Magnetic Resonance Image-Guided Hypofractionated Ablative Radiation Therapy for Hepatocellular Carcinoma With Tumor Thrombus Extending to the Right Atrium

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Abstract

Hepatocellular carcinoma (HCC) presenting with tumor thrombus (TT) and inferior vena cava (IVC)/right atrium (RA) infringement point to an advanced-stage disease that is deemed inoperable. Stereotactic body radiotherapy is an emerging treatment option for this group of patients with promising outcomes in recent studies that are comparable to conventional treatment methods, namely, transarterial chemoembolization and transarterial radioembolization. Here, we report a case of HCC with RA extension through the IVC. The patient was referred to our clinic for treatment options, and he was found suitable for magnetic resonance imaging-guided radiotherapy (MRgRT). We treated the patient with MRgRT in five fractions to a total dose of 40 Gray. The tumor was tracked during the treatment sessions, and adaptive treatment planning was performed before each fraction. The patient tolerated the treatment well with no acute grade 3–4 toxicities. The last follow-up showed that the patient had a complete biochemical response and is now a candidate for an orthotopic liver transplant. To our knowledge, this report is the first to document the MRgRT treatment of an HCC with TT and RA extension. MRgRT is safe and feasible for this patient group and can be an effective bridging therapy for liver transplants.

Introduction

Hepatocellular cancer (HCC) is the most common primary liver malignancy with an increased incidence over the last four decades [1]. Although the treatment of choice is surgery, fewer than 20% of patients are amenable to surgery at the time of presentation [2]. Until recently, transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) were the preferred non-curative methods for patients unsuitable for surgery [3]. With the new technologies that enable administering high doses to the tumor with safer side effect profiles, radiotherapy (RT) can be a potential alternative to the abovementioned methods.

HCC presenting with tumor thrombus (TT) is considered inoperable and has an even worse prognosis. Studies reporting treatment of HCC with TT via surgical resection, TACE, and TARE have been reported in the literature [4]. Stereotactic body radiotherapy (SBRT) has previously been reported to be effective in HCC patients with TT in the portal vein [5,6]. In such cases, adaptive treatment under daily image guidance should be considered to cover the target volume. Computed tomography (CT) images do not allow precise identification of liver volumes, as well as daily in-place adaptive planning; thus, magnetic resonance imaging-guided radiotherapy (MRgRT) can be beneficial in HCC, especially in the presence of TT [7,8]. Here, we present a case of HCC with TT extending to the right atrium (RA) treated with MRgRT. To our knowledge, this is the first report to document the MRgRT treatment of an HCC with TT and RA extension.

Case Presentation

Our patient is a 64-year-old male. His medical history included thalassemia and diabetes mellitus. His family history was free of malignant diseases. In 2020, the patient presented to a tertiary care center with complaints of fatigue and pain in the right lumbar area. Serology revealed that the patient was positive for hepatitis C virus. The patient was diagnosed with cirrhosis with a Child-Pugh score of 6 and a Model for End-Stage Liver Disease (MELD) score of 12. Further workup was consistent with portal hypertension and esophageal varices secondary to cirrhosis. Alpha-fetoprotein (AFP) level was 658 ng/mL which was extremely above the normal reference range. CT was consistent with an inoperable HCC at segments three and four of the liver. Laparoscopic biopsy ensued CT, and the pathology report confirmed the diagnosis. In September 2020, the patient underwent TACE. CT was performed one month after the procedure and showed a residual mass of 18 × 14 mm at segment three, as well as a TT in the portal vein and lymph nodes in the liver. The patient was referred to our clinic for treatment options, and he was found suitable for MRgRT. To our knowledge, this is the first report to document the MRgRT treatment of an HCC with TT and RA extension.

