toxic effects of grade 3 or greater. One patient with pancreas cancer who was heavily pretreated with chemotherapy and then definitive chemoradiation experienced acute grade 2 fatigue after reRT. All other patients experienced no toxic effects greater than grade 1.

Discussion

Magnetic resonance–guided RT represents a fundamental paradigm shift in how RT is fundamentally delivered by providing superior soft-tissue visualization compared with CT, continuous intrafraction imaging,

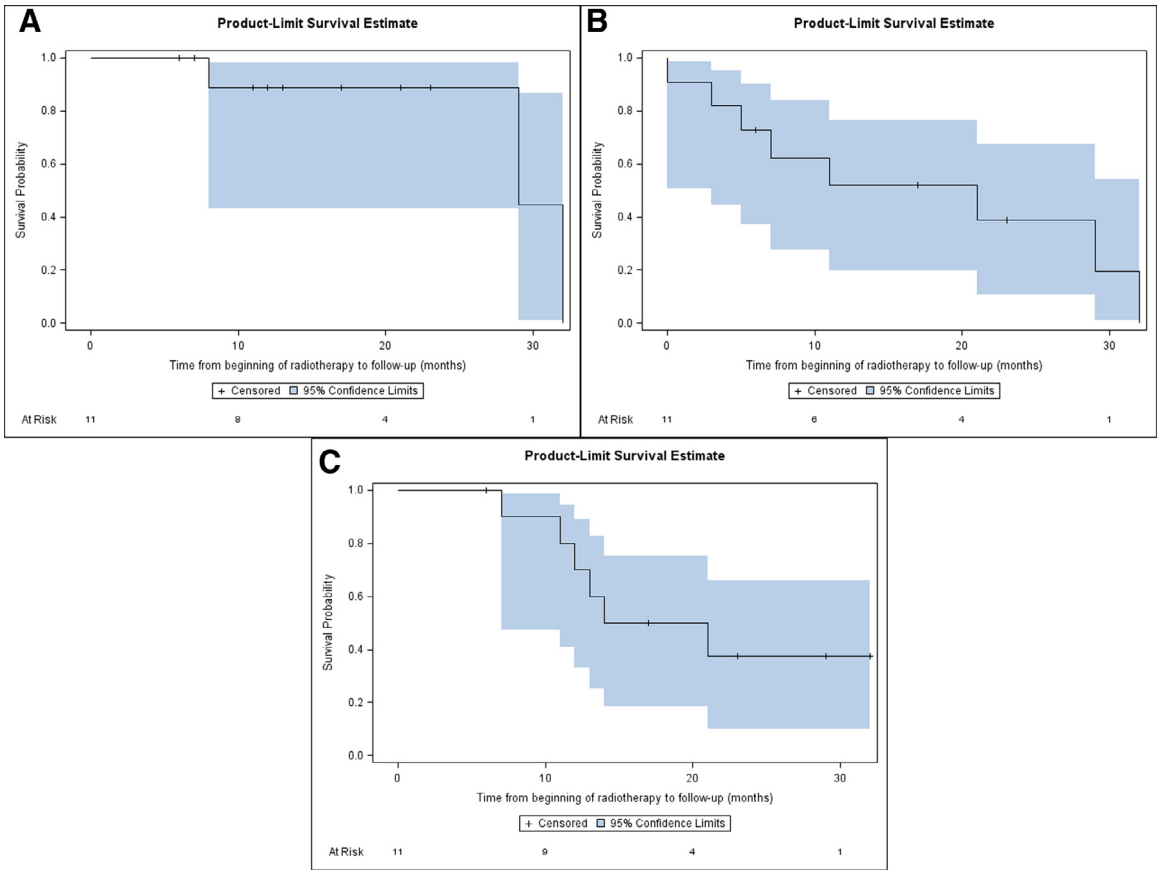

Fig. 2 Kaplan-Meier plots. (A) Freedom from local progression. (B) Progression-free survival. C, Overall survival from the start of reirradiation.

advanced motion management capabilities, and on-table adaptive replanning.[11] This novel technology can achieve excellent OAR sparing by reducing uncertainty margins, avoiding internal target volumes, and accounting for interfraction changes in anatomy through on-table adaptive replanning that is completed within only a few minutes (Fig 3). Although the dosimetric advantages of MR-guided RT may improve the therapeutic ratio of reRT, the only published clinical outcomes to our knowledge are case reports. Investigators from the University of California, Los Angeles, suggested the feasibility of pelvic reRT on an MR-Cobalt device in a patient with recurrent rectal cancer who was prescribed 35 Gy in 5 fractions, although follow-up was very short.[14] We previously reported no significant toxic effects in a patient with pancreas cancer reirradiated to 50 Gy in 5 fractions with on-table adaptive replanning on the MRIdian Linac after previously receiving 59.4 Gy in 33 fractions with concurrent chemotherapy.[15]

