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Technical Note

Feasibility and safety of contrast-enhanced magnetic resonance-guided adaptive radiotherapy for upper abdominal tumors: A preliminary exploration

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ABSTRACT

This study investigates the use of contrast-enhanced magnetic resonance (MR) in MR-guided adaptive radiotherapy (MRgART) for upper abdominal tumors. Contrast-enhanced T1-weighted MR (cT1w MR) using half doses of gadoterate was used to guide daily adaptive radiotherapy for tumors poorly visualized without contrast. The use of gadoterate was found to be feasible and safe in 5-fraction MRgART and could improve the contrast-to-noise ratio of MR images. And the use of cT1w MR could reduce the interobserver variation of adaptive tumor delineation compared to plain T1w MR (4.41 vs. 6.58, $p < 0.001$) and T2w MR (4.41 vs. 7.42, $p < 0.001$).

1. Introduction

The advent of MR-guided radiotherapy (MRgRT), have greatly improved the precision of abdominal radiotherapy (RT) [1]. One system currently available for MRgRT, the Unity 1.5 T MR-linac (Elekta, Stockholm, Sweden), can acquire daily MR images of patients at each fraction of RT, allowing radiation oncologists to verify and adaptively adjust the reference plan based on changes in anatomic structures during treatment, ensuring target dose coverage while protecting organs at risk [2–7]. However, despite the theoretical advantages of MR for soft tissue resolution, not all abdominal tumors can be clearly displayed on Unity MR images during adaptive RT.

One way of addressing this is to use MR contrast agents to enhance the contrast between tissues on MR images by modifying tissue relaxation times, thereby making lesions more visible [8]. The most widely used MR contrast agents are those based on gadolinium, which can enhance the T1w signal of tissues while reducing the T2w signal. Dynamic contrast-enhanced MR with gadolinium-based contrast agents is now being widely used for the diagnosis of many abdominal tumors [9–13]. Although the introduction of MR contrast agents in MRgRT is receiving increased attention, reports of using gadolinium-based agents are still quite limited. A recent survey indicates that some institutions are using MR contrast agents for MRgRT. However, detailed reports on the safety and efficacy in this context are not available [14]. As a type of gadolinium-based contrast agent, gadoterate has good safety and efficacy in MR diagnosis [15–19]. However, to date no reports are available regarding its use in MRgRT, aside from some experiments suggesting that irradiation does not lead to chemical alterations of gadolinium-based contrast agents [20–22].

In this study, we first evaluated the feasibility and safety of gadoterate-enhanced T1-weighted MR (cT1w MR) for tumor visualization of a variety of upper abdominal tumors in the context of adaptive MRgRT, and then we explored the value of gadoterate in facilitating tumor delineation during adaptive RT.

2. Materials and methods

2.1. Patients

Eligible patients had upper abdominal tumors suitable for RT. The tumors evaluated were pancreatic ductal adenocarcinoma (PDAC), pancreatic metastases, splenic metastases, hepatocellular carcinoma (HCC), and hepatic metastases. All patients provided written informed consent to participate and to provide clinical and technical data related to treatment. The Medical Ethics Committee of Shandong Cancer Hospital and Institute approved the study protocol.

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2.2. MR contrast agent

Gadoterate meglumine was obtained from Jiangsu Hengrui Pharmaceuticals Co. Ltd (China) in 15-mL bottles of gadoterate meglumine injection preparation, each of which contains 5.654 g of gadoterate meglumine. The recommended dose is 0.1 mmol (i.e., 0.2 mL) per kg of body weight for adults, children, and infants. In this study, half doses (0.1 mL per kg body weight) were used for simulation and MRgRT.

2.3. Simulation, planning and online adaptive treatment

Simulations involved three component sessions: Unity MR; Big Bore CT; and 3 T MR. Abdominal compression was used to control tumor motion. The Unity-MR simulation included T1w MR, T2w MR, cT1w MR, and 2D cine MR based on the btFFE sequence. Main parameters of Unity-MR sequences are shown in Table S1. The contrast injection was performed manually. The cT1w MR scans were started immediately after the injection of a half-dose of contrast agent (0.1 mL per kg body weight) and took about 3 min. All simulation data were transferred to an Eclipse treatment planning system (Varian, Palo Alto, CA, USA) to generate reference contours and plans. The internal target volume (ITV) was defined using 4D CT or 4D MR. The planning target volume (PTV) was defined as a 5 mm uniform geometric expansion of the GTV or ITV. Reference plans were then transferred to a Monaco v5.4 system (Elekta AB, Stockholm, Sweden) for daily adaptive treatments.