Keywords: mr-linac, sbrt, tumor thrombus, inoperable, hepatocellular cancer
The patient was found unsuitable for transplantation, and radioembolization was recommended for him. Although the liver function tests were slightly above the normal reference range, the patient had an increased bilirubin level, so radioembolization could not be performed. In January 2021, the patient consulted our clinic with his current CT and magnetic resonance imaging (MRI) scans. His general health was good, and he had no restrictions in performing his daily activities. His blood test results were significant for AFP level of 653 ng/mL and total bilirubin of 104 µmol/L. He had mild anemia (hemoglobin was 10.4 g/dL). His current radiological imaging showed HCC at segments three and four with a thrombus in the inferior vena cava (IVC). The patient was presented to a multidisciplinary tumor board for treatment options, namely, radioembolization and radiotherapy. Because radioembolization was found to be unsuitable for the patient, we decided that the patient was an eligible candidate for SBRT.

MRI-guided SBRT at the MRIdian Linac (ViewRay Inc, Mountain View, CA, USA) was deemed suitable for this patient. The patient was put on a simulation through MRIdian Linac to ensure that the target volumes are clearly visible and distinguishable from the normal tissue in the MRIdian Linac System. The image was acquired in 25 seconds via TrueFISP sequence in three-dimensional 0.35 Tesla MRI with no contrast material injection as the tumor was visible in non-contrast images. Thereafter, the patient underwent simulation CT. Both simulations were performed with the deep-inspiration breath-hold (DIBH) technique. Pretreatment simulation MR Linac scans were fused with the simulation CT scans and other available diagnostic images. Gross tumor volume (GTV) was delineated as the primary liver lesion and the TT extending to the RA. The planning target volume (PTV) was extended 3 mm in all directions from the GTV. Organs at risk (OARs) were determined as the esophagus, stomach, spinal cord, superior mesenteric artery, portal vein, pancreas, lungs, liver, bowels, right and left kidney, heart, duodenum, celiac artery, and aorta. Volumes are presented in Table 1. A total dose of 40 Gray (Gy) in five fractions (8 Gy/fraction) was prescribed for the lesion. A step and shoot intensity-modulated radiotherapy (IMRT) treatment plan was generated according to departmental dosimetric dose constraints (Table 2) with both arms-down positions (patient was unable to lay in arms-up position for a whole treatment session) with 23 fields and one isocenter and 6 MV flattening filter-free (FFF) photons. Pixel size and dose grid resolution were 0.3 cm, and the number of multileaf collimators (MLC) was 92. IMRT efficiency was 8. V89 of PTV had 40 Gy and V95 of GTV had 39 Gy. This reference plan was denoted as "Plan 0." Dose-volume histograms are shown in Figure 1, and Figure 2 shows the GTV, PTV, and isodose lines with the tumor extending to the IVC and heart.

| Structure       | Volume (cc) |
|-----------------|-------------|
| GTV             | 83.2        |
| PTV             | 128.5       |
| Liver           | 1833        |
| Large bowel     | 219         |
| Right kidney    | 207         |
| Left kidney     | 171.2       |
| Heart           | 554         |
| Duodenum        | 77          |
| Stomach         | 252         |

**TABLE 1: Volumes of structures in the reference plan (Plan 0).**

GTV: gross tumor volume; PTV: planning target volume
| Structure       | Maximum dose (Gy) | Dose to volume         |
|-----------------|-------------------|------------------------|
| PTV             | N/A               | >95% at 40 Gy          |
| Duodenum        | N/A               | ≤1 cc at 33 Gy         |
| Duodenum        | N/A               | ≤0.5 cc at 36 Gy       |
| Large bowel     | N/A               | ≤1 cc at 33 Gy         |
| Large bowel     | N/A               | ≤0.5 cc at 36 Gy       |
| Stomach         | N/A               | ≤1 cc at 33 Gy         |
| Stomach         | N/A               | ≤0.5 cc at 36 Gy       |
| Spinal cord     | 25                | ≤10 cc at 25 Gy        |
| Spinal cord     | 25                | ≤1.2 cc at 14.5 Gy     |
| Spinal cord     | 25                | ≤0.35 cc at 23 Gy      |
| Aorta           | 53                | N/A                    |
| IVC             | 53                | N/A                    |
| Esophagus       | 35                | ≤5 cc at 19.5 Gy       |
| SMA             | 53                | N/A                    |
| Portal vein     | 53                | N/A                    |
| Liver           | N/A               | ≤700 cc at 15 Gy       |
| Right kidney    | 10                | N/A                    |
| Left kidney     | 10                | N/A                    |
| Heart           | 36                | ≤15 cc at 32 Gy        |