To our knowledge, we report the first case series of abdominopelvic reRT delivered on an MR-Linac. With a median follow-up of 14 months from reRT completion, our early experience has been encouraging compared with that of other published reRT studies (Table 3). In this study, ReRT was tolerated surprisingly well, with only 1 patient experiencing toxic effects of grade 2 and none experiencing toxic effects of grade 3 or greater. Our 1-year FFLP of nearly 90% is notable, especially because no patient had surgery after reRT.[6]

Historically, reRT has been prescribed to 30 to 40 Gy $EQD2_{10}$ to minimize the risk of severe toxic effects, although these modest doses are not associated with durable LC, especially in patients who do not proceed to surgery.[4] Owing to the exceptional OAR sparing uniquely achieved with an MR-Linac, we used a dose escalation strategy for most patients; nearly all were prescribed ≥40 Gy $EDQ2_{10}$, and nearly half were prescribed ≥50 Gy $EDQ2_{10}$. Our use of higher prescription doses was motivated by data suggesting that this can improve long-term treatment efficacy.[4,5,17,18] Koom and colleagues reported significantly higher LC among patients with locally recurrent rectal cancer who were prescribed >50 Gy $EQD2_{10}$ and who did not have subsequent surgery.[5] Chung and colleagues showed that a subset of patients with recurrent rectal cancer who were prescribed >50 Gy $EQD2_{10}$ had superior LC, PFS, and OS.[17] Both studies used generous PTV margins up to 3 cm, which may have contributed to a high incidence (approximately 40%) of late toxic effects of grade 3 or greater. In contrast, Abusaris and colleagues reported no severe toxic effects using stereotactic body

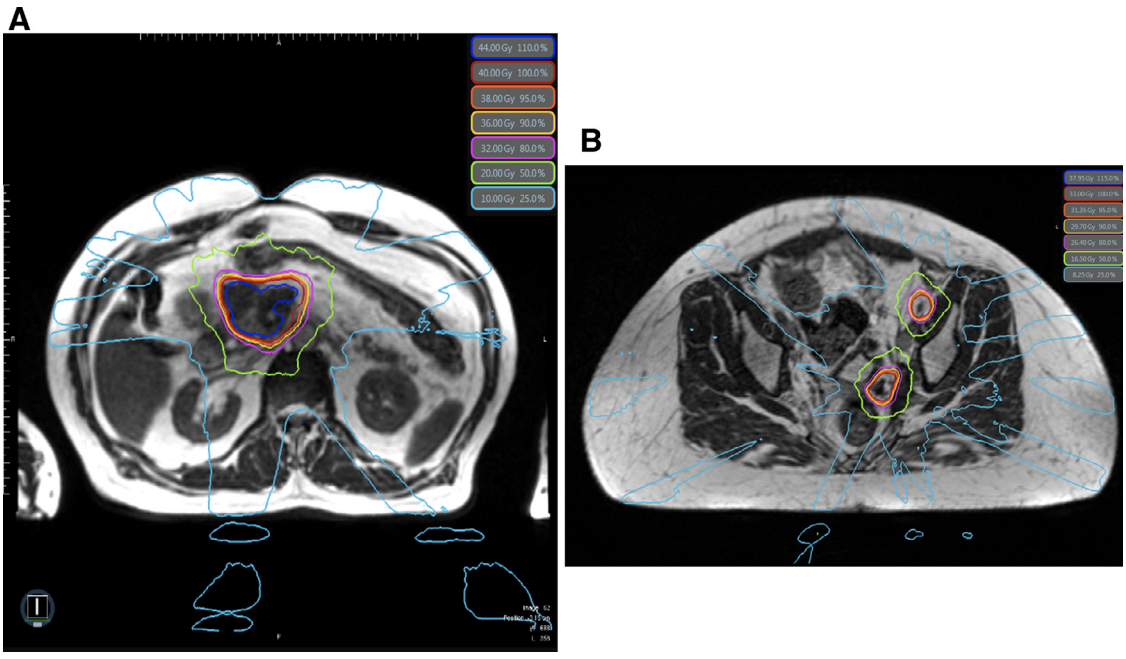

Fig. 3 (A) Isodose lines from a pancreas reirradiation plan prescribed to 40 Gy in 5 fractions. (B) Isodose lines from a pelvic lymph node reirradiation plan prescribed to 33 Gy in 6 fractions. Daily on-table adaptive replanning was indicated in nearly all fractions for both patients to ensure that organ-at-risk dose constraints were met.

radiation therapy (SBRT) reRT with only 2- to 3-mm PTV margins; >60 Gy $EQD2_{10}$ was associated with significantly higher 1-year LC versus ≤60 Gy $EQD2_{10}$ (100% vs 53%; $P = .04$).[18]