Given tumor visualization and potential safety concerns with gadoterate, only patients with tumors best visualized by cT1 MR and who were receiving stereotactic body radiotherapy (SBRT) with 5 fractions were treated with cT1w MR-guided radiotherapy. For patients who received cT1w MR, a T1w MR scan was obtained during each treatment fraction before contrast injection for comparison. After the data were transferred to the online Monaco system, the reference CT and daily MR data were rigidly registered. The "Adapt to Position" (ATP) or "Adapt to Shape" (ATS) method was chosen by radiation oncologists based on the anatomic change of tumors and organs at risk (OARs). The ATP method adjusts only the position of contours, while the ATS method corrects both position and shape [23,3,4]. Before the start of treatment, a T2w MR scan and 2D cine imaging were conducted for verification.

2.4. Unity-MR image evaluation

The contrast-to-noise ratio (CNR) was calculated to quantitatively evaluate the contrast resolution of the different Unity-MR modalities [24].

$$CNR = \left|SI_{tumor} - SI_{background}\right| / \sqrt{\left(SD_{tumor}{}^2 + SD_{background}{}^2\right)/2}$$

A signal region of interest (ROI) was created within the tumor on the MR image, and a background ROI was created in adjacent normal tissue at the identical anatomic depth as the tumor. The standard deviation (SD) of the signal within each ROI was used to represent the noise SD. We kept the sizes and shapes of the ROIs identical for all measurements.

2.5. Offline registration and delineation

For the each of patients who underwent online adaptive RT under the guidance of cT1w MR, we fused the T2w MR, T1w MR, and the cT1w MR data from the first fraction with the reference CT data on the offline Monaco system. Five radiation oncologists performed the ATP/ATS workflow and generated adaptive GTVs independently with the fused CT/MR data obtained from each patient. An intersection of five GTVs on each MR sequence image for each patient was generated to represent the consensus of five observers on the tumor contour, and the Hausdorff distance (HD) from each GTV to the intersection was calculated to evaluate the deviation of each observer from the consensus.

2.6. Data acquisition and analysis

The Monaco system was used to generate CNRs on the Unity-MR images. MIM software (MIM Software Inc., Cleveland, OH, USA) was used to generate intersections of GTVs and to calculate the HD. Paired *t* tests were used to compare the CNRs and HDs of the different MR sequences. Data were analyzed by using SPSS Version 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

2.7. Safety assessment

The patients who received the contrast agent repeatedly during SBRT with 5 fractions were followed at 1-month intervals for 3 months for safety assessment. The occurrence of adverse events and serious adverse events during treatment and follow-up were documented and graded according to the Common Terminology Criteria for Adverse Events version 5.0.

3. Results

3.1. Patients

From September 2022 through April 2023, 20 patients with upper abdominal tumors participated in this study. Seven patients had PDAC, six had HCC, five had hepatic metastases, one had splenic metastases, and one had pancreatic metastases. After Unity-MR simulation, 7 patients (5 with PDAC, 1 with hepatic metastases, and 1 with splenic metastases) were chosen to undergo cT1w MR-guided adaptive SBRT. For these patients, all planned fractions were completed, and the median in-room time was 35.6 min. Patient, disease, treatment, and contrast agent administration details are shown in Table S2.

3.2. Contrast resolution

Representative Unity-MR images of patients with good enhancement are shown in Fig. 1, images from five consecutive fractions are shown in Fig. S1; summarized CNRs of patients with different tumor types are shown in Fig. S2. Detailed CNR values are shown in Table S3. In summary, cT1w MR had the highest contrast resolution for PDAC. In patients with HCC, cT1w MR showed high CNR in a subset of patients, including one patient with portal vein tumor thrombus (PVTT); T2w MR seemed to have better and more stable contrast resolution. For patients with hepatic metastases, large individual variations obscured relative differences in contrast resolution between different MR sequences.