**TABLE 2: Institutional constraints for OAR doses in MRgRT.**

OAR: organs at risk; MRgRT: magnetic resonance imaging-guided radiotherapy; Gy: Gray; cc: cubic centimeter; PTV: planning target volume; IVC: inferior vena cava; SMA: superior mesenteric artery
The patient was treated every other day. An adaptive online plan was generated while the patient was on the treatment table, and online quality assurance (QA) was obtained before each radiotherapy fraction. A radiation oncologist evaluated the daily anatomy and contoured the GTV, and adaptive planning was performed at the beginning of each fraction. An adaptive approach was applied in all fractions. Two plans were generated during each fraction; the baseline plan was recalculated on the anatomy of the day and a reoptimized plan which used the same number and direction as the baseline plan. The daily plan adaption is comprehensively described in our previous case report \cite{9}. The reasons for reoptimized adaptive plans were...
SBRT requires high precision, accuracy, and reproducibility as it delivers high doses in fewer fractions compared with conventional RT. Even though CT-based approaches targeted the tumor by inhibiting the respiratory motion, respiratory tracking, accounting for the tumor motion by creating a larger safety margin,

SBRT was found to be non-inferior to IMRT regarding overall survival, progression-free survival, and local control with the additional advantage of decreased overall treatment duration [22]. Xi et al. retrospectively evaluated 41 HCC patients with TT in either the portal vein or IVC treated with SBRT. Overall, 36.6% of the patients reached complete response with no grade 4-5 toxicity in any of the patients. They reported that SBRT was safe and effective and that more prospective trials were needed [24]. A subsequent study compared SBRT and three-dimensional conformal radiotherapy for the same patient group and analyses revealed that SBRT results in a higher survival rate of 53.6% and 34.4% without significant heterogeneity between the studies [25].
and tracking marker, interfraction reproducibility was found to be low [26,27]. In addition, the low visibility of liver tumors on X-ray imaging is another limitation for tumor tracking and target precision. Another challenge in liver RT is the nearby tissues that are vulnerable to radiation-induced damage such as luminal gastrointestinal organs and bile ducts. As mentioned above, healthy liver tissue should also be avoided from irradiation at high doses.

MRgRT unites the linear accelerator device with MRI images, and therefore, benefits from the high soft-tissue contrast of MRI. Although MRI-CT fusions have been used for many years, MRgRT enables the acquisition of real-time images during the course of treatment so that irradiation can be performed when the PTV is within the desired target region. MRgRT also allows the user to apply daily adaptive plans with the image of the current fraction. The online system permits the corrections of interfraction as well as intrafractional variations. Other benefits include avoidance of CT radiation dose.

MRgRT has the potential to improve SBRT in HCC patients. The only available retrospective study available in the literature reported the result of 12 patients with HCC and TT treated with MRgRT. Either 50 Gy in 10 fractions or 36–50 Gy in four to five fractions was used. Overall, 83.3% of patients showed an objective response. The study concluded that MRgRT is effective and feasible in HCC with TT in the main trunk or first branch of the portal vein [28].

Conclusions

Here, to our knowledge, we present the first documented case of HCC with RA extension treated with MRgRT. The tumor was not amenable to surgery nor suitable for other alternative methods due to basal poor prognostic factors. MRgRT allowed us daily planning and tumor tracking with no compromise from our PTV coverage. The change of the tumor location during the treatment was no question for us as the tracking was done online during the whole session under continuous online cine-MRI. No dose violation was noted during any of the fractions which can be attributed to two reasons: (1) our PTV margin was 3 mm which is a margin that cannot be safely given without online continuous tumor tracking, and (2) a new plan was performed before each fraction and any dose violation was intervened before the fraction. The patient responded well to the treatment with no greater than grade 3 side effects and with evidence of complete biochemical response with AFP levels.

MRgRT is a novel approach in RT that leads to tumor tracking and adaptive planning in each fraction resulting in good OAR preservation without compromising PTV coverage. MRgRT can be safely performed in HCC patients with TT and even RA extension and can be a bridging therapy for orthotopic liver transplantation in this patient group.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors declare that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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