Most of the published data establishing the feasibility of reRT for abdominopelvic cancers includes patients with locally recurrent rectal cancer, and as shown in a recently published systematic review,[19] this has predominantly been delivered using hyperfractionation. In 2006, Valentini and colleagues published the results of a multicenter phase 2 study of 59 patients with recurrent rectal cancer treated with 3-dimensional conformal RT to 40.8 Gy in 1.2-Gy fractions twice daily with a PTV of up to 4 cm, resulting in margins that included minimal toxic effects of grade 3 or greater and encouraging long-term LC and OS.[2] Tao and colleagues from the MD Anderson Cancer Center retrospectively evaluated 102 patients with rectal cancer who preoperatively received a median of 50.4 Gy in 28 fractions, and after a median of 30 months, received reRT to a median of 39 Gy in 1.5-Gy fractions twice daily.[6] Nearly all were treated with 3-dimensional conformal RT and generous PTV margins up to 2.5 cm. The incidence of toxic effects of grade 3 or greater was thought to be acceptable (34%), and patients who were able to undergo subsequent surgery had especially promising LC and OS. In addition to locally recurrent rectal cancer, reRT is also feasible for anal canal, gynecologic, prostate, and other abdominopelvic cancers.[7,20-22]

Whereas radiobiologic principles indicate that hyperfractionation using a lower dose per fraction should be preferred for reRT, in recent years, there has been greater interest in delivering ultrahypofractionated reRT with SBRT that features steep dose gradients and tight margins.[23-27] Abusaris and colleagues reported no toxic effects of grade 3 or greater in 33 patients, most with rectal or cervical cancer, who were reirradiated using SBRT with 2- to 3-mm PTV margins.[18] A multi-institution retrospective study reported favorable outcomes in patients with pancreas cancer reirradiated with SBRT to a median of 25 Gy in 5 fractions; most of the patients experienced symptom palliation, 1-year FFLP was 62%, and there were no toxic effects of grade 3 or greater.[27] A retrospective study from the United Kingdom of 30 patients with recurrent rectal cancer reirradiated to 30 Gy in 5 fractions reported no toxic effects of grade 3 or greater, improved quality of life after reRT, and 1-year LC of 84.9%.[28] Thus, it is reasonable to consider SBRT reRT to the abdomen and pelvis, which we have routinely adopted at our institution, especially when delivered using the enhanced abilities of an MR-Linac.

This study has some limitations, including its retrospective nature, the small number of patients, heterogeneous dose fractionation schedules, and various tumor types and histologies. Although the median follow-up was relatively short, it was similar to that of other published reRT studies (Table 3) and long enough to meaningfully assess acute toxic effects and early treatment efficacy.

In conclusion, our early experience suggests that dose-escalated reRT to the abdomen and pelvis using an MR-Linac is feasible. Based on these encouraging outcomes, we are planning to conduct a prospective trial for dose-escalated MR-guided reRT.

Table 3 Select reirradiation studies

Authors	Publication year	N	Primary cancer	Prior RT dose, median, Gy/fx,	Interval to reRT, median, mo	reRT total dose/fx, median	reRT $EQD2_{10}$, median, Gy median	reRT $EQD2_{3}$, median, Gy	Surgery after reRT	Follow-up, median, mo	Local control	Overall survival	Acute or late grade ≥3 toxic effects
Valentini et al[2]	2006	59	Rectum	50.4/28	27	40.8/34	38.1	34.3	50.8%	36	1-y 76.3%	1 y (87.5%)	5.1%/1.7%
Tao et al[6]	2017	102	Rectum	50.4/28	30	39/26	37.4	35.1	45%	28	3-y 40%	3 y (39%)	NR/34%
Koroulakis et al[10]	2020	28	Rectum	54/30	48.5	44.4/NR	NA	NA	21.4%	28.6	1-y 66.3%	1 y (81.8%)	10.7%/21.4%
Lominska et al[24]	2012	28	Pancreas	50.4/28	NR	22.5/3	32.8	47.3	0%	5.9	1-y 85.7%	Median 5.9 mo	0%/7.1%
Dagoglu et al[25]	2016	30	Pancreas	50.4/28	18	25/5	31.3	40	0%	11	1-y 78%	1 y (50%)	10%/7%
Koong et al[26]	2017	23	Pancreas	50.4/28	13	25/5	31.3	40	0%	28	1-y 81%	Median 8.5 mo	8.7%/0%
Hunt et al[4]	2018	24	Various	45/25	27.9	39/26	37.4	35.1	0%	16.8	1-y 38%	1 y (50%)	16.7%/NR
Abusaris et al[18]	2012	33	Various	NR	NR	32/4	45.3	64	0%	15	1-y 64%	1 y (52%)	0%/0%
Current study	2021	11	Various	50/25	26.8	40/6	44.7	56.1	0%	14	1-y 88.9%	1 y (70%)	0%/0%

Abbreviations: EQD2 = equivalent dose in 2-Gy fractions; fx = fraction; NA = not available; NR = not reported; reRT = reirradiation; RT = radiation therapy.

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