3.3. Influence of gadoterate on adaptive GTV definition

Five radiation oncologists independently reviewed three types of MR data from the first treatment fractions of patients receiving gadoterate for daily MR guidance and generated GTVs offline using either the ATP or ATS method depending on their judgment. Finally, only the ATP method was selected. The raw data of the HDs are shown in Table S4, and representative images of the GTVs are shown in Fig. S3. The mean HDs from GTVs of each MR image to their intersections were 4.41 ± 2.48 mm, 6.58 ± 2.41 mm, and 7.92 ± 2.63 mm for cT1w, T1w, and T2w MR, respectively. Significant differences were observed between the mean HDs of cT1w MR and T1w MR ($p < 0.001$) as well as between cT1w MR and T2w MR ($p < 0.001$).

3.4. Safety

We evaluated the safety and toxicity of gadoterate in patients who received repeated doses of this contrast agent during SBRT with 5 fractions. Details of the adverse events experienced by these patients are shown in Table 1. No acute toxic reactions occurred during RT, and no grade 3 or higher events took place within the 3-month follow-up. Grade

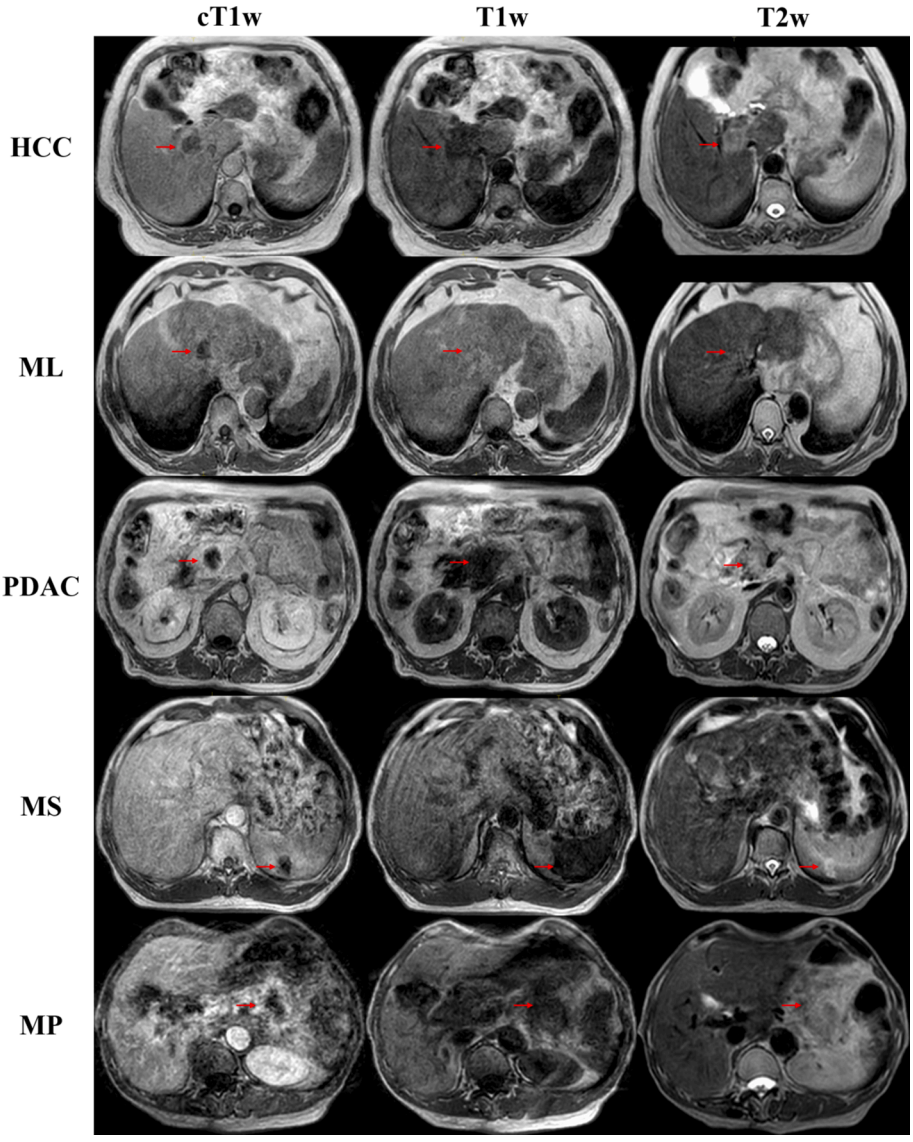

Fig. 1. Representative axial Unity-MR images of tumors show enhancement from the contrast agent gadoterate in patients with hepatocellular carcinoma (HCC), hepatic metastases (ML), pancreatic ductal adenocarcinoma (PDAC), splenic metastases (MS), and pancreatic metastases (MP). Red arrows indicate the locations of the lesions. Abbreviations: cT1w, contrast-enhanced T1-weighted MR; T1w, T1-weighted MR; T2w, T2-weighted MR. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Gadoterate-related toxic effects during and for the first 3 months after treatment.

Adverse Event	Grade 1	Grade 2	Grade ≥ 3
Clinical			
Fatigue	2	0	0
Anorexia	3	0	0
Nausea	0	1	0
Diarrhea	1	0	0
Dizziness	1	0	0
Abdominal pain	1	1	0
Fever	1	0	0
Biochemical			
AST/ALT	1	0	0
Bilirubin	1	0	0
Albumin	3	0	0
Creatinine	0	0	0
Hematologic			
Hemoglobin	3	0	0
Leukocytes	1	1	0
Platelets	3	0	0

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase.

2 adverse events were nausea (n = 1), abdominal pain (n = 1) and leukopenia (n = 1). The leukopenia and nausea were attributed to subsequent chemotherapy, and the abdominal pain was considered to be related to the tumor progression. No adverse events were considered to be related to the contrast agent.

4. Discussion

In this study, we reasoned that the use of a contrast agent may solve the ambiguous visualization of tumors in MRgRT of upper abdominal tumors. A workflow was established in which the MR contrast agent gadoterate was applied for MRgRT of upper abdominal tumors. For patients receiving contrast, the median in-room time was acceptable and the completion rate of RT was high, indicating good feasibility of this workflow.

In terms of tumor visualization, patients with PDAC were more likely to benefit from the use of gadoterate, and the contrast agent was also found to be useful in a patient with liver metastases from rectal cancer and another with spleen metastases from gastric cancer. These tumors

showed a similar enhancement pattern: low signal tumors on bright backgrounds, which could be attributed to the hypovascularity of the tumors and the relative hypervascularity of the parenchymatous organ like the liver, spleen and pancreas [25–27]. To evaluate the benefit of gadoterate bringing to GTV delineation during adaptive RT, offline delineation was conducted by five radiation oncologists. The results indicated that the use of gadoterate reduced the interobserver variability in GTV definition, reflecting better visualization of tumor contours. Regarding the display of OARs, the cT1w MR was able to visualize hollow organs, such as the stomach and intestine, as well as the T1w MR and T2w MR. However, due to the enhancement of pancreatic parenchyma, cT1w MR can differentiate the duodenum and pancreatic head better, which is especially helpful for radiotherapy of pancreatic head cancer. For organs such as the liver, spleen, pancreas, and kidney, gadoterate reduces their contrast against abdominal fat. However, the presence of the organ capsule still allows us to distinguish them.

Others have reported that gadolinium-based contrast agents can accumulate in tissues such as the liver, brain, bone, and kidney and potentially cause neurological, musculoskeletal, and dermatologic symptoms [28].. In this study, a total of 7 patients received more than one half-dose of gadoterate during the course of MRgRT, that is, one half-dose at simulation and one half-dose at each of 5 treatment fractions. About one week elapsed between simulation and RT, and each treatment fraction of SBRT was separated by one day. According to the ESUR Guidelines on Contrast Agents (version 10.0), there was plenty of time for gadoterate to excrete [29]. Notably, there were no adverse events related to the contrast agent in our study. Thus, the results showed satisfactory contrast enhancement and good safety when using half-doses of contrast agent, providing preliminary guidance for the future use of gadoterate in MRgRT for pancreatic cancer.

In conclusion, for patients with upper abdominal tumors treated with five-fraction SBRT, the use of MR contrast agent gadoterate can be an effective, safe, and convenient solution to the poor visualization of tumor contours during adaptive MRgRT.

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CRediT authorship contribution statement

Wenheng Jiang: Methodology, Data curation, Formal analysis, Investigation, Writing – original draft, Visualization. **Xihua Shi:** Data curation. **Xiang Zhang:** Conceptualization, Writing – review & editing, Visualization. **Zhenjiang Li:** Methodology, Data curation, Writing – review & editing. **Jinbo Yue:** Conceptualization, Supervision, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2024.100582.